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PAE 506

PAEDIATRIC ONCOLOGY

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Course code: PAE 506

Course title: Paediatric Oncology

Course credit load: 2 Units

Series 1: Epidemiology and Risk Factors of Childhood Cancer

- **Part 1.1: Age-Related Incidence of Childhood Cancer**
  - Sub Part 1.1.1: General epidemiology of childhood cancer
  - Sub Part 1.1.2: Age-related incidence patterns
  - Sub Part 1.1.3: The clinical significance of age-related incidence
- **Part 1.2: Race-Related Incidence and Genetic Factors**
  - Sub Part 1.2.1: Race-related incidence patterns
  - Sub Part 1.2.2: Genetic factors in childhood cancer causation
  - Sub Part 1.2.3: Genetic syndromes associated with increased cancer risk
- **Part 1.3: Chemical-Related Factors**
  - Sub Part 1.3.1: Chemical exposures and childhood cancer risk
  - Sub Part 1.3.2: Specific chemical associations
  - Sub Part 1.3.3: Challenges in establishing chemical causation
- **Part 1.4: Environmental Factors**
  - Sub Part 1.4.1: Ionising radiation and childhood cancer risk
  - Sub Part 1.4.2: Infectious and other environmental associations
  - Sub Part 1.4.3: The interplay of epidemiological and risk factors

Introduction

Picture a five year old brought to clinic with unexplained fevers, pallor, and easy bruising over several weeks, findings that, while common to many childhood illnesses, occasionally point towards an underlying malignancy. Childhood cancer, though far less common than cancer in adults, remains an important cause of childhood death, and understanding its epidemiology and the factors that increase risk provides the essential foundation for recognising, diagnosing, and managing the specific tumours discussed later in this PAE 506 course.

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The aim of this Series is to equip you with an understanding of the epidemiology of childhood cancer, including age- and race-related incidence patterns, and the genetic, chemical, and environmental factors associated with increased risk.

This Series begins with the **age-related incidence** of childhood cancer, before turning to **race-related incidence and genetic factors**. Next, we examine **chemical-related factors**, before concluding with **environmental factors** associated with childhood cancer.

Series Learning Outcomes

At the end of this Series, you should be able to:

- **SLO 1.1:** describe the general epidemiology of childhood cancer,
- **SLO 1.2:** describe the age-related incidence pattern of childhood cancer,
- **SLO 1.3:** describe the race-related incidence pattern of childhood cancer,
- **SLO 1.4:** describe the genetic factors associated with childhood cancer,
- **SLO 1.5:** list the genetic syndromes associated with increased childhood cancer risk,
- **SLO 1.6:** describe the chemical factors associated with childhood cancer,
- **SLO 1.7:** describe the environmental factors associated with childhood cancer, and
- **SLO 1.8:** discuss the interplay of epidemiological and risk factors in childhood cancer causation.

1.1 Age-Related Incidence of Childhood Cancer

1.1.1 general epidemiology of childhood cancer

Rare overall, but a significant cause of childhood death

Childhood cancer is considerably **rarer** than cancer in adults, accounting for a relatively small proportion of the overall global cancer burden, yet remains an important cause of childhood **morbidity and mortality**, since malignancy is among the leading causes of death in children beyond infancy in many settings, once the most common infectious and nutritional causes of death have been addressed through improved public health measures.

Unlike the great majority of adult cancers, which are predominantly **carcinomas** arising from epithelial tissue and often linked to cumulative lifestyle exposures over many years, childhood cancers are more often **embryonal tumours**, **leukaemias**, and **lymphomas**, reflecting the distinct **developmental** and **biological origins** of malignancy in this age group, a distinction

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with important implications for understanding both causation and the specific tumour types discussed later in this course.

Fill in the blank: Childhood cancers are more often embryonal tumours, leukaemias, and _____.

1.1.2 age-related incidence patterns

The **incidence** of specific childhood cancers varies considerably by **age**, with certain tumours showing a characteristic peak incidence within a particular, relatively narrow age range, reflecting their **embryonal origin**, since these tumours arise from cells that retain developmental potential most actively during specific periods of fetal and early postnatal life, before this potential is normally lost as tissues mature.

Embryonal tumours, including **neuroblastoma**, **nephroblastoma**, and **retinoblastoma**, discussed in detail in later Series of this course, characteristically present in **infancy** and **early childhood**, often before **5 years** of age, while other tumours, such as **Hodgkin's lymphoma**, show a different age pattern, becoming relatively more common in **later childhood** and **adolescence**, illustrating how age at presentation itself provides an important diagnostic clue.

Fill in the blank: Embryonal tumours characteristically present in infancy and early childhood, often before _____ years of age.

1.1.3 the clinical significance of age-related incidence

Understanding **age-related incidence patterns** is clinically valuable, since the age of a child presenting with a mass, organomegaly, or other feature suggestive of malignancy directly informs the **differential diagnosis**, with a very young child presenting with an abdominal mass, for example, appropriately raising greater suspicion for **neuroblastoma** or **nephroblastoma** than for a tumour type more typical of older children or adolescents.

This principle of using **age as a diagnostic clue** applies broadly across paediatric oncology, and will be revisited repeatedly across the tumour-specific Series later in this course, since recognising the **expected age range** for a specific tumour, alongside its other characteristic clinical features, meaningfully narrows the differential diagnosis and helps guide the initial diagnostic evaluation of a child with a suspected malignancy.

Fill in the blank: Understanding age-related incidence patterns directly informs the _____ diagnosis of a child with a suspicious presentation.

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Figure 1.1: A paediatric oncologist speaking with a family during a clinic consultation.

Pilot questions 1.1

1. Describe how childhood cancer differs from adult cancer in overall frequency and typical tumour type. (Linked to SLO 1.1)
2. Explain why embryonal tumours characteristically present in infancy and early childhood. (Linked to SLO 1.2)
3. List three embryonal tumours discussed later in this course. (Linked to SLO 1.2)
4. Describe the age pattern of Hodgkin's lymphoma compared with embryonal tumours. (Linked to SLO 1.2)
5. Explain how age at presentation informs the differential diagnosis of a child with a suspected malignancy. (Linked to SLO 1.2)

1.2 Race-Related Incidence and Genetic Factors

1.2.1 race-related incidence patterns

Some tumours show striking geographic and population differences

Certain childhood cancers show notable variation in **incidence** according to **race** and **geographic region**, with **Burkitt's lymphoma**, discussed in detail in the next Series of this

course, showing a particularly striking example of this pattern, occurring at a considerably **higher incidence** in **equatorial Africa**, where it is closely associated with **Epstein-Barr virus** infection and **malaria**, compared with its incidence in other parts of the world, where it occurs sporadically and at a much lower frequency.

Other tumours also show recognised variation in incidence between different **population groups**, though the underlying reasons for these differences are often **multifactorial**, reflecting a genuine combination of **genetic susceptibility**, differing patterns of **environmental exposure**, and, in some cases, differences in **diagnostic capacity** and reporting between regions, meaning race-related incidence data should be interpreted with appropriate caution rather than assuming a purely genetic explanation in every instance.

Fill in the blank: Burkitt's lymphoma occurs at a considerably higher incidence in equatorial _____.

1.2.2 genetic factors in childhood cancer causation

Genetic factors contribute to childhood cancer risk through several mechanisms, including **inherited germline mutations** in specific **tumour suppressor genes** or **oncogenes**, which predispose an affected child to developing a specific cancer, sometimes at a considerably **younger age** or with **multiple, bilateral** tumours compared with children who develop the same cancer type without an underlying inherited predisposition.

A well recognised example is the inherited form of **retinoblastoma**, discussed in detail in a later Series of this course, resulting from a germline mutation in the **RB1 tumour suppressor gene**, which not only increases the risk of retinoblastoma itself, often presenting **bilaterally** and at a younger age, but also confers an increased lifelong risk of certain other malignancies, illustrating how a single genetic predisposition can have implications extending well beyond the initial childhood cancer diagnosis.

Fill in the blank: Inherited retinoblastoma results from a germline mutation in the _____ tumour suppressor gene.

1.2.3 genetic syndromes associated with increased cancer risk

Several recognised **genetic syndromes** carry an increased risk of specific childhood cancers, including **Li-Fraumeni syndrome**, associated with a broad range of malignancies including sarcomas and early-onset breast cancer later in life, **Beckwith-Wiedemann syndrome**, associated with increased risk of **nephroblastoma** and **hepatoblastoma**, and **Down syndrome**, associated with an increased risk of **leukaemia**, illustrating the diversity of genetic conditions relevant to paediatric oncology risk.

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Recognising these associations is clinically valuable, since children with a known genetic syndrome carrying increased cancer risk may benefit from **structured surveillance** programmes, allowing earlier detection of a malignancy should one develop, and genetic counselling, discussed in an earlier course, plays an important role in informing affected families about these risks and the rationale for any recommended surveillance.

Fill in the blank: Beckwith-Wiedemann syndrome is associated with increased risk of nephroblastoma and _____.

Table 1.2: Genetic syndromes associated with increased childhood cancer risk.

Syndrome	Associated cancer risk
Li-Fraumeni syndrome	Broad range of malignancies, including sarcomas
Beckwith-Wiedemann syndrome	Nephroblastoma and hepatoblastoma
Down syndrome	Leukaemia
Hereditary retinoblastoma (RB1 mutation)	Bilateral retinoblastoma and later secondary malignancies

Pilot questions 1.2

1. Describe the race-related incidence pattern of Burkitt's lymphoma. (Linked to SLO 1.3)
2. Explain why race-related incidence differences should be interpreted with appropriate caution. (Linked to SLO 1.3)
3. Describe how inherited germline mutations contribute to childhood cancer risk. (Linked to SLO 1.4)
4. Describe the genetics and clinical significance of hereditary retinoblastoma. (Linked to SLO 1.4)
5. List two genetic syndromes associated with increased childhood cancer risk and their associated tumours. (Linked to SLO 1.5)

1.3 Chemical-Related Factors

1.3.1 chemical exposures and childhood cancer risk

Fewer well-established links than in adult cancer

Chemical factors are established causes of certain adult cancers through cumulative, prolonged exposure, but their role in **childhood cancer causation** is generally **less well established**, reflecting both the comparatively brief period of potential exposure in a child's life and the

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genuine difficulty of studying rare exposures against the backdrop of a relatively **rare** group of diseases overall.

Nonetheless, certain chemical exposures have been specifically linked to increased childhood cancer risk, including **prenatal exposure** to certain chemicals during critical periods of fetal development, when rapidly dividing cells may be particularly **vulnerable** to chemical carcinogenic effects, and specific **occupational exposures** of parents prior to or during pregnancy, which have been investigated as potential contributors to certain childhood cancers in some epidemiological studies.

Fill in the blank: Chemical exposures during critical periods of fetal development may affect rapidly dividing cells that are particularly _____.

1.3.2 specific chemical associations

Pesticide exposure, whether prenatal or in early childhood, has been investigated as a potential risk factor for certain childhood cancers, particularly **leukaemia**, in various epidemiological studies, though establishing definitive **causation** remains genuinely challenging given the numerous other variables that typically differ between exposed and unexposed populations in observational research of this kind.

Prior chemotherapy exposure, whether for a previous childhood cancer or, in some circumstances, maternal treatment during pregnancy, is a recognised risk factor for a **subsequent, secondary malignancy**, reflecting the genuinely **genotoxic** mechanism by which many chemotherapeutic agents act, a consideration of particular relevance to the long-term follow up of children previously treated for cancer, discussed further in the final Series of this course.

Fill in the blank: Prior chemotherapy exposure is a recognised risk factor for a subsequent, _____ malignancy.

1.3.3 challenges in establishing chemical causation

Establishing a definitive **causal relationship** between a specific chemical exposure and childhood cancer is genuinely challenging, given the relative **rarity** of childhood cancer overall, the typically long and variable **latency period** between exposure and cancer development, and the practical **difficulty** of accurately measuring and quantifying past exposure, particularly for exposures occurring during pregnancy or very early childhood, well before any cancer diagnosis is eventually made.

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As a result, most recognised chemical associations in childhood cancer are supported by **epidemiological association** rather than fully established, direct **causal mechanism**, meaning ongoing research in this area continues to refine our understanding, and clinicians should be aware that the evidence base for specific chemical causation in childhood cancer remains considerably **less developed** than the corresponding evidence base for many adult cancers.

Fill in the blank: Most recognised chemical associations in childhood cancer are supported by epidemiological association rather than fully established _____ mechanism.

Figure 1.3: A researcher reviewing epidemiological data related to childhood cancer risk factors.

Pilot questions 1.3

1. Explain why the role of chemical factors in childhood cancer causation is less well established than in adult cancer. (Linked to SLO 1.6)
2. Describe the potential significance of prenatal chemical exposure during fetal development. (Linked to SLO 1.6)
3. Describe the association between pesticide exposure and childhood leukaemia. (Linked to SLO 1.6)

4. Explain why prior chemotherapy is a recognised risk factor for secondary malignancy. (Linked to SLO 1.6)
5. List two challenges in establishing definitive chemical causation in childhood cancer. (Linked to SLO 1.6)

1.4 Environmental Factors

1.4.1 ionising radiation and childhood cancer risk

One of the more clearly established environmental risk factors

Ionising radiation exposure is among the more clearly established **environmental risk factors** for childhood cancer, with evidence from historical population exposures, including survivors of nuclear events, demonstrating a clear, **dose-dependent** relationship between radiation exposure and subsequent cancer risk, particularly **leukaemia** and certain **solid tumours**, with risk generally greater the **younger** the age at exposure.

Diagnostic medical radiation, such as computed tomography imaging, while providing essential diagnostic information when genuinely clinically indicated, carries a small but measurable associated cancer risk, meaning the principle of using the **lowest necessary radiation dose** and avoiding unnecessary imaging, particularly in children given their greater relative sensitivity to radiation compared with adults, remains an important practical consideration in everyday paediatric clinical practice.

Fill in the blank: The relationship between ionising radiation exposure and subsequent cancer risk is described as _____.

1.4.2 infectious and other environmental associations

Viral infection represents an important environmental contributor to certain childhood cancers, with **Epstein-Barr virus**, discussed earlier in this Series in the context of Burkitt's lymphoma, and, in some settings, **malaria**, acting as important cofactors, and **Human Immunodeficiency Virus**, discussed in an earlier course, associated with an increased risk of certain lymphomas, reflecting the broader relationship between chronic infection, immune dysfunction, and malignancy risk.

Maternal factors during pregnancy, including certain maternal illnesses and, in some studies, specific dietary factors, have also been investigated as potential environmental contributors to childhood cancer risk, though, as with the chemical factors discussed earlier in this Series,

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establishing definitive causation for many of these specific associations remains an area of ongoing research rather than firmly established fact.

Fill in the blank: Epstein-Barr virus and malaria act as important cofactors in the development of _____ lymphoma.

1.4.3 the interplay of epidemiological and risk factors

Childhood cancer causation is best understood as **multifactorial**, generally reflecting a genuine **interplay** between underlying **genetic susceptibility**, specific **environmental** or **chemical exposures**, and, in some cases, chance events occurring during normal cellular division, rather than any single factor acting entirely in isolation, meaning most childhood cancers cannot be attributed to one clearly identifiable single cause even after careful evaluation.

This multifactorial understanding has important **clinical implications**, since it means most childhood cancers are **not preventable** through simple avoidance of a single identified risk factor, unlike some adult cancers with a clear, dominant lifestyle-related cause, and families should be appropriately and honestly reassured that a childhood cancer diagnosis is very rarely attributable to anything the family did or failed to do, an important, genuinely reassuring message when discussing epidemiology and risk with an affected family.

Fill in the blank: Childhood cancer causation is best understood as _____, reflecting an interplay of genetic and environmental factors.

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Figure 1.4: A radiographer carefully positioning imaging equipment for a paediatric patient.

Pilot questions 1.4

1. Describe the relationship between ionising radiation exposure and childhood cancer risk. (Linked to SLO 1.7)
2. Explain why the lowest necessary radiation dose should be used in paediatric diagnostic imaging. (Linked to SLO 1.7)
3. Describe the role of Epstein-Barr virus as an environmental cofactor in childhood cancer. (Linked to SLO 1.7)
4. Explain why childhood cancer causation is best understood as multifactorial. (Linked to SLO 1.8)
5. Explain why most childhood cancers cannot be attributed to a single identifiable cause. (Linked to SLO 1.8)

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Series Summary

This Series introduced the **epidemiology of childhood cancer**, beginning with its **age-related incidence** pattern, before turning to **race-related incidence and genetic factors**.

We then examined **chemical-related factors**, before concluding with **environmental factors** and the overall **multifactorial nature** of childhood cancer causation. Having worked through this Series, you should now understand the epidemiology and risk factors relevant to childhood cancer, a foundation for the tumour-specific Series that follow. The next Series turns to **lymphomas in children, non-Hodgkin's and Hodgkin's lymphoma**.

Glossary of Terms

- **Embryonal tumour:** a childhood cancer arising from cells retaining developmental potential, typically presenting in early childhood.
- **Burkitt's lymphoma:** a lymphoma showing markedly higher incidence in equatorial Africa, associated with Epstein-Barr virus and malaria.
- **Germline mutation:** an inherited genetic mutation present in all cells, which can predispose to childhood cancer.
- **RB1 gene:** the tumour suppressor gene mutated in hereditary retinoblastoma.
- **Li-Fraumeni syndrome:** a genetic syndrome associated with a broad range of childhood and later-life malignancies.
- **Beckwith-Wiedemann syndrome:** a genetic syndrome associated with increased risk of nephroblastoma and hepatoblastoma.
- **Latency period:** the interval between an exposure and the eventual development of cancer.
- **Ionising radiation:** a well-established environmental risk factor for childhood cancer, particularly leukaemia.
- **Epstein-Barr virus:** a virus acting as an important cofactor in the development of Burkitt's lymphoma and certain other malignancies.
- **Secondary malignancy:** a new cancer arising as a late effect of prior cancer treatment.
- **Multifactorial causation:** the principle that most childhood cancers result from an interplay of genetic and environmental factors rather than a single cause.
- **Structured surveillance:** a programme of regular monitoring for children with a known genetic predisposition to cancer.

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Concept Check Questions [Series 1]

Objective questions

1. Childhood cancers are more often embryonal tumours, leukaemias, and _____.
2. Embryonal tumours characteristically present in infancy and early childhood, often before _____ years of age.
3. Burkitt's lymphoma occurs at a considerably higher incidence in equatorial _____.
4. Inherited retinoblastoma results from a germline mutation in the _____ tumour suppressor gene.
5. The relationship between ionising radiation exposure and subsequent cancer risk is described as _____.

Short-answer questions

6. Explain why embryonal tumours characteristically present in infancy and early childhood.
7. Describe the race-related incidence pattern of Burkitt's lymphoma.
8. List two genetic syndromes associated with increased childhood cancer risk and their associated tumours.
9. Describe the association between pesticide exposure and childhood leukaemia.
10. Explain why most childhood cancers cannot be attributed to a single identifiable cause.

Long-answer questions

11. Discuss the general epidemiology and age-related incidence of childhood cancer. (Linked to SLO 1.1, SLO 1.2)
12. Discuss race-related incidence and genetic factors in childhood cancer. (Linked to SLO 1.3, SLO 1.4, SLO 1.5)
13. Discuss chemical-related factors in childhood cancer causation. (Linked to SLO 1.6)
14. Discuss environmental factors, including ionising radiation and infection, in childhood cancer. (Linked to SLO 1.7)
15. Discuss the multifactorial nature of childhood cancer causation and its clinical implications. (Linked to SLO 1.8)

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Answers to Concept Check Questions [Series 1]

Objective questions

1. Lymphomas.
2. 5.
3. Africa.
4. RB1.
5. Dose-dependent.

Short-answer questions

6. Embryonal tumours arise from cells retaining developmental potential most actively during early life, before this potential is lost as tissues mature.
7. Burkitt's lymphoma occurs at considerably higher incidence in equatorial Africa, linked to Epstein-Barr virus and malaria.
8. Li-Fraumeni syndrome is associated with a broad range of malignancies; Beckwith-Wiedemann syndrome with nephroblastoma and hepatoblastoma.
9. Pesticide exposure, whether prenatal or in early childhood, has been investigated as a potential risk factor for leukaemia in various studies.
10. Childhood cancer causation is multifactorial, generally reflecting an interplay of genetic and environmental factors rather than a single cause.

Long-answer questions

11. **Basic response:** Childhood cancer is rarer than adult cancer, more often involving embryonal tumours, leukaemias, and lymphomas, with age-related incidence reflecting the developmental origin of specific tumour types.

Value-added response: Embryonal tumours such as neuroblastoma and nephroblastoma peak in early childhood, while Hodgkin's lymphoma becomes more common later, making age a useful diagnostic clue.

12. **Basic response:** Race-related incidence differences, such as the higher incidence of Burkitt's lymphoma in equatorial Africa, reflect genetic susceptibility, environmental exposure, and reporting differences.

Value-added response: Genetic factors include inherited germline mutations such as RB1 in retinoblastoma, and recognised syndromes such as Li-Fraumeni and Beckwith-Wiedemann syndrome carrying specific cancer risks.

13. **Basic response:** Chemical factors are less well established in childhood cancer than in adult cancer, with prenatal exposure and pesticide exposure investigated as potential contributors, particularly to leukaemia.

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Value-added response: Prior chemotherapy is a recognised risk factor for secondary malignancy, though establishing definitive chemical causation remains challenging given rarity and long latency periods.

14. **Basic response:** Environmental factors include ionising radiation, with a clear dose-dependent relationship to cancer risk, and infections such as Epstein-Barr virus acting as important cofactors.

Value-added response: The lowest necessary radiation dose should be used in paediatric imaging given greater relative radiation sensitivity in children compared with adults.

15. **Basic response:** Childhood cancer causation is multifactorial, reflecting an interplay of genetic susceptibility, environmental exposure, and chance cellular events rather than a single cause.

Value-added response: This understanding means most childhood cancers are not preventable through avoiding a single risk factor, and families can be reassured the diagnosis is rarely attributable to anything they did.

Answers to Pilot Questions [Series 1]

Part 1.1

1. Childhood cancer is rarer overall and more often embryonal tumours, leukaemias, and lymphomas rather than carcinomas.
2. Embryonal tumours arise from cells retaining developmental potential most actively during early life.
3. Neuroblastoma, nephroblastoma, and retinoblastoma are examples of embryonal tumours.
4. Hodgkin's lymphoma becomes relatively more common in later childhood and adolescence, unlike embryonal tumours.
5. The expected age range for a tumour narrows the differential diagnosis for a child with a suspicious presentation.

Part 1.2

1. Burkitt's lymphoma shows markedly higher incidence in equatorial Africa, linked to Epstein-Barr virus and malaria.

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2. Differences may reflect genetic susceptibility, environmental exposure, and differences in diagnostic capacity between regions.
3. Inherited germline mutations in tumour suppressor genes or oncogenes predispose to cancer, often at a younger age or with multiple tumours.
4. Hereditary retinoblastoma results from an RB1 germline mutation, often presenting bilaterally with increased lifelong cancer risk.
5. Li-Fraumeni syndrome (broad malignancies) and Beckwith-Wiedemann syndrome (nephroblastoma, hepatoblastoma) are examples.

Part 1.3

1. Childhood cancer is rare overall, making chemical causation genuinely difficult to study and establish definitively.
2. Rapidly dividing fetal cells may be particularly vulnerable to chemical carcinogenic effects during critical developmental periods.
3. Pesticide exposure has been investigated as a potential risk factor for childhood leukaemia in various epidemiological studies.
4. Chemotherapy agents act through a genotoxic mechanism, increasing the risk of a subsequent, secondary malignancy.
5. Rarity of childhood cancer and long, variable latency periods are challenges in establishing chemical causation.

Part 1.4

1. Ionising radiation exposure shows a clear, dose-dependent relationship with subsequent cancer risk, particularly leukaemia.
2. Children have greater relative sensitivity to radiation than adults, so the lowest necessary dose should always be used.
3. Epstein-Barr virus acts as an important cofactor in the development of Burkitt's lymphoma.
4. Multiple factors, including genetic susceptibility and environmental exposure, generally interact rather than acting alone.
5. Most cases reflect a combination of factors and chance cellular events rather than one clearly identifiable single cause.

References and Attributions [Series 1]

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- Steliarova-Foucher, E. et al. (2017). International incidence of childhood cancer, 2001 to 2010. The Lancet Oncology, 18(6), 719 to 731.
- Spector, L. G., Pankratz, N. and Marcotte, E. L. (2015). Genetic and nongenetic risk factors for childhood cancer. Pediatric Clinics of North America, 62(1), 11 to 25.
- International Agency for Research on Cancer (2017). International Incidence of Childhood Cancer, Volume III.

Figures, Plates, Tables, and Boxes

- Figure 1.1: A paediatric oncologist speaking with a family during a clinic consultation. AI-generated using the prompt: "A calm, respectful clinical illustration of a paediatric oncologist sitting with a family, including a young child, in a warm, softly lit consultation room. Single clean medical illustration, soft natural lighting, no text overlays, no multiple panels, sensitive and accurate depiction."
- Table 1.2: Genetic syndromes associated with increased childhood cancer risk. AI-generated using the prompt: "Create a clean reference table titled Genetic Syndromes Associated with Increased Childhood Cancer Risk, listing syndrome and associated cancer risk. Simple clinical reference table style with outside border."
- Figure 1.3: A researcher reviewing epidemiological data related to childhood cancer risk factors. AI-generated using the prompt: "A professional illustration of a researcher seated at a desk reviewing printed charts and data sheets in a bright office setting. Single clean illustration, natural office lighting, no text overlays, no multiple panels, professional and accurate depiction."
- Figure 1.4: A radiographer carefully positioning imaging equipment for a paediatric patient. AI-generated using the prompt: "A realistic clinical illustration of a radiographer gently adjusting imaging equipment positioned over a calm child lying on an examination table, with a caregiver nearby. Single clean medical illustration, clinical lighting, no text overlays, no multiple panels, accurate and professional depiction."

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Course code: PAE 506

Course title: Paediatric Oncology

Course credit load: 2 Units

Series 2: Lymphomas in Children: Non-Hodgkin's and Hodgkin's Lymphoma

- **Part 2.1: Burkitt's Lymphoma**
  - Sub Part 2.1.1: Classification and pathology of Burkitt's lymphoma
  - Sub Part 2.1.2: Clinical presentation of Burkitt's lymphoma
  - Sub Part 2.1.3: Diagnosis and staging of Burkitt's lymphoma
- **Part 2.2: Non-Burkitt's Non-Hodgkin's Lymphoma**
  - Sub Part 2.2.1: Overview of non-Burkitt's non-Hodgkin's lymphoma subtypes
  - Sub Part 2.2.2: Clinical features of lymphoblastic lymphoma
  - Sub Part 2.2.3: Diagnosis and staging of non-Hodgkin's lymphoma
- **Part 2.3: Hodgkin's Lymphoma**
  - Sub Part 2.3.1: Clinical presentation of Hodgkin's lymphoma
  - Sub Part 2.3.2: Pathology and diagnosis of Hodgkin's lymphoma
  - Sub Part 2.3.3: Staging of Hodgkin's lymphoma
- **Part 2.4: Treatment and Prognosis of Childhood Lymphoma**
  - Sub Part 2.4.1: Chemotherapy for childhood lymphoma
  - Sub Part 2.4.2: Supportive care in childhood lymphoma
  - Sub Part 2.4.3: Prognosis of childhood lymphoma

Introduction

In the last Series, we explored the epidemiology and risk factors of childhood cancer. We now turn to the lymphomas, among the more common malignancies of childhood, beginning with non-Hodgkin's lymphoma and concluding with Hodgkin's lymphoma. Picture an eight year old presenting with a rapidly enlarging jaw mass, alongside a fifteen year old with painless,

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persistent neck swelling and drenching night sweats. Both presentations, though caused by different lymphoma types, require prompt recognition and referral, since childhood lymphoma is often highly treatable when identified and managed appropriately.

The aim of this Series is to equip you with the knowledge required to recognise, diagnose, stage, and understand the treatment and prognosis of non-Hodgkin's and Hodgkin's lymphoma in children.

This Series begins with **Burkitt's lymphoma**, before turning to **non-Burkitt's non-Hodgkin's lymphoma**. Next, we examine **Hodgkin's lymphoma**, before concluding with the **treatment and prognosis** of childhood lymphoma.

Series Learning Outcomes

At the end of this Series, you should be able to:

- **SLO 1.1:** describe the classification and pathology of Burkitt's lymphoma,
- **SLO 1.2:** describe the clinical presentation, diagnosis, and staging of Burkitt's lymphoma,
- **SLO 1.3:** describe the non-Burkitt's subtypes of non-Hodgkin's lymphoma and their clinical features,
- **SLO 1.4:** describe the diagnosis and staging of non-Hodgkin's lymphoma,
- **SLO 1.5:** describe the clinical presentation of Hodgkin's lymphoma,
- **SLO 1.6:** describe the diagnosis and staging of Hodgkin's lymphoma,
- **SLO 1.7:** describe the treatment of childhood lymphoma, including chemotherapy and supportive care, and
- **SLO 1.8:** describe the prognosis of childhood lymphoma.

2.1 Burkitt's Lymphoma

2.1.1 classification and pathology of Burkitt's lymphoma

A rapidly growing tumour with a characteristic microscopic appearance

Burkitt's lymphoma is a highly **aggressive**, rapidly growing form of **non-Hodgkin's lymphoma**, arising from **B lymphocytes**, and is classified into three recognised clinical variants: **endemic Burkitt's lymphoma**, occurring predominantly in **equatorial Africa** and strongly associated with **Epstein-Barr virus** and **malaria**, as introduced in the previous Series, **sporadic Burkitt's lymphoma**, occurring worldwide with a lower and less consistent association with

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Epstein-Barr virus, and **immunodeficiency-associated Burkitt's lymphoma**, occurring in the context of **HIV** or other immunosuppression.

Microscopically, Burkitt's lymphoma characteristically shows a **starry sky appearance**, reflecting numerous rapidly dividing tumour cells interspersed with **macrophages** that have engulfed cellular debris, appearing as pale areas against the darker background of densely packed tumour cells, a distinctive histological pattern reflecting the tumour's remarkably **rapid proliferation rate**, among the fastest of any human malignancy.

Fill in the blank: Burkitt's lymphoma is classified into endemic, sporadic, and _____-associated variants.

2.1.2 clinical presentation of Burkitt's lymphoma

Endemic Burkitt's lymphoma classically presents with a **jaw** or **facial mass**, reflecting the tumour's characteristic tendency to involve the jaw bones in this variant, often growing with striking **rapidity** over a period of just days to weeks, while **sporadic Burkitt's lymphoma** more commonly presents with an **abdominal mass**, sometimes causing **intestinal obstruction** or **intussusception**, reflecting a different characteristic pattern of organ involvement between the two variants.

Given the tumour's rapid growth, children can present with significant **tumour bulk** at diagnosis, and, due to the very high rate of cellular turnover, are at particular risk of **tumour lysis syndrome**, either spontaneously or shortly after starting treatment, discussed further later in this Series, a metabolic emergency resulting from rapid release of intracellular contents as tumour cells break down, requiring specific, proactive management.

Fill in the blank: Endemic Burkitt's lymphoma classically presents with a jaw or _____ mass.

2.1.3 diagnosis and staging of Burkitt's lymphoma

Diagnosis of Burkitt's lymphoma requires **tissue biopsy**, with characteristic **histological** and **immunohistochemical** features confirming the diagnosis, together with assessment of **disease extent**, including **bone marrow examination** and, where indicated, **cerebrospinal fluid analysis**, since Burkitt's lymphoma has a recognised tendency to involve the **bone marrow** and **central nervous system**, particularly in more advanced disease.

Staging follows a structured system assessing the extent of disease, generally the **St Jude**, or **Murphy**, staging system, widely used for childhood non-Hodgkin's lymphoma, ranging from **Stage I**, a single tumour site, to **Stage IV**, involving the central nervous system or bone marrow,

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with stage directly informing the intensity of treatment required, discussed further later in this Series.

Fill in the blank: The staging system widely used for childhood non-Hodgkin's lymphoma is the St Jude, or _____, staging system.

Figure 2.1: A clinician examining a child with facial swelling during an oncology assessment.

Pilot questions 2.1

- List the three clinical variants of Burkitt's lymphoma. (Linked to SLO 2.1)
- Describe the characteristic microscopic appearance of Burkitt's lymphoma. (Linked to SLO 2.1)
- Distinguish the typical presentation of endemic from sporadic Burkitt's lymphoma. (Linked to SLO 2.2)
- Explain why children with Burkitt’s lymphoma are at particular risk of tumour lysis syndrome. (Linked to SLO 2.2)
- Describe the staging system used for childhood non-Hodgkin's lymphoma. (Linked to SLO 2.2)

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2.2 Non-Burkitt's Non-Hodgkin's Lymphoma

2.2.1 overview of non-Burkitt's non-Hodgkin's lymphoma subtypes

A more heterogeneous group than Burkitt's lymphoma alone

Beyond **Burkitt's lymphoma**, other important subtypes of childhood **non-Hodgkin's lymphoma** include **lymphoblastic lymphoma**, arising from immature **precursor T** or, less commonly, **precursor B lymphocytes**, and closely related biologically to **acute lymphoblastic leukaemia**, and **diffuse large B-cell lymphoma**, together with **anaplastic large cell lymphoma**, each with distinct typical clinical presentations and underlying biological features.

Unlike Burkitt's lymphoma, which is classified by geographic and immune status variant, these other subtypes are classified predominantly by their **cell of origin** and **histological appearance**, and, while sharing the general principle of aggressive, rapidly progressive disease characteristic of childhood non-Hodgkin's lymphoma overall, each subtype has its own somewhat distinct typical presentation and treatment approach.

Fill in the blank: Lymphoblastic lymphoma is closely related biologically to acute lymphoblastic _____.

2.2.2 clinical features of lymphoblastic lymphoma

Lymphoblastic lymphoma, particularly the more common **T-cell** variant, characteristically presents with a **mediastinal mass**, which can cause **respiratory distress** through airway compression, or **superior vena cava syndrome**, presenting with facial swelling and distended neck veins from compression of the superior vena cava, both representing potential **oncological emergencies** requiring prompt recognition and urgent management.

Given the close biological relationship with **acute lymphoblastic leukaemia**, lymphoblastic lymphoma frequently shows **bone marrow involvement**, and the distinction between the two conditions is conventionally made based on the **degree of bone marrow involvement** at diagnosis, with predominant nodal or mass disease and minimal marrow involvement classified as lymphoma, while extensive marrow involvement is classified as leukaemia, reflecting a continuum rather than an entirely distinct biological process.

Fill in the blank: T-cell lymphoblastic lymphoma characteristically presents with a _____ mass.

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2.2.3 diagnosis and staging of non-Hodgkin’s lymphoma

Diagnosis of non-Burkitt's non-Hodgkin's lymphoma, as with Burkitt's lymphoma discussed in the previous Part of this Series, requires **tissue biopsy** with **histological** and **immunohistochemical** analysis to confirm the specific subtype, since treatment approach and intensity can differ meaningfully between subtypes despite the shared general category of non-Hodgkin's lymphoma.

Staging investigations are similar across the various non-Hodgkin's lymphoma subtypes, including **imaging** to assess disease extent, **bone marrow examination**, and **cerebrospinal fluid analysis**, using the same **St Jude staging system** discussed in the previous Part, and a mediastinal mass, where present, requires particularly careful assessment given the potential for airway compromise during any sedation or anaesthesia required for diagnostic procedures.

Fill in the blank: A mediastinal mass requires particularly careful assessment given the potential for airway _____ during sedation.

Table 2.2: Subtypes of childhood non-Hodgkin's lymphoma.

Subtype	Cell of origin	Typical presentation
Burkitt's lymphoma	B lymphocyte	Jaw mass (endemic) or abdominal mass (sporadic)
Lymphoblastic lymphoma	Precursor T or B lymphocyte	Mediastinal mass (T-cell variant)
Diffuse large B-cell lymphoma	Mature B lymphocyte	Nodal or extranodal mass
Anaplastic large cell lymphoma	T lymphocyte	Variable nodal and extranodal involvement

Pilot questions 2.2

1. List two subtypes of non-Hodgkin’s lymphoma other than Burkitt’s lymphoma. (Linked to SLO 2.3)
2. Describe the typical presentation of T-cell lymphoblastic lymphoma. (Linked to SLO 2.4)
3. Explain how lymphoblastic lymphoma is distinguished from acute lymphoblastic leukaemia. (Linked to SLO 2.4)
4. Describe superior vena cava syndrome and its clinical significance. (Linked to SLO 2.4)
5. Describe the staging investigations used for non-Hodgkin’s lymphoma. (Linked to SLO 2.4)

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2.3 Hodgkin's Lymphoma

2.3.1 clinical presentation of Hodgkin's lymphoma

Painless lymphadenopathy is the classic presenting feature

Hodgkin's lymphoma, in contrast to the typically rapid presentation of non-Hodgkin's lymphoma discussed earlier in this Series, more commonly presents with **painless**, **progressive lymphadenopathy**, most often involving the **cervical** or **supraclavicular** lymph nodes, developing gradually over **weeks to months** rather than the days to weeks more typical of Burkitt's lymphoma, reflecting the generally somewhat less aggressive biological behaviour of Hodgkin's lymphoma.

Systemic symptoms, termed **B symptoms**, including **fever**, **drenching night sweats**, and **unintentional weight loss** exceeding 10 percent of body weight, are present in a proportion of affected children and carry both diagnostic and prognostic significance, since their presence or absence is incorporated directly into the staging system discussed later in this Part.

Fill in the blank: Hodgkin's lymphoma most commonly presents with painless, progressive _____, most often cervical or supraclavicular.

2.3.2 pathology and diagnosis of Hodgkin's lymphoma

The pathological hallmark of Hodgkin's lymphoma is the **Reed-Sternberg cell**, a large, characteristic tumour cell with a distinctive **binucleate**, or **owl-eye**, appearance, found within a background of numerous **reactive inflammatory cells**, distinguishing Hodgkin's lymphoma histologically from the various non-Hodgkin's lymphoma subtypes discussed earlier in this Series, where the malignant cells themselves typically predominate the tissue sample.

Diagnosis requires **lymph node biopsy**, ideally an **excisional biopsy** removing an entire lymph node where feasible, since this provides the best tissue architecture for confident histological diagnosis, together with **immunohistochemical staining**, since Reed-Sternberg cells express a characteristic pattern of surface markers that helps confirm the diagnosis and distinguish Hodgkin's lymphoma from other conditions that can occasionally mimic it.

Fill in the blank: The pathological hallmark cell of Hodgkin’s lymphoma is the _____ cell.

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2.3.3 staging of Hodgkin's lymphoma

Staging of Hodgkin's lymphoma uses the **Ann Arbor** staging system, or its modern equivalent, ranging from **Stage I**, involvement of a single lymph node region, through **Stage IV**, involvement of extranodal organs such as the liver or bone marrow, with each stage further subdivided into **A**, absence of B symptoms, or **B**, presence of B symptoms, reflecting the prognostic importance of these systemic features discussed in the previous sub-Part.

Staging investigations include **imaging**, typically **computed tomography** or, increasingly, **positron emission tomography**, to accurately assess the full extent of nodal and extranodal disease, and, in selected cases, **bone marrow examination**, with the resulting stage directly guiding the intensity and duration of treatment recommended, discussed in the final Part of this Series.

Fill in the blank: The Ann Arbor staging system subdivides each stage into A, absence of B symptoms, or B, presence of _____ symptoms.

Figure 2.3: A clinician palpating the neck lymph nodes of a child during examination.

Pilot questions 2.3

1. Describe the typical clinical presentation of Hodgkin's lymphoma. (Linked to SLO 2.5)
2. Define B symptoms and explain their significance. (Linked to SLO 2.5)
3. Describe the Reed-Sternberg cell and its diagnostic importance. (Linked to SLO 2.6)
4. Describe the preferred biopsy approach for diagnosing Hodgkin's lymphoma. (Linked to SLO 2.6)
5. Describe the Ann Arbor staging system. (Linked to SLO 2.6)

2.4 Treatment and Prognosis of Childhood Lymphoma

2.4.1 chemotherapy for childhood lymphoma

Combination chemotherapy remains the treatment backbone

Chemotherapy is the cornerstone of treatment for both **non-Hodgkin's** and **Hodgkin's lymphoma** in children, generally using **combination regimens**, combining multiple chemotherapeutic agents with different mechanisms of action to maximise tumour cell killing while managing toxicity, with the specific regimen, **intensity**, and **duration** tailored according to the specific lymphoma subtype and disease stage discussed earlier in this Series.

Burkitt's lymphoma, given its exceptionally rapid growth rate, is generally treated with **short, intensive** chemotherapy regimens, reflecting the tumour's high sensitivity to chemotherapy despite its aggressive behaviour, while **Hodgkin's lymphoma** treatment intensity is more directly guided by **stage** and the presence of **B symptoms**, sometimes combined with **radiotherapy** in specific circumstances, particularly for residual disease after chemotherapy.

Fill in the blank: Burkitt's lymphoma is generally treated with short, _____ chemotherapy regimens.

2.4.2 supportive care in childhood lymphoma

Supportive care is an essential component of childhood lymphoma treatment, including proactive management of **tumour lysis syndrome**, particularly relevant in rapidly growing tumours such as Burkitt's lymphoma, using **aggressive hydration**, **urate-lowering therapy**, and careful **electrolyte monitoring**, since this metabolic emergency can be genuinely life-

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threatening if not anticipated and managed proactively before and during the initial phase of chemotherapy.

Additional supportive care includes management of **chemotherapy-related toxicity**, particularly **myelosuppression** and the resulting increased risk of **infection**, requiring prompt recognition and treatment of **febrile neutropenia**, together with **nutritional support** and **psychosocial support** for the child and family throughout the often lengthy and demanding treatment course.

Fill in the blank: Febrile neutropenia requires prompt recognition and treatment given the risk from chemotherapy-related _____.

2.4.3 prognosis of childhood lymphoma

The **prognosis** of childhood lymphoma has improved considerably over recent decades with modern combination chemotherapy regimens, with **Burkitt's lymphoma** and other non-Hodgkin's lymphoma subtypes, and **Hodgkin's lymphoma**, both now associated with **high cure rates** in many settings when diagnosed at an appropriate stage and treated with an adequate, complete course of therapy, reflecting one of the genuine success stories of modern paediatric oncology.

Prognostic factors include disease **stage** at diagnosis, **response** to initial treatment, and, for some subtypes, specific **biological features** of the tumour, and, while overall outcomes are generally favourable, ongoing attention to **treatment-related late effects**, discussed in the final Series of this course, remains an important component of long-term follow up for children successfully treated for lymphoma.

Fill in the blank: Ongoing attention to treatment-related late effects remains important for long-term _____ of successfully treated children.

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Figure 2.4: A child receiving chemotherapy in a supportive, comfortable hospital setting.

Pilot questions 2.4

1. Describe the general approach to chemotherapy in childhood lymphoma. (Linked to SLO 2.7)
2. Describe the management of tumour lysis syndrome. (Linked to SLO 2.7)
3. Explain why febrile neutropenia requires prompt recognition and treatment. (Linked to SLO 2.7)
4. Describe the general prognosis of childhood lymphoma with modern treatment. (Linked to SLO 2.8)
5. List two factors that influence the prognosis of childhood lymphoma. (Linked to SLO 2.8)

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Series Summary

This Series examined **childhood lymphomas**, beginning with **Burkitt's lymphoma**, before turning to other **non-Burkitt's non-Hodgkin's lymphoma** subtypes.

We then examined **Hodgkin's lymphoma**, before concluding with the **treatment and prognosis** of childhood lymphoma overall. Having worked through this Series, you should now be able to recognise, diagnose, stage, and understand the treatment of childhood lymphoma. The next Series turns to **retinoblastoma and neuroblastoma**.

Glossary of Terms

1. **Burkitt's lymphoma:** a highly aggressive B-cell non-Hodgkin's lymphoma with endemic, sporadic, and immunodeficiency-associated variants.
2. **Starry sky appearance:** the characteristic histological pattern of Burkitt's lymphoma.
3. **Tumour lysis syndrome:** a metabolic emergency from rapid tumour cell breakdown, particularly relevant in Burkitt's lymphoma.
4. **St Jude (Murphy) staging system:** the staging system widely used for childhood non-Hodgkin's lymphoma.
5. **Lymphoblastic lymphoma:** a non-Hodgkin's lymphoma subtype closely related to acute lymphoblastic leukaemia.
6. **Superior vena cava syndrome:** facial swelling and distended neck veins from compression of the superior vena cava, an oncological emergency.
7. **B symptoms:** systemic symptoms of fever, night sweats, and weight loss, with diagnostic and prognostic significance in lymphoma.
8. **Reed-Sternberg cell:** the pathological hallmark cell of Hodgkin's lymphoma.
9. **Ann Arbor staging system:** the staging system used for Hodgkin's lymphoma.
10. **Febrile neutropenia:** fever occurring with a low neutrophil count, a medical emergency in a child receiving chemotherapy.
11. **Combination chemotherapy:** the use of multiple chemotherapeutic agents together to maximise tumour cell killing.
12. **Late effects:** long-term treatment-related complications requiring ongoing follow up after successful cancer treatment.

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Concept Check Questions [Series 2]

Objective questions

- Burkitt's lymphoma is classified into endemic, sporadic, and _____-associated variants.
- Endemic Burkitt's lymphoma classically presents with a jaw or _____ mass.
- T-cell lymphoblastic lymphoma characteristically presents with a _____ mass.
- The pathological hallmark cell of Hodgkin's lymphoma is the _____ cell.
- Burkitt's lymphoma is generally treated with short, _____ chemotherapy regimens.

Short-answer questions

1. Describe the characteristic microscopic appearance of Burkitt's lymphoma.
2. Describe superior vena cava syndrome and its clinical significance.
3. Define B symptoms and explain their significance.
4. Describe the Ann Arbor staging system.
5. Describe the management of tumour lysis syndrome.

Long-answer questions

6. Discuss the classification, clinical presentation, and staging of Burkitt's lymphoma. (Linked to SLO 2.1, SLO 2.2)
7. Discuss the clinical features and diagnosis of non-Burkitt's non-Hodgkin's lymphoma. (Linked to SLO 2.3, SLO 2.4)
8. Discuss the clinical presentation, pathology, and staging of Hodgkin's lymphoma. (Linked to SLO 2.5, SLO 2.6)
9. Discuss the chemotherapy and supportive care used in childhood lymphoma. (Linked to SLO 2.7)
10. Discuss the prognosis of childhood lymphoma and factors that influence it. (Linked to SLO 2.8)

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Answers to Concept Check Questions [Series 2]

Objective questions

11. Immunodeficiency.
12. Abdominal.
13. Mediastinal.
14. Reed-Sternberg.
15. Intensive.

Short-answer questions

16. A starry sky appearance, reflecting numerous rapidly dividing tumour cells interspersed with macrophages engulfing debris.
17. Compression of the superior vena cava causing facial swelling and distended neck veins, an oncological emergency.
18. Fever, drenching night sweats, and weight loss exceeding 10 percent, with diagnostic and prognostic significance.
19. Stages I to IV based on nodal and extranodal involvement, each subdivided into A (no B symptoms) or B (B symptoms present).
20. Aggressive hydration, urate-lowering therapy, and careful electrolyte monitoring, proactively before and during initial chemotherapy.

Long-answer questions

21. **Basic response:** Burkitt's lymphoma is classified into endemic, sporadic, and immunodeficiency-associated variants, presenting with jaw or abdominal masses, staged using the St Jude system.

Value-added response: Rapid growth places children at risk of tumour lysis syndrome, requiring proactive management before and during initial treatment.

22. **Basic response:** Non-Burkitt's non-Hodgkin's lymphoma includes lymphoblastic lymphoma and diffuse large B-cell lymphoma, diagnosed by biopsy and staged similarly to Burkitt's lymphoma.

Value-added response: T-cell lymphoblastic lymphoma can present with a mediastinal mass causing respiratory distress or superior vena cava syndrome, requiring urgent recognition.

23. **Basic response:** Hodgkin's lymphoma presents with painless lymphadenopathy, diagnosed by finding Reed-Sternberg cells on biopsy, and staged using the Ann Arbor system.

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Value-added response: B symptoms are incorporated into staging and carry prognostic significance, distinguishing the more indolent presentation from non-Hodgkin's lymphoma.

24. **Basic response:** Combination chemotherapy is the cornerstone of treatment, with regimen intensity tailored to lymphoma subtype and stage.

Value-added response: Supportive care, including management of tumour lysis syndrome and febrile neutropenia, is essential alongside chemotherapy itself.

25. **Basic response:** Prognosis for childhood lymphoma has improved considerably, with high cure rates now achieved for both non-Hodgkin's and Hodgkin's lymphoma.

Value-added response: Stage, treatment response, and biological features influence prognosis, and long-term follow up for late effects remains important after successful treatment.

Answers to Pilot Questions [Series 2]

Part 2.1

1. Endemic, sporadic, and immunodeficiency-associated are the three clinical variants.
2. A starry sky appearance, from rapidly dividing tumour cells interspersed with macrophages, is characteristic.
3. Endemic disease typically presents with a jaw mass, while sporadic disease presents with an abdominal mass.
4. Its exceptionally high cellular turnover puts children at risk of rapid release of intracellular contents.
5. The St Jude, or Murphy, staging system is used.

Part 2.2

6. Lymphoblastic lymphoma and diffuse large B-cell lymphoma are examples of other subtypes.
7. A mediastinal mass, sometimes causing respiratory distress, is typical of T-cell lymphoblastic lymphoma.
8. The distinction is based on the degree of bone marrow involvement at diagnosis.

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9. It results from compression of the superior vena cava, causing facial swelling and distended neck veins.
10. Imaging, bone marrow examination, and cerebrospinal fluid analysis are used for staging.

Part 2.3

11. Painless, progressive lymphadenopathy, often cervical or supraclavicular, developing over weeks to months.
12. B symptoms are fever, night sweats, and weight loss, carrying diagnostic and prognostic significance.
13. The Reed-Sternberg cell is a large, binucleate cell that is the pathological hallmark of the disease.
14. An excisional biopsy of an entire lymph node is generally preferred.
15. It classifies disease from Stage I to IV, subdivided into A or B based on presence of B symptoms.

Part 2.4

1. Combination chemotherapy, tailored to lymphoma subtype and stage, is the general approach.
2. Aggressive hydration, urate-lowering therapy, and electrolyte monitoring manage tumour lysis syndrome.
3. It can be life-threatening given the risk of severe infection during chemotherapy-induced myelosuppression.
4. Prognosis is generally favourable, with high cure rates for both non-Hodgkin's and Hodgkin's lymphoma.
5. Disease stage and response to initial treatment are factors influencing prognosis.

References and Attributions [Series 2]

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Figures, Plates, Tables, and Boxes

1. Figure 2.1: A clinician examining a child with facial swelling during an oncology assessment. AI-generated using the prompt: "A calm, respectful clinical illustration of a clinician gently examining a child's jaw and neck area during an assessment, with a caregiver present. Single clean medical illustration, soft clinical lighting, no text overlays, no multiple panels, sensitive and accurate depiction, no graphic detail."
2. Table 2.2: Subtypes of childhood non-Hodgkin's lymphoma. AI-generated using the prompt: "Create a clean reference table titled Subtypes of Childhood Non-Hodgkin's Lymphoma, listing subtype, cell of origin, and typical presentation. Simple clinical reference table style with outside border."
3. Figure 2.3: A clinician palpating the neck lymph nodes of a child during examination. AI-generated using the prompt: "A calm, respectful clinical illustration of a clinician gently palpating the neck of a seated child during an examination, with a caregiver present nearby. Single clean medical illustration, soft clinical lighting, no text overlays, no multiple panels, sensitive and accurate depiction."
4. Figure 2.4: A child receiving chemotherapy in a supportive, comfortable hospital setting. AI-generated using the prompt: "A warm, respectful clinical illustration of a child sitting comfortably in a hospital chair with a small intravenous line, a caregiver holding their hand, and a nurse checking the equipment nearby. Single clean medical illustration, soft warm lighting, no text overlays, no multiple panels, sensitive and reassuring depiction, no graphic medical detail."

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Course code: PAE 506

Course title: Paediatric Oncology

Course credit load: 2 Units

Series 3: Retinoblastoma and Neuroblastoma

- **Part 3.1: Retinoblastoma: Genetics, Clinical Presentation, and Diagnosis**
  - Sub Part 3.1.1: Genetics and pathology of retinoblastoma
  - Sub Part 3.1.2: Clinical presentation of retinoblastoma
  - Sub Part 3.1.3: Diagnosis of retinoblastoma
- **Part 3.2: Retinoblastoma: Staging, Treatment, and Prognosis**
  - Sub Part 3.2.1: Staging of retinoblastoma
  - Sub Part 3.2.2: Treatment of retinoblastoma
  - Sub Part 3.2.3: Prognosis of retinoblastoma
- **Part 3.3: Neuroblastoma: Epidemiology, Clinical Presentation, and Diagnosis**
  - Sub Part 3.3.1: Epidemiology and pathology of neuroblastoma
  - Sub Part 3.3.2: Clinical presentation of neuroblastoma
  - Sub Part 3.3.3: Diagnosis of neuroblastoma
- **Part 3.4: Neuroblastoma: Staging, Treatment, and Prognosis**
  - Sub Part 3.4.1: Staging of neuroblastoma
  - Sub Part 3.4.2: Treatment of neuroblastoma
  - Sub Part 3.4.3: Prognosis of neuroblastoma

Introduction

In the last Series, we explored childhood lymphomas. We now turn to two embryonal tumours introduced in Series 1 of this course, retinoblastoma and neuroblastoma, both arising from cells retaining developmental potential most actively in early childhood. Picture a mother who notices an unusual white reflection in a photograph of her one year old's eye, alongside a different infant found to have a firm abdominal mass on routine examination. Both presentations, though affecting very different organ systems, illustrate the characteristic early childhood onset of embryonal tumours.

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The aim of this Series is to equip you with the knowledge required to recognise, diagnose, stage, and understand the treatment and prognosis of retinoblastoma and neuroblastoma in children.

This Series begins with the **genetics, clinical presentation, and diagnosis of retinoblastoma**, before turning to its **staging, treatment, and prognosis**. Next, we examine the **epidemiology, clinical presentation, and diagnosis of neuroblastoma**, before concluding with its **staging, treatment, and prognosis**.

Series Learning Outcomes

At the end of this Series, you should be able to:

- **SLO 1.1:** describe the genetics and pathology of retinoblastoma,
- **SLO 1.2:** describe the clinical presentation and diagnosis of retinoblastoma,
- **SLO 1.3:** describe the staging and treatment of retinoblastoma,
- **SLO 1.4:** describe the prognosis of retinoblastoma,
- **SLO 1.5:** describe the epidemiology and pathology of neuroblastoma,
- **SLO 1.6:** describe the clinical presentation and diagnosis of neuroblastoma,
- **SLO 1.7:** describe the staging and treatment of neuroblastoma, and
- **SLO 1.8:** describe the prognosis of neuroblastoma.

3.1 Retinoblastoma: Genetics, Clinical Presentation, and Diagnosis

3.1.1 genetics and pathology of retinoblastoma

A tumour that taught medicine about tumour suppressor genes

Retinoblastoma, introduced in Series 1 of this course, is the most common **intraocular** malignancy of childhood, arising from immature **retinal cells**, and results from **inactivation** of both copies of the **RB1 tumour suppressor gene**, following the **two-hit hypothesis** first proposed to explain this specific tumour, in which cancer develops only once both functional copies of a tumour suppressor gene have been lost or inactivated within a cell.

Retinoblastoma occurs in two recognised forms: **heritable retinoblastoma**, in which a germline RB1 mutation is inherited or arises early in development, present in **all body cells**, typically presenting **earlier** and often **bilaterally**, since only a single further genetic event is required in any given retinal cell to trigger tumour formation, and **non-heritable retinoblastoma**, in which

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both RB1 mutations occur **sporadically** within a single retinal cell, typically presenting **later** and **unilaterally**.

Fill in the blank: Retinoblastoma results from inactivation of both copies of the _____ tumour suppressor gene.

3.1.2 clinical presentation of retinoblastoma

The most common presenting feature of retinoblastoma is **leukocoria**, a white pupillary reflex, often first noticed by a parent in a photograph taken with flash, replacing the normal red-eye reflex with an abnormal white or yellowish appearance, reflecting light reflecting off the tumour mass within the eye rather than the normal retina, and representing the single most important, and most easily recognised, warning sign of this tumour.

Other presenting features include **strabismus**, a squint, resulting from disrupted vision in the affected eye, **decreased visual acuity**, which may be difficult to recognise in a very young child, and, in more advanced disease, visible **eye redness** or **pain**, and any child presenting with a suspicious white pupillary reflex requires prompt, urgent referral to an ophthalmologist for definitive assessment, given the time-sensitive nature of both diagnosis and, ultimately, vision and life preservation.

Fill in the blank: Leukocoria refers to a white _____ reflex, the most common presenting feature of retinoblastoma.

3.1.3 diagnosis of retinoblastoma

Diagnosis of retinoblastoma is generally made through **examination under anaesthesia**, allowing detailed, dilated **fundoscopic examination** of the retina by an experienced ophthalmologist, since a young child cannot cooperate with the detailed examination required, together with **ocular ultrasound**, which can help characterise the tumour and detect **calcification**, a characteristic feature of retinoblastoma.

Magnetic resonance imaging is generally preferred over computed tomography for further assessment, given the need to avoid unnecessary ionising radiation exposure, particularly relevant in children with the **heritable form** of retinoblastoma, who carry an increased lifelong sensitivity to radiation-induced secondary malignancy, discussed further later in this Series, and MRI also allows assessment for **optic nerve** or **extraocular extension** of the tumour, important for staging and treatment planning.

Fill in the blank: Magnetic resonance imaging is generally preferred over computed tomography to avoid unnecessary ionising _____ exposure.

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Figure 3.1: An ophthalmologist performing a dilated eye examination on a young child.

Pilot questions 3.1

- Explain the two-hit hypothesis as it applies to retinoblastoma. (Linked to SLO 3.1)
- Distinguish heritable from non-heritable retinoblastoma. (Linked to SLO 3.1)
- Define leukocoria and describe its clinical significance. (Linked to SLO 3.2)
- List two other clinical features of retinoblastoma besides leukocoria. (Linked to SLO 3.2)
- Explain why MRI is generally preferred over CT in the assessment of retinoblastoma. (Linked to SLO 3.2)

3.2 Retinoblastoma: Staging, Treatment, and Prognosis

3.2.1 staging of retinoblastoma

Staging guides the balance between cure and eye preservation

Staging of retinoblastoma uses a system specifically designed to guide **treatment decisions** around **eye preservation**, most commonly the **International Classification of Retinoblastoma**, which groups intraocular disease from **Group A**, small tumours confined away from critical

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structures, through **Group E**, extensive disease with a poor prognosis for saving the eye, together with separate staging for **extraocular** disease, where tumour has spread beyond the eye itself.

This staging approach reflects the genuinely **dual treatment goal** in retinoblastoma, namely curing the cancer while, wherever safely possible, **preserving useful vision** and the eye itself, a balance that becomes progressively more difficult to achieve as tumour extent and group increase, meaning accurate staging is essential to appropriately counsel families about the realistic range of treatment options available for their child's specific tumour.

Fill in the blank: Retinoblastoma staging groups range from Group A, small confined tumours, to Group _____, extensive disease.

3.2.2 treatment of retinoblastoma

Treatment of retinoblastoma is highly **individualised**, depending on **laterality**, tumour **group**, and whether disease is confined to the eye, and options include **focal therapies**, such as **laser photocoagulation** or **cryotherapy**, for small tumours, **intra-arterial** or **systemic chemotherapy** to reduce tumour size before focal therapy, or as primary treatment for larger tumours, and, where the eye cannot be safely preserved or vision cannot be meaningfully saved, **enucleation**, surgical removal of the affected eye.

For **bilateral disease**, treatment aims to preserve vision in **at least one eye** wherever possible, and management decisions require close **multidisciplinary** collaboration between paediatric oncology and ophthalmology, given the genuinely complex balance between oncological cure, vision preservation, and, for the heritable form, ongoing surveillance for both the fellow eye and future secondary malignancy risk.

Fill in the blank: Enucleation is surgical removal of the affected _____.

3.2.3 prognosis of retinoblastoma

The overall **survival** for retinoblastoma is excellent in settings with access to timely diagnosis and appropriate treatment, generally exceeding **90 percent**, reflecting both the tumour's general sensitivity to available treatments and the benefit of early detection through recognition of leukocoria and prompt referral, though outcomes remain considerably poorer in settings where diagnosis and treatment are delayed, often due to limited awareness or access to specialist ophthalmological care.

Children with **heritable retinoblastoma** require long-term follow up given their increased lifelong risk of **secondary malignancy**, including **osteosarcoma** and other tumours, particularly

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if treated with radiotherapy, meaning survivors of heritable retinoblastoma benefit from structured, ongoing surveillance well beyond the initial period of cancer treatment itself, an example of the late effects considerations discussed more broadly in the final Series of this course.

Fill in the blank: Overall survival for retinoblastoma generally exceeds _____ percent in settings with timely diagnosis and treatment.

Table 3.2: Overview of retinoblastoma treatment options by clinical scenario.

Scenario	Typical treatment approach
Small, confined tumour	Focal therapy such as laser photocoagulation or cryotherapy
Larger intraocular tumour	Systemic or intra-arterial chemotherapy, often combined with focal therapy
Extensive disease, eye not salvageable	Enucleation
Bilateral disease	Individualised approach aiming to preserve vision in at least one eye

Pilot questions 3.2

1. Describe the purpose and general structure of retinoblastoma staging. (Linked to SLO 3.3)
2. List two focal treatment options for small retinoblastoma tumours. (Linked to SLO 3.3)
3. Describe the role of enucleation in retinoblastoma treatment. (Linked to SLO 3.3)
4. Describe the general survival outcome for retinoblastoma with timely treatment. (Linked to SLO 3.4)
5. Explain why children with heritable retinoblastoma require long-term follow up. (Linked to SLO 3.4)

3.3 Neuroblastoma: Epidemiology, Clinical Presentation, and Diagnosis

3.3.1 epidemiology and pathology of neuroblastoma

A tumour of the sympathetic nervous system

Neuroblastoma, introduced in Series 1 of this course as another embryonal tumour, arises from primitive cells of the **sympathetic nervous system**, and is the most common **extracranial solid**

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tumour of childhood, typically presenting in **infancy** or **early childhood**, with the median age at diagnosis under **2 years**, consistent with its embryonal origin discussed earlier in this course.

Neuroblastoma can arise anywhere along the sympathetic nervous system, though most commonly originates in the **adrenal medulla** or elsewhere within the **abdominal sympathetic chain**, and shows considerable **biological heterogeneity**, ranging from tumours that can spontaneously **regress** without treatment in very young infants, to highly aggressive, rapidly progressive disease in older children, a range of behaviour unusual among childhood malignancies.

Fill in the blank: Neuroblastoma arises from primitive cells of the _____ nervous system.

3.3.2 clinical presentation of neuroblastoma

Clinical presentation of neuroblastoma depends on the **primary tumour site** and the presence of **metastatic disease**, with an **abdominal mass**, often noted incidentally by a parent or on routine examination, the most common presentation, together with symptoms related to mass effect and, in some cases, **systemic symptoms** such as fever, weight loss, and irritability, reflecting the tumour's production of **catecholamines** and other biologically active substances.

Metastatic disease is present in a substantial proportion of children at diagnosis, particularly older children, and can present with **bone pain**, **periorbital ecchymosis**, sometimes termed **raccoon eyes**, from metastatic infiltration around the orbits, and, in infants specifically, a distinctive pattern of widespread **skin nodules** and **hepatomegaly** without bone involvement, termed **stage MS disease**, which paradoxically carries a comparatively favourable prognosis despite its widespread appearance.

Fill in the blank: Periorbital ecchymosis from metastatic infiltration around the orbits is sometimes termed _____ eyes.

3.3.3 diagnosis of neuroblastoma

Diagnosis of neuroblastoma requires **tissue biopsy**, together with characteristic elevation of **urinary catecholamine metabolites**, specifically **vanillylmandelic acid** and **homovanillic acid**, which are elevated in the majority of children with neuroblastoma and provide a valuable, relatively non-invasive diagnostic and monitoring tool, given the tumour's origin from catecholamine-producing sympathetic tissue.

Imaging, including **ultrasound**, **computed tomography**, or **magnetic resonance imaging**, assesses the primary tumour and local extent, while a specific **MIBG scan**, using a radiolabelled compound taken up selectively by neuroblastoma cells, assesses for **metastatic disease**

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throughout the body, and **bone marrow examination** completes the standard staging work up, given the tumour's recognised tendency for bone marrow involvement.

Fill in the blank: A specific MIBG scan uses a radiolabelled compound taken up selectively by _____ cells to assess for metastatic disease.

Figure 3.3: A clinician gently palpating a child's abdomen during examination.

Pilot questions 3.3

1. Describe the origin and typical age of presentation of neuroblastoma. (Linked to SLO 3.5)
2. Explain the biological heterogeneity of neuroblastoma, from spontaneous regression to aggressive disease. (Linked to SLO 3.5)
3. Describe the most common presenting feature of neuroblastoma. (Linked to SLO 3.6)
4. Describe stage MS disease and its distinctive prognosis. (Linked to SLO 3.6)
5. Describe the role of urinary catecholamine metabolites and MIBG scanning in diagnosing neuroblastoma. (Linked to SLO 3.6)

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3.4 Neuroblastoma: Staging, Treatment, and Prognosis

3.4.1 staging of neuroblastoma

Biology matters as much as anatomical extent

Staging of neuroblastoma has evolved to incorporate both **anatomical extent** of disease and specific **biological features** of the tumour, with the **International Neuroblastoma Risk Group Staging System** incorporating imaging-defined risk factors to classify disease **before** any surgical intervention, allowing more consistent staging and risk stratification across different treatment centres.

Risk stratification, combining stage with biological features such as tumour **histology**, **MYCN gene amplification**, a particularly important adverse biological marker associated with more aggressive disease, and **age at diagnosis**, classifies children into **low**, **intermediate**, or **high-risk** groups, with risk group directly determining treatment intensity, reflecting the recognition that anatomical stage alone does not fully capture the biological behaviour of this genuinely heterogeneous tumour.

Fill in the blank: MYCN gene amplification is a particularly important adverse biological marker associated with more aggressive neuroblastoma _____.

3.4.2 treatment of neuroblastoma

Treatment intensity for neuroblastoma is directly guided by **risk group**, discussed in the previous sub-Part, with **low-risk disease** sometimes managed with **surgery alone**, or even **observation** in selected very young infants given the tumour's capacity for spontaneous regression, while **intermediate-risk disease** generally requires **surgery** combined with **moderate-intensity chemotherapy**.

High-risk disease requires considerably more intensive, **multimodal treatment**, including **induction chemotherapy**, **surgical resection**, **high-dose chemotherapy** with **autologous stem cell rescue**, **radiotherapy**, and, increasingly, **immunotherapy** targeting specific tumour antigens, reflecting the genuinely challenging nature of achieving cure in this specific, biologically aggressive disease category.

Fill in the blank: Low-risk neuroblastoma disease is sometimes managed with surgery alone, or even _____ in selected very young infants.

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3.4.3 prognosis of neuroblastoma

Prognosis of neuroblastoma varies dramatically according to **risk group**, with **low-risk disease** associated with **excellent survival**, generally exceeding 90 percent, and **high-risk disease**, despite intensive multimodal treatment, associated with considerably lower survival, reflecting the genuinely wide spectrum of biological behaviour that makes neuroblastoma one of the more prognostically variable tumours in paediatric oncology.

Age at diagnosis is itself an important independent prognostic factor, with **younger children**, particularly infants, generally having a more favourable prognosis than older children with biologically similar disease, and ongoing research continues to refine **risk stratification** and develop new treatment approaches, particularly for the high-risk group, where improving outcomes remains an important, active area of paediatric oncology research.

Fill in the blank: Younger children, particularly infants, generally have a more favourable prognosis than _____ children with similar disease.

Figure 3.4: A child undergoing a scan as part of neuroblastoma staging investigation.

Pilot questions 3.4

1. Describe the general approach to staging neuroblastoma. (Linked to SLO 3.7)

2. Explain the significance of MYCN gene amplification in neuroblastoma. (Linked to SLO 3.7)
3. Describe the treatment approach for low-risk versus high-risk neuroblastoma. (Linked to SLO 3.7)
4. Describe the general prognosis of neuroblastoma by risk group. (Linked to SLO 3.8)
5. Explain why age at diagnosis is an important prognostic factor in neuroblastoma. (Linked to SLO 3.8)

Series Summary

This Series examined **retinoblastoma**, beginning with its genetics, clinical presentation, and diagnosis, before turning to its **staging, treatment, and prognosis**.

We then examined **neuroblastoma**, its epidemiology, clinical presentation, and diagnosis, before concluding with its **staging, treatment, and prognosis**. Having worked through this Series, you should now be able to recognise, diagnose, stage, and understand the treatment of retinoblastoma and neuroblastoma. The next Series turns to **rhabdomyosarcoma and nephroblastoma**.

Glossary of Terms

1. **Retinoblastoma:** the most common intraocular malignancy of childhood, arising from immature retinal cells.
2. **Two-hit hypothesis:** the principle that cancer develops once both copies of a tumour suppressor gene are inactivated.
3. **Leukocoria:** a white pupillary reflex, the most common presenting feature of retinoblastoma.
4. **International Classification of Retinoblastoma:** a staging system for intraocular retinoblastoma guiding treatment and eye preservation decisions.
5. **Enucleation:** surgical removal of the eye, used for retinoblastoma that cannot be safely preserved.
6. **Neuroblastoma:** the most common extracranial solid tumour of childhood, arising from sympathetic nervous system cells.

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7. **Stage MS disease:** a pattern of widespread neuroblastoma metastasis in infants with a comparatively favourable prognosis.
8. **Vanillylmandelic acid:** a urinary catecholamine metabolite elevated in most children with neuroblastoma.
9. **MIBG scan:** an imaging study using a radiolabelled compound selectively taken up by neuroblastoma cells.
10. **MYCN amplification:** an adverse biological marker associated with more aggressive neuroblastoma.
11. **International Neuroblastoma Risk Group Staging System:** a staging system incorporating imaging-defined risk factors before surgery.
12. **Autologous stem cell rescue:** a component of high-risk neuroblastoma treatment following high-dose chemotherapy.

Concept Check Questions [Series 3]

Objective questions

- Retinoblastoma results from inactivation of both copies of the _____ tumour suppressor gene.
- Leukocoria refers to a white _____ reflex, the most common presenting feature of retinoblastoma.
- Overall survival for retinoblastoma generally exceeds _____ percent in settings with timely diagnosis and treatment.
- Neuroblastoma arises from primitive cells of the _____ nervous system.
- MYCN gene amplification is a particularly important adverse biological marker associated with more aggressive neuroblastoma _____.

Short-answer questions

1. Distinguish heritable from non-heritable retinoblastoma.
2. Describe the purpose and general structure of retinoblastoma staging.
3. Describe the most common presenting feature of neuroblastoma.
4. Describe stage MS disease and its distinctive prognosis.
5. Describe the treatment approach for low-risk versus high-risk neuroblastoma.

Long-answer questions

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6. Discuss the genetics, clinical presentation, and diagnosis of retinoblastoma. (Linked to SLO 3.1, SLO 3.2)
7. Discuss the staging, treatment, and prognosis of retinoblastoma. (Linked to SLO 3.3, SLO 3.4)
8. Discuss the epidemiology, clinical presentation, and diagnosis of neuroblastoma. (Linked to SLO 3.5, SLO 3.6)
9. Discuss the staging and treatment of neuroblastoma. (Linked to SLO 3.7)
10. Discuss the prognosis of neuroblastoma and the factors that influence it. (Linked to SLO 3.8)

Answers to Concept Check Questions [Series 3]

Objective questions

11. RB1.
12. Pupillary.
13. 90.
14. Sympathetic.
15. Disease.

Short-answer questions

16. Heritable disease presents earlier and often bilaterally from a germline mutation; non-heritable disease presents later and unilaterally.
17. Staging groups intraocular disease from A to E to guide treatment decisions balancing cure with eye and vision preservation.
18. An abdominal mass, often noted incidentally, is the most common presenting feature of neuroblastoma.
19. Stage MS disease is widespread skin, liver, and marrow involvement in infants without bone disease, carrying a favourable prognosis.
20. Low-risk disease may be managed with surgery alone or observation; high-risk disease requires intensive multimodal treatment.

Long-answer questions

21. **Basic response:** Retinoblastoma results from RB1 gene inactivation, occurring in heritable and non-heritable forms, most commonly presenting with leukocoria.

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Value-added response: Diagnosis relies on examination under anaesthesia and imaging, with MRI preferred over CT to avoid radiation exposure, particularly in heritable disease.

22. **Basic response:** Staging guides treatment choice between focal therapy, chemotherapy, and enucleation, aiming to balance cure with vision and eye preservation.

Value-added response: Survival generally exceeds 90 percent with timely treatment, though heritable survivors require long-term surveillance for secondary malignancy.

23. **Basic response:** Neuroblastoma arises from sympathetic nervous system cells, typically presenting as an abdominal mass, diagnosed through biopsy, catecholamine metabolites, and MIBG scanning.

Value-added response: Presentation varies from spontaneous regression in infants to aggressive metastatic disease in older children, reflecting significant biological heterogeneity.

24. **Basic response:** Staging incorporates both anatomical extent and biological features such as MYCN amplification, guiding classification into low, intermediate, and high-risk groups.

Value-added response: Treatment intensity is directly guided by risk group, ranging from observation in low-risk infants to intensive multimodal therapy in high-risk disease.

25. **Basic response:** Prognosis varies dramatically by risk group, with low-risk disease having excellent survival and high-risk disease considerably poorer outcomes despite intensive treatment.

Value-added response: Younger age at diagnosis is an independent favourable prognostic factor, and ongoing research continues to refine treatment for high-risk disease.

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Answers to Pilot Questions [Series 3]

Part 3.1

1. Cancer develops once both copies of the RB1 gene are inactivated within a retinal cell.
2. Heritable disease involves a germline mutation present in all cells, presenting earlier and often bilaterally.
3. Leukocoria is a white pupillary reflex, often first noticed in a flash photograph, and is the key warning sign.
4. Strabismus and decreased visual acuity are other clinical features.
5. MRI avoids ionising radiation exposure, particularly important given increased radiation sensitivity in heritable disease.

Part 3.2

6. Staging groups intraocular disease from A to E, guiding treatment decisions around cure and eye preservation.
7. Laser photocoagulation and cryotherapy are focal treatment options for small tumours.
8. Enucleation removes the eye when it cannot be safely preserved or vision cannot be saved.
9. Survival generally exceeds 90 percent with timely diagnosis and treatment.
10. They have an increased lifelong risk of secondary malignancy, requiring ongoing surveillance.

Part 3.3

11. Neuroblastoma arises from sympathetic nervous system cells, typically presenting under 2 years of age.
12. It ranges from spontaneous regression in infants to aggressive, rapidly progressive disease in older children.
13. An abdominal mass, often noted incidentally, is the most common presenting feature.
14. Stage MS disease is widespread skin and liver involvement in infants without bone disease, with a favourable prognosis.
15. Elevated catecholamine metabolites support diagnosis, and MIBG scanning assesses for metastatic disease.

Part 3.4

1. Staging incorporates anatomical extent using imaging-defined risk factors before surgical intervention.
2. MYCN amplification is associated with more aggressive disease and worse prognosis.

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3. Low-risk disease may be managed with surgery alone or observation; high-risk disease requires intensive multimodal therapy.
4. Low-risk disease has excellent survival, while high-risk disease has considerably lower survival despite treatment.
5. Younger children, particularly infants, generally have a more favourable prognosis than older children with similar disease.

References and Attributions [Series 3]

1. Kliegman, R. M., St Geme, J. W., Blum, N. J., Shah, S. S., Tasker, R. C. and Wilson, K. M. (2020). Nelson Textbook of Pediatrics (21st ed.). Elsevier.
2. Dimaras, H. et al. (2012). Retinoblastoma. The Lancet, 379(9824), 1436 to 1446.
3. Maris, J. M. (2010). Recent advances in neuroblastoma. New England Journal of Medicine, 362(23), 2202 to 2211.
4. Fabian, I. D. et al. (2020). Global retinoblastoma presentation and analysis by national income level. JAMA Oncology, 6(5), 685 to 695.

Figures, Plates, Tables, and Boxes

1. Figure 3.1: An ophthalmologist performing a dilated eye examination on a young child. AI-generated using the prompt: "A calm, respectful clinical illustration of an ophthalmologist gently examining a young child's eye with an ophthalmoscope, with a caregiver present nearby. Single clean medical illustration, soft clinical lighting, no text overlays, no multiple panels, sensitive and accurate depiction."
2. Table 3.2: Overview of retinoblastoma treatment options by clinical scenario. AI-generated using the prompt: "Create a clean reference table titled Retinoblastoma Treatment Options by Clinical Scenario, listing scenario and typical treatment approach. Simple clinical reference table style with outside border."
3. Figure 3.3: A clinician gently palpating a child's abdomen during examination. AI-generated using the prompt: "A calm, respectful clinical illustration of a clinician gently examining a young child's abdomen on an examination table, with a caregiver standing supportively nearby. Single clean medical illustration, soft clinical lighting, no text overlays, no multiple panels, sensitive and accurate depiction."

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4. Figure 3.4: A child undergoing a scan as part of neuroblastoma staging investigation. AI-generated using the prompt: "A calm, realistic clinical illustration of a child lying still on an imaging scanner table, gently supported by positioning aids, with a technician nearby monitoring equipment. Single clean medical illustration, clinical lighting, no text overlays, no multiple panels, reassuring and accurate depiction."

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Course code: PAE 506

Course title: Paediatric Oncology

Course credit load: 2 Units

Series 4: Rhabdomyosarcoma and Nephroblastoma

- **Part 4.1: Rhabdomyosarcoma: Epidemiology, Pathology, and Clinical Presentation**
  - Sub Part 4.1.1: Epidemiology and pathology of rhabdomyosarcoma
  - Sub Part 4.1.2: Common sites of rhabdomyosarcoma
  - Sub Part 4.1.3: Clinical presentation of rhabdomyosarcoma
- **Part 4.2: Rhabdomyosarcoma: Diagnosis, Staging, and Treatment**
  - Sub Part 4.2.1: Diagnosis of rhabdomyosarcoma
  - Sub Part 4.2.2: Staging and risk stratification of rhabdomyosarcoma
  - Sub Part 4.2.3: Treatment and prognosis of rhabdomyosarcoma
- **Part 4.3: Nephroblastoma: Epidemiology, Pathology, and Clinical Presentation**
  - Sub Part 4.3.1: Epidemiology and pathology of nephroblastoma
  - Sub Part 4.3.2: Pathology and bilateral disease
  - Sub Part 4.3.3: Clinical presentation of nephroblastoma
- **Part 4.4: Nephroblastoma: Diagnosis, Staging, and Treatment**
  - Sub Part 4.4.1: Diagnosis of nephroblastoma
  - Sub Part 4.4.2: Staging of nephroblastoma
  - Sub Part 4.4.3: Treatment and prognosis of nephroblastoma

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Introduction

In the last Series, we explored retinoblastoma and neuroblastoma. We now turn to two further important childhood solid tumours, rhabdomyosarcoma and nephroblastoma, both introduced in Series 1 of this course. Picture a six year old presenting with a firm, painless swelling in the thigh that has been slowly enlarging over several weeks, alongside a three year old found to have

a smooth, non-tender abdominal mass on routine examination. Recognising these two important paediatric solid tumours, and understanding their diagnosis, staging, and treatment, is the focus of this Series.

The aim of this Series is to equip you with the knowledge required to recognise, diagnose, stage, and understand the treatment and prognosis of rhabdomyosarcoma and nephroblastoma in children.

This Series begins with the **epidemiology, pathology, and clinical presentation of rhabdomyosarcoma**, before turning to its **diagnosis, staging, and treatment**. Next, we examine the **epidemiology, pathology, and clinical presentation of nephroblastoma**, before concluding with its **diagnosis, staging, and treatment**.

Series Learning Outcomes

At the end of this Series, you should be able to:

- **SLO 1.1:** describe the epidemiology and pathology of rhabdomyosarcoma,
- **SLO 1.2:** describe the clinical presentation of rhabdomyosarcoma,
- **SLO 1.3:** describe the diagnosis and staging of rhabdomyosarcoma,
- **SLO 1.4:** describe the treatment and prognosis of rhabdomyosarcoma,
- **SLO 1.5:** describe the epidemiology and pathology of nephroblastoma,
- **SLO 1.6:** describe the clinical presentation of nephroblastoma,
- **SLO 1.7:** describe the diagnosis and staging of nephroblastoma, and
- **SLO 1.8:** describe the treatment and prognosis of nephroblastoma.

4.1 Rhabdomyosarcoma: Epidemiology, Pathology, and Clinical Presentation

4.1.1 epidemiology and pathology of rhabdomyosarcoma

The most common soft tissue sarcoma of childhood

Rhabdomyosarcoma is the most common **soft tissue sarcoma** of childhood, arising from primitive **mesenchymal cells** with the capacity to differentiate towards **skeletal muscle**, and, notably, can arise in almost any anatomical site, including locations where mature skeletal muscle is not normally found, such as the **bladder** or **bile ducts**, reflecting its origin from primitive precursor cells rather than mature muscle tissue itself.

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Two main histological subtypes are recognised: **embryonal rhabdomyosarcoma**, the more common subtype, typically affecting **younger children** and generally associated with a somewhat more favourable prognosis, and **alveolar rhabdomyosarcoma**, typically affecting **older children and adolescents**, characterised by specific recurrent **chromosomal translocations**, and generally associated with more aggressive clinical behaviour.

Fill in the blank: Rhabdomyosarcoma arises from primitive mesenchymal cells with the capacity to differentiate towards skeletal _____.

4.1.2 common sites of rhabdomyosarcoma

The **head and neck region**, including the **orbit**, **parameningeal sites** such as the nasopharynx and middle ear, and other head and neck locations, represents the most common overall site of origin for rhabdomyosarcoma, followed by the **genitourinary tract**, including the bladder, prostate, and paratesticular region, and the **extremities**, with the specific site of origin influencing both typical clinical presentation and treatment approach.

Parameningeal tumours, arising close to the base of the skull, carry particular clinical significance given their potential for direct **intracranial extension**, and tumours in this location require specific attention to signs of **cranial nerve involvement** or **meningeal** spread during evaluation, since this specific anatomical location meaningfully influences both staging and treatment intensity compared with rhabdomyosarcoma arising elsewhere.

Fill in the blank: Parameningeal tumours carry particular significance given their potential for direct _____ extension.

4.1.3 clinical presentation of rhabdomyosarcoma

Clinical presentation of rhabdomyosarcoma varies considerably by **site**, with orbital tumours presenting with **proptosis**, bulging of the eye, or **ptosis**, drooping eyelid, genitourinary tumours presenting with **haematuria**, **urinary obstruction**, or a visible or palpable **vaginal mass** in girls, and extremity tumours presenting with a **painless**, gradually enlarging **soft tissue mass**, often initially mistaken for a benign lesion or minor injury.

Given the varied and sometimes subtle presentation, rhabdomyosarcoma can occasionally be **misdiagnosed** or have its diagnosis **delayed**, particularly when presenting with a soft tissue mass that is initially assumed to be benign, meaning any child with a persistent, enlarging soft tissue mass, particularly without a clear traumatic cause, warrants further evaluation rather than simple reassurance and watchful waiting alone.

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Fill in the blank: A persistent, enlarging soft tissue mass without a clear traumatic cause warrants further _____ rather than reassurance alone.

Figure 4.1: A clinician examining a soft tissue swelling on a child's limb.

Pilot questions 4.1

- Describe the cell of origin and two histological subtypes of rhabdomyosarcoma. (Linked to SLO 4.1)
- Distinguish embryonal from alveolar rhabdomyosarcoma. (Linked to SLO 4.1)
- List the three most common anatomical sites of rhabdomyosarcoma. (Linked to SLO 4.1)
- Explain the particular clinical significance of a parameningeal tumour location. (Linked to SLO 4.1)
- Describe the typical clinical presentation of rhabdomyosarcoma by site. (Linked to SLO 4.2)

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4.2 Rhabdomyosarcoma: Diagnosis, Staging, and Treatment

4.2.1 diagnosis of rhabdomyosarcoma

Confirming the diagnosis and mapping its full extent

Diagnosis of rhabdomyosarcoma requires **tissue biopsy**, with **histological** and **immunohistochemical** analysis confirming the diagnosis and distinguishing it from other soft tissue tumours that can occasionally mimic its appearance, together with **molecular testing** to identify the specific **chromosomal translocations** characteristic of alveolar rhabdomyosarcoma, which carries both diagnostic and prognostic significance.

Imaging of the primary tumour site, typically **magnetic resonance imaging** for extremity and head and neck sites given superior soft tissue detail, together with **staging investigations** to assess for **metastatic disease**, including **chest imaging**, **bone scan** or **PET scan**, and **bone marrow examination**, completes the standard diagnostic and staging work up before treatment planning begins.

Fill in the blank: Molecular testing identifies the specific chromosomal _____ characteristic of alveolar rhabdomyosarcoma.

4.2.2 staging and risk stratification of rhabdomyosarcoma

Staging of rhabdomyosarcoma incorporates **anatomical site**, **tumour size**, **nodal involvement**, and **presence of metastatic disease**, together with the **extent of surgical resection** achieved, if surgery is performed as part of initial management, and this staging information is combined with **histological subtype** to place each child into a defined **risk group**, guiding subsequent treatment intensity in a manner conceptually similar to the risk stratification discussed for neuroblastoma in the previous Series.

Favourable sites, such as the orbit, generally carry a better prognosis than **unfavourable sites**, such as parameningeal locations, independent of other staging factors, reflecting genuine anatomical differences in the feasibility of achieving complete surgical resection and the proximity of critical structures at each specific site, both of which meaningfully influence overall treatment approach and outcome.

Fill in the blank: Favourable sites, such as the orbit, generally carry a better _____ than unfavourable sites such as parameningeal locations.

4.2.3 treatment and prognosis of rhabdomyosarcoma

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Treatment of rhabdomyosarcoma generally combines **chemotherapy**, **surgery**, and, in many cases, **radiotherapy**, in a **multimodal approach**, with the specific sequence and intensity of each modality tailored according to risk group, and complete **surgical resection**, where achievable without unacceptable functional or cosmetic consequence, remains an important component of local disease control alongside systemic chemotherapy.

Prognosis varies according to risk group, histological subtype, and site, with **embryonal histology** and **favourable sites** generally associated with better outcomes than **alveolar histology** or **unfavourable sites**, and, as with the other tumours discussed in this course, **metastatic disease** at diagnosis is associated with a considerably poorer prognosis than localised disease, underscoring the importance of prompt recognition and diagnosis before disease has had the opportunity to spread.

Fill in the blank: Complete surgical resection, where achievable without unacceptable functional or cosmetic consequence, remains an important component of local disease _____.

Table 4.2: Factors influencing rhabdomyosarcoma risk stratification.

Factor	Favourable	Unfavourable
Histology	Embryonal	Alveolar
Site	Orbit, non-parameningeal head and neck	Parameningeal, extremity
Extent at diagnosis	Localised, completely resectable	Metastatic or unresectable

Pilot questions 4.2

1. Describe the diagnostic work up for suspected rhabdomyosarcoma. (Linked to SLO 4.3)
2. Explain the significance of chromosomal translocation testing in rhabdomyosarcoma. (Linked to SLO 4.3)
3. Describe how favourable and unfavourable sites influence rhabdomyosarcoma prognosis. (Linked to SLO 4.3)
4. Describe the general treatment approach for rhabdomyosarcoma. (Linked to SLO 4.4)
5. List two factors that influence the prognosis of rhabdomyosarcoma. (Linked to SLO 4.4)

4.3 Nephroblastoma: Epidemiology, Pathology, and Clinical Presentation

4.3.1 epidemiology and pathology of nephroblastoma

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Also known as Wilms tumour, a classic embryonal renal tumour

Nephroblastoma, also known as **Wilms tumour**, is the most common **renal malignancy** of childhood, arising from primitive **metanephric blastema**, embryonal kidney precursor tissue, and typically presents in **early childhood**, with the majority of cases diagnosed **before 5 years** of age, consistent with its embryonal origin discussed in Series 1 of this course.

Nephroblastoma shows recognised associations with several **congenital anomalies** and **genetic syndromes**, including **Beckwith-Wiedemann syndrome**, discussed in Series 1, **WAGR syndrome**, comprising Wilms tumour, Aniridia, Genitourinary anomalies, and intellectual disability, and isolated **hemihypertrophy**, meaning children with any of these recognised associations benefit from structured **surveillance** to allow earlier tumour detection.

Fill in the blank: Nephroblastoma arises from primitive metanephric blastema, embryonal _____ precursor tissue.

4.3.2 pathology and bilateral disease

Histologically, nephroblastoma classically shows a **triphasic pattern**, comprising **blastemal**, **epithelial**, and **stromal** components in varying proportions, reflecting the tumour's origin from primitive tissue capable of differentiating along multiple different lineages, and the specific histological pattern, together with the presence or absence of **anaplasia**, contributes to overall risk stratification, discussed further later in this Series.

Bilateral disease, affecting both kidneys either simultaneously or at different times, occurs in a proportion of children with nephroblastoma, particularly those with an underlying genetic predisposition, and requires specific treatment consideration aimed at preserving as much functioning renal tissue as possible on both sides, given the genuine long-term importance of preserving adequate overall renal function in an affected child.

Fill in the blank: Nephroblastoma classically shows a triphasic pattern comprising blastemal, epithelial, and _____ components.

4.3.3 clinical presentation of nephroblastoma

The most common presenting feature of nephroblastoma is an **asymptomatic abdominal mass**, often noticed incidentally by a parent while bathing or dressing the child, or identified on routine examination, characteristically **smooth**, **firm**, and typically confined to **one side** of the abdomen, generally not crossing the midline, a feature that can help distinguish it clinically from neuroblastoma, discussed in the previous Series, which more often does cross the midline.

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Other presenting features include **haematuria**, **hypertension**, resulting from renin production by the tumour or compression of renal vasculature, and, less commonly, **abdominal pain** or symptoms related to **tumour rupture**, a rare but recognised complication requiring urgent recognition, and any child presenting with a suspicious abdominal mass should be examined and imaged **gently**, avoiding excessive or repeated palpation, given a theoretical, though small, risk of provoking tumour rupture with vigorous abdominal examination.

Fill in the blank: A nephroblastoma abdominal mass is characteristically smooth, firm, and typically confined to one side, generally not crossing the _____.

Figure 4.3: A clinician gently palpating a young child's abdomen to assess a mass.

Pilot questions 4.3

1. Describe the cell of origin and typical age of presentation of nephroblastoma. (Linked to SLO 4.5)
2. List two genetic syndromes or conditions associated with increased nephroblastoma risk. (Linked to SLO 4.5)
3. Describe the triphasic histological pattern of nephroblastoma. (Linked to SLO 4.6)
4. Describe the most common presenting feature of nephroblastoma and how it can be distinguished from neuroblastoma. (Linked to SLO 4.6)
5. Explain why abdominal examination should be gentle in a child with a suspected nephroblastoma. (Linked to SLO 4.6)

4.4 Nephroblastoma: Diagnosis, Staging, and Treatment

4.4.1 diagnosis of nephroblastoma

Imaging often precedes biopsy in this specific tumour

Diagnosis of nephroblastoma typically begins with **abdominal imaging**, most commonly **ultrasound**, followed by **computed tomography** or **magnetic resonance imaging**, to characterise the renal mass, assess for involvement of the **renal vein** or **inferior vena cava**, and evaluate the contralateral kidney for evidence of **bilateral disease**, discussed in the previous Part of this Series.

Unlike many other childhood solid tumours, initial **biopsy** is not always required before starting treatment in many protocols, since the imaging appearance in a young child with a typical presentation is often considered sufficiently characteristic to proceed directly to treatment, with **upfront surgical resection**, or, in some treatment approaches, **pre-operative chemotherapy** followed by surgery, providing definitive tissue diagnosis at the time of the surgical procedure itself.

Fill in the blank: Diagnosis of nephroblastoma typically begins with abdominal _____.

4.4.2 staging of nephroblastoma

Staging of nephroblastoma is generally determined at the time of **surgical resection**, ranging from **Stage I**, tumour confined to the kidney and completely resected, through **Stage V**, bilateral renal involvement, with intermediate stages reflecting progressively more extensive local or **extrarenal** spread, including lymph node involvement and tumour rupture during removal, and staging, together with **histology**, directly determines subsequent treatment intensity.

Histological risk stratification distinguishes **favourable histology**, without significant anaplasia, generally associated with a good prognosis, from **unfavourable, or anaplastic, histology**, associated with a considerably worse prognosis and requiring more intensive treatment, meaning both anatomical stage and histological features together determine the overall treatment plan for an individual child, similar in principle to the risk stratification approach discussed for rhabdomyosarcoma earlier in this Series.

Fill in the blank: Histological risk stratification distinguishes favourable histology from unfavourable, or _____, histology.

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4.4.3 treatment and prognosis of nephroblastoma

Treatment of nephroblastoma combines **surgery**, typically **nephrectomy**, removal of the affected kidney, with **chemotherapy**, and, in higher-stage or unfavourable histology disease, **radiotherapy**, with the specific sequence, for example whether surgery is performed upfront or after a period of pre-operative chemotherapy, varying somewhat between different treatment protocols and approaches used internationally.

Prognosis of nephroblastoma is generally **excellent**, among the most favourable of the major childhood solid tumours, with overall survival exceeding **90 percent** for favourable histology, localised disease, reflecting the tumour's genuine sensitivity to available chemotherapy agents, though outcomes are considerably less favourable for **anaplastic histology** or advanced-stage disease, and, as with the other tumours discussed throughout this course, long-term follow up remains important to monitor for treatment-related late effects.

Fill in the blank: Overall survival for nephroblastoma exceeds _____ percent for favourable histology, localised disease.

Figure 4.4: A surgical team preparing a child for a planned nephroblastoma operation.

Pilot questions 4.4

1. Describe the diagnostic imaging approach to a suspected nephroblastoma. (Linked to SLO 4.7)
2. Explain why biopsy is not always required before treatment in nephroblastoma. (Linked to SLO 4.7)
3. Describe the staging system used for nephroblastoma. (Linked to SLO 4.7)
4. Distinguish favourable from unfavourable histology in nephroblastoma. (Linked to SLO 4.7)
5. Describe the general prognosis of nephroblastoma with favourable histology and localised disease. (Linked to SLO 4.8)

Series Summary

This Series examined **rhabdomyosarcoma**, the most common soft tissue sarcoma of childhood, beginning with its epidemiology and pathology, including the distinction between embryonal and alveolar histological subtypes, and its varied clinical presentation across the head and neck, genitourinary, and extremity sites where it most commonly arises, before turning to its **diagnosis, staging, and treatment**, exploring how anatomical site, histology, and extent of disease together determine risk group and guide the intensity of multimodal treatment combining chemotherapy, surgery, and radiotherapy.

We then examined **nephroblastoma**, also known as Wilms tumour, its epidemiology, pathology, and clinical presentation, before concluding with its **diagnosis, staging, and treatment**. Having worked through this Series, you should now be able to recognise, diagnose, stage, and understand the treatment of rhabdomyosarcoma and nephroblastoma. The final Series of this course turns to **treatment principles, supportive care, prognosis, and late effects in paediatric oncology**.

Glossary of Terms

1. **Rhabdomyosarcoma:** the most common soft tissue sarcoma of childhood, arising from primitive mesenchymal cells.
2. **Embryonal rhabdomyosarcoma:** the more common histological subtype, typically affecting younger children with a more favourable prognosis.

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3. **Alveolar rhabdomyosarcoma:** a histological subtype typically affecting older children, associated with more aggressive behaviour.
4. **Parameningeal site:** a rhabdomyosarcoma location near the skull base with potential for intracranial extension.
5. **Favourable site:** an anatomical location, such as the orbit, associated with a better rhabdomyosarcoma prognosis.
6. **Nephroblastoma:** the most common renal malignancy of childhood, also known as Wilms tumour.
7. **Metanephric blastema:** the embryonal kidney precursor tissue from which nephroblastoma arises.
8. **WAGR syndrome:** a genetic syndrome comprising Wilms tumour, Aniridia, Genitourinary anomalies, and intellectual disability.
9. **Triphasic pattern:** the classic histological pattern of nephroblastoma, comprising blastemal, epithelial, and stromal components.
10. **Anaplastic histology:** an unfavourable histological pattern in nephroblastoma associated with a worse prognosis.
11. **Nephrectomy:** surgical removal of the kidney, a core component of nephroblastoma treatment.
12. **Multimodal treatment:** treatment combining chemotherapy, surgery, and radiotherapy, used for both rhabdomyosarcoma and nephroblastoma.

Concept Check Questions [Series 4]

Objective questions

- Rhabdomyosarcoma arises from primitive mesenchymal cells with the capacity to differentiate towards skeletal _____.
- Molecular testing identifies the specific chromosomal _____ characteristic of alveolar rhabdomyosarcoma.
- Nephroblastoma arises from primitive metanephric blastema, embryonal _____ precursor tissue.
- A nephroblastoma abdominal mass is characteristically smooth, firm, and typically confined to one side, generally not crossing the _____.
- Overall survival for nephroblastoma exceeds _____ percent for favourable histology, localised disease.

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Short-answer questions

1. Distinguish embryonal from alveolar rhabdomyosarcoma.
2. Describe how favourable and unfavourable sites influence rhabdomyosarcoma prognosis.
3. List two genetic syndromes or conditions associated with increased nephroblastoma risk.
4. Describe the triphasic histological pattern of nephroblastoma.
5. Distinguish favourable from unfavourable histology in nephroblastoma.

Long-answer questions

6. Discuss the epidemiology, pathology, and clinical presentation of rhabdomyosarcoma. (Linked to SLO 4.1, SLO 4.2)
7. Discuss the diagnosis, staging, and treatment of rhabdomyosarcoma. (Linked to SLO 4.3, SLO 4.4)
8. Discuss the epidemiology, pathology, and clinical presentation of nephroblastoma. (Linked to SLO 4.5, SLO 4.6)
9. Discuss the diagnosis and staging of nephroblastoma. (Linked to SLO 4.7)
10. Discuss the treatment and prognosis of nephroblastoma. (Linked to SLO 4.8)

Answers to Concept Check Questions [Series 4]

Objective questions

11. Muscle.
12. Translocations.
13. Kidney.
14. Midline.
15. 90.

Short-answer questions

16. Embryonal affects younger children with a more favourable prognosis; alveolar affects older children with more aggressive behaviour.
17. Favourable sites such as the orbit carry a better prognosis than unfavourable sites such as parameningeal locations.
18. Beckwith-Wiedemann syndrome and WAGR syndrome are associated with increased nephroblastoma risk.

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19. Blastemal, epithelial, and stromal components in varying proportions make up the triphasic pattern.
20. Favourable histology lacks significant anaplasia and has a good prognosis; unfavourable, or anaplastic, histology has a worse prognosis.

Long-answer questions

21. **Basic response:** Rhabdomyosarcoma arises from mesenchymal cells, with embryonal and alveolar subtypes presenting most commonly in the head and neck, genitourinary tract, and extremities.

Value-added response: Presentation varies by site, from orbital proptosis to painless extremity masses, and parameningeal tumours carry specific risk of intracranial extension.

22. **Basic response:** Diagnosis requires biopsy with molecular testing, and staging incorporates site, size, nodal status, and metastasis to determine risk group and treatment intensity.

Value-added response: Treatment combines chemotherapy, surgery, and radiotherapy, with prognosis influenced by histology, site, and presence of metastatic disease.

23. **Basic response:** Nephroblastoma arises from metanephric blastema, typically presenting as an asymptomatic abdominal mass in early childhood, associated with specific genetic syndromes.

Value-added response: The mass is typically unilateral and does not cross the midline, distinguishing it clinically from neuroblastoma discussed in the previous Series.

24. **Basic response:** Diagnosis relies on imaging, often without upfront biopsy, and staging is determined at surgical resection, incorporating both anatomical extent and histology.

Value-added response: Favourable histology is distinguished from anaplastic histology, with the combination of stage and histology determining treatment intensity.

25. **Basic response:** Treatment combines nephrectomy with chemotherapy and, in higher-risk disease, radiotherapy, with prognosis generally excellent for favourable histology, localised disease.

Value-added response: Survival exceeds 90 percent in favourable cases, though anaplastic histology and advanced stage carry a considerably poorer prognosis requiring long-term follow up.

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Answers to Pilot Questions [Series 4]

Part 4.1

1. Rhabdomyosarcoma arises from mesenchymal cells; embryonal and alveolar are the two main subtypes.
2. Embryonal affects younger children with a more favourable prognosis; alveolar affects older children with more aggressive disease.
3. Head and neck, genitourinary tract, and extremities are the three most common sites.
4. Parameningeal tumours carry risk of direct intracranial extension given their proximity to the skull base.
5. Presentation varies by site, including orbital proptosis, genitourinary symptoms, or a painless extremity mass.

Part 4.2

6. Biopsy with histological and molecular analysis, plus imaging and metastatic work up, comprise the diagnostic approach.
7. Chromosomal translocation testing helps identify alveolar histology, which carries prognostic significance.
8. Favourable sites such as the orbit have a better prognosis than unfavourable sites such as parameningeal locations.
9. Treatment combines chemotherapy, surgery, and often radiotherapy in a multimodal approach.
10. Histological subtype and site are factors influencing prognosis.

Part 4.3

11. Nephroblastoma arises from metanephric blastema, typically presenting before 5 years of age.
12. Beckwith-Wiedemann syndrome and WAGR syndrome are associated with increased risk.
13. Blastemal, epithelial, and stromal components together make up the classic triphasic pattern.
14. An asymptomatic abdominal mass, typically unilateral and not crossing the midline, unlike neuroblastoma.
15. Vigorous examination carries a small theoretical risk of provoking tumour rupture.

Part 4.4

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1. Ultrasound followed by CT or MRI characterises the mass and assesses for bilateral disease.
2. The imaging appearance is often sufficiently characteristic to proceed directly to treatment in many protocols.
3. Staging is determined at surgical resection, from Stage I to Stage V for bilateral disease.
4. Favourable histology lacks significant anaplasia; unfavourable, or anaplastic, histology has a worse prognosis.
5. Prognosis is generally excellent, with survival exceeding 90 percent for favourable histology, localised disease.

References and Attributions [Series 4]

1. Kliegman, R. M., St Geme, J. W., Blum, N. J., Shah, S. S., Tasker, R. C. and Wilson, K. M. (2020). Nelson Textbook of Pediatrics (21st ed.). Elsevier.
2. Skapek, S. X. et al. (2019). Rhabdomyosarcoma. Nature Reviews Disease Primers, 5, 1.
3. Dome, J. S. et al. (2015). Advances in Wilms tumor treatment and biology. Journal of Clinical Oncology, 33(27), 2999 to 3007.
4. Malempati, S. and Hawkins, D. S. (2012). Rhabdomyosarcoma: review of the Children's Oncology Group experience. Pediatric Blood and Cancer, 59(1), 5 to 10.

Figures, Plates, Tables, and Boxes

1. Figure 4.1: A clinician examining a soft tissue swelling on a child’s limb. AI-generated using the prompt: "A calm, respectful clinical illustration of a clinician gently examining a child’s leg for a soft tissue swelling during an assessment, with a caregiver present. Single clean medical illustration, soft clinical lighting, no text overlays, no multiple panels, sensitive and accurate depiction, no graphic detail."
2. Table 4.2: Factors influencing rhabdomyosarcoma risk stratification. AI-generated using the prompt: "Create a clean reference table titled Factors Influencing Rhabdomyosarcoma Risk Stratification, listing factor, favourable, and unfavourable characteristics. Simple clinical reference table style with outside border."

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3. Figure 4.3: A clinician gently palpating a young child's abdomen to assess a mass. AI-generated using the prompt: "A calm, respectful clinical illustration of a clinician gently examining a young child's abdomen with careful, light touch, with a caregiver present nearby. Single clean medical illustration, soft clinical lighting, no text overlays, no multiple panels, sensitive and accurate depiction."
4. Figure 4.4: A surgical team preparing a child for a planned nephroblastoma operation. AI-generated using the prompt: "A professional clinical illustration of a small surgical team reviewing imaging on a screen together in a preparation area before an operation. Single clean medical illustration, clinical lighting, no text overlays, no multiple panels, accurate and professional depiction, no graphic surgical detail."

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Course code: PAE 506

Course title: Paediatric Oncology

Course credit load: 2 Units

Series 5: Treatment Principles, Supportive Care, Prognosis, and Late Effects in Paediatric Oncology

- **Part 5.1: Principles of Chemotherapy in Paediatric Oncology**
  - Sub Part 5.1.1: General principles of chemotherapy
  - Sub Part 5.1.2: Classes of chemotherapy agents
  - Sub Part 5.1.3: General side effects of chemotherapy
- **Part 5.2: Supportive Care in Paediatric Oncology**
  - Sub Part 5.2.1: Infection prevention and management
  - Sub Part 5.2.2: Transfusion and nutritional support
  - Sub Part 5.2.3: Psychosocial and other supportive care
- **Part 5.3: Prognosis and Complications of Childhood Cancer**
  - Sub Part 5.3.1: Factors influencing prognosis
  - Sub Part 5.3.2: Complications of childhood cancer and its treatment
  - Sub Part 5.3.3: The overall outlook in childhood cancer
- **Part 5.4: Late Effects of Childhood Cancer Treatment**
  - Sub Part 5.4.1: Defining late effects
  - Sub Part 5.4.2: Organ-specific late effects
  - Sub Part 5.4.3: Long-term follow up and survivorship care

Introduction

In the last Series, we explored rhabdomyosarcoma and nephroblastoma, completing our review of the specific tumour types covered in this course. We now draw together the shared principles

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of chemotherapy, supportive care, prognosis, and late effects that apply broadly across the range of childhood cancers discussed throughout this course. Picture a child midway through an intensive treatment course, requiring careful supportive care to safely tolerate chemotherapy, alongside a young adult, now years beyond successful treatment for a childhood cancer, attending a dedicated survivorship clinic to monitor for potential late effects of the treatment that once saved their life.

The aim of this Series is to equip you with an understanding of the general principles of chemotherapy and supportive care, the factors influencing prognosis, and the potential complications and late effects of childhood cancer and its treatment.

This Series begins with the **principles of chemotherapy**, before turning to **supportive care** in paediatric oncology. Next, we examine **prognosis and complications** of childhood cancer, before concluding with its **late effects** and the approach to long-term survivorship care.

Series Learning Outcomes

At the end of this Series, you should be able to:

- **SLO 1.1:** describe the general principles and classes of chemotherapy used in paediatric oncology,
- **SLO 1.2:** describe the general side effects of chemotherapy in children,
- **SLO 1.3:** describe the principles of supportive care in paediatric oncology,
- **SLO 1.4:** describe the recognition and management of common oncological emergencies,
- **SLO 1.5:** describe the factors influencing prognosis in childhood cancer,
- **SLO 1.6:** describe common complications of childhood cancer and its treatment,
- **SLO 1.7:** describe the late effects of childhood cancer treatment, and
- **SLO 1.8:** describe the approach to long-term follow up and survivorship care.

5.1 Principles of Chemotherapy in Paediatric Oncology

5.1.1 general principles of chemotherapy

Attacking rapidly dividing cells, with predictable trade-offs

Chemotherapy works principally by targeting **rapidly dividing cells**, exploiting the characteristically high **proliferation rate** of most childhood malignancies compared with normal tissue, though this same mechanism explains why chemotherapy also affects other normal,

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rapidly dividing tissues in the body, including **bone marrow**, the **gastrointestinal epithelium**, and **hair follicles**, accounting for many of the common side effects discussed later in this Part.

Combination chemotherapy, using multiple agents with different mechanisms of action given together, is standard practice across virtually all childhood cancers discussed throughout this course, since this approach both **maximises tumour cell killing** through complementary mechanisms and **reduces the risk of resistance** developing to any single agent, an approach already introduced in the context of childhood lymphoma earlier in this course.

Fill in the blank: Chemotherapy works principally by targeting rapidly _____ cells.

5.1.2 classes of chemotherapy agents

Major classes of chemotherapy agents used in paediatric oncology include **alkylating agents**, which directly damage **DNA**, **antimetabolites**, which interfere with **DNA synthesis** by mimicking normal cellular building blocks, **anthracyclines**, which intercalate into DNA and inhibit key enzymes required for replication, and **vinca alkaloids**, which disrupt the **microtubules** required for normal cell division, each class contributing a distinct mechanism to the overall combination regimen.

Corticosteroids are also frequently incorporated into chemotherapy regimens for several childhood cancers, particularly lymphomas and leukaemias, given their own direct **anti-tumour effect** against lymphoid malignancies, alongside their valuable role in managing certain treatment-related **side effects**, illustrating how individual agents within a combination regimen can serve more than one therapeutic purpose simultaneously.

Fill in the blank: Anthracyclines intercalate into DNA and inhibit key enzymes required for _____.

5.1.3 general side effects of chemotherapy

Common, generally **acute** side effects of chemotherapy include **nausea and vomiting**, **mucositis**, painful inflammation of the mucous membranes lining the mouth and gastrointestinal tract, **alopecia**, hair loss, and, most clinically significant, **myelosuppression**, suppression of bone marrow function leading to **neutropenia**, **anaemia**, and **thrombocytopenia**, each carrying distinct clinical implications requiring specific monitoring and management.

Neutropenia, in particular, carries genuine clinical significance given the associated risk of serious **infection**, discussed further in the next Part of this Series, and understanding the expected **timing** of myelosuppression following a specific chemotherapy regimen, since blood counts typically reach their lowest point, or **nadir**, at a predictable interval after treatment,

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allows anticipatory monitoring and appropriate precautions during the period of greatest vulnerability.

Fill in the blank: Blood counts typically reach their lowest point, or _____, at a predictable interval after chemotherapy.

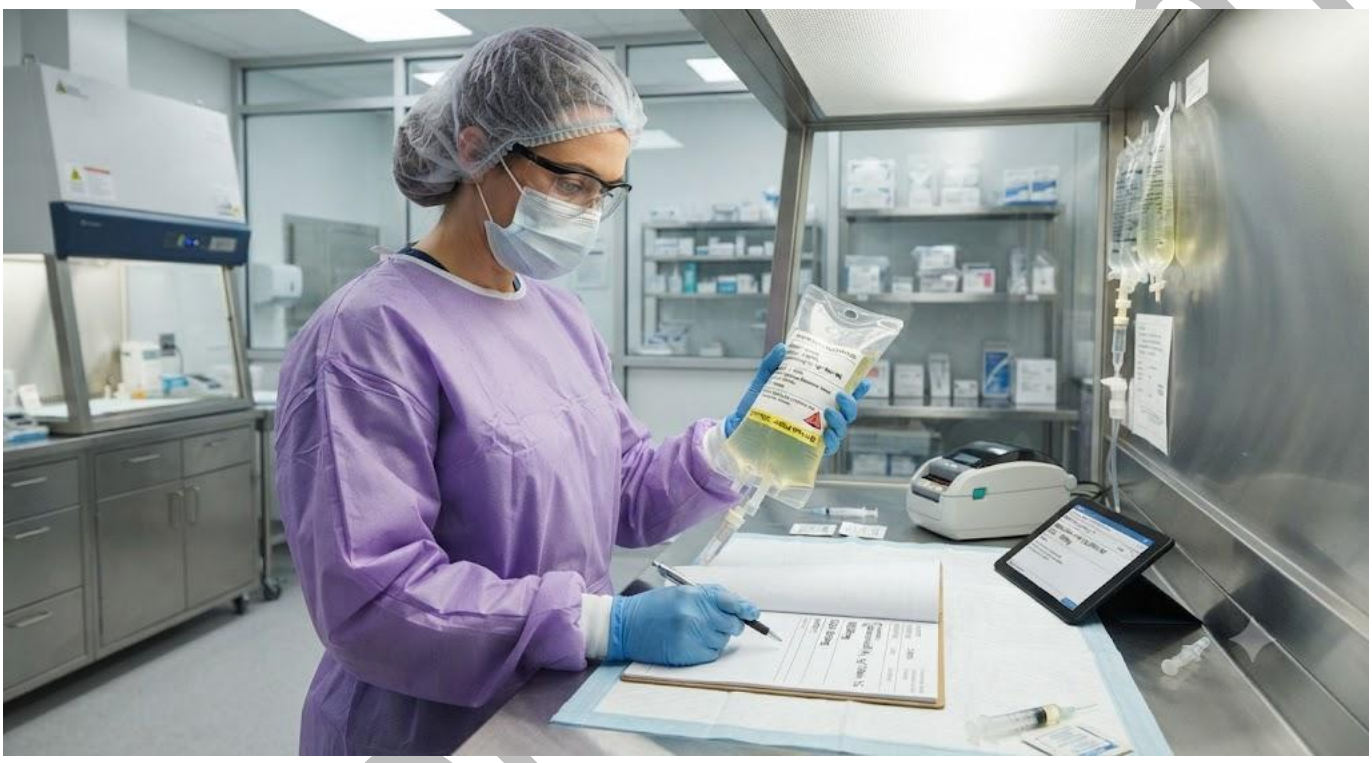

Figure 5.1: A nurse preparing and checking chemotherapy medication before administration.

Pilot questions 5.1

- Explain the general mechanism by which chemotherapy targets cancer cells. (Linked to SLO 5.1)
- Explain the rationale for using combination chemotherapy. (Linked to SLO 5.1)
- List four major classes of chemotherapy agents and their general mechanism. (Linked to SLO 5.1)
- List four common acute side effects of chemotherapy. (Linked to SLO 5.2)
- Define nadir and explain its clinical relevance. (Linked to SLO 5.2)

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5.2 Supportive Care in Paediatric Oncology

5.2.1 infection prevention and management

Infection remains a leading cause of treatment-related morbidity

Infection is among the most significant causes of morbidity and mortality during childhood cancer treatment, given the **immunosuppression** resulting from both the underlying malignancy and its treatment, meaning **prevention strategies**, including good **hand hygiene**, avoiding unnecessary exposure to unwell contacts, and, where appropriate, **prophylactic antimicrobial medication**, form an essential component of routine supportive care throughout treatment.

Febrile neutropenia, fever occurring in a child with a significantly low neutrophil count, discussed briefly in an earlier course in the context of general paediatric emergencies, is considered a genuine **medical emergency** in the oncology setting, requiring **prompt assessment**, **blood cultures**, and **immediate empirical broad-spectrum antibiotic therapy**, since a delay in treatment can allow rapid, life-threatening progression of an underlying, initially localised infection.

Fill in the blank: Febrile neutropenia requires prompt assessment and immediate empirical broad-spectrum _____ therapy.

5.2.2 transfusion and nutritional support

Blood product transfusion is frequently required during intensive chemotherapy, including **red cell transfusion** for significant anaemia and **platelet transfusion** for significant thrombocytopenia with bleeding risk, with specific transfusion thresholds guided by the child's clinical status and the intensity of treatment being received, and, where relevant, transfused blood products may be **irradiated** to reduce a specific risk of transfusion-associated complications in significantly immunocompromised children.

Nutritional support is essential given the combined effects of the underlying malignancy, chemotherapy-related **mucositis** and **nausea**, and the general metabolic demands of intensive treatment on growth and nutritional status, with support ranging from simple **dietary advice** and appetite stimulation, through **nasogastric tube feeding**, to **parenteral nutrition** in children unable to tolerate adequate enteral intake during particularly intensive phases of treatment.

Fill in the blank: Nutritional support may range from dietary advice through nasogastric tube feeding to _____ nutrition in the most severe cases.

5.2.3 psychosocial and other supportive care

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Psychosocial support for the child and family throughout the often lengthy, demanding treatment course is an essential, integral component of comprehensive paediatric oncology care, including access to **psychology services**, **child life specialists**, who help children cope with and understand medical procedures through age-appropriate techniques, and structured **peer support** for both affected children and their siblings, who can experience significant psychological impact themselves.

Pain management, using an appropriately structured, **stepwise approach** tailored to the specific cause and severity of pain, whether related to the underlying malignancy, a specific procedure, or treatment-related mucositis, and management of **oncological emergencies** more broadly, including tumour lysis syndrome, discussed earlier in this course in the context of Burkitt's lymphoma, together complete the comprehensive supportive care framework required throughout childhood cancer treatment.

Fill in the blank: A child life specialist helps children cope with and understand medical procedures through age-appropriate _____.

Table 5.2: Key components of supportive care in paediatric oncology.

Component	Key focus
Infection prevention and management	Hygiene, prophylaxis, and urgent treatment of febrile neutropenia
Transfusion support	Red cell and platelet transfusion as clinically indicated
Nutritional support	From dietary advice through to parenteral nutrition as needed
Psychosocial support	Psychology, child life specialists, and peer support for child and family
Pain management	Stepwise approach tailored to cause and severity of pain

Pilot questions 5.2

1. Explain why infection is a particularly significant concern during childhood cancer treatment. (Linked to SLO 5.3)
2. Describe the immediate management of febrile neutropenia. (Linked to SLO 5.4)
3. Describe the indications for red cell and platelet transfusion during chemotherapy. (Linked to SLO 5.3)
4. Describe the range of nutritional support options available during intensive treatment. (Linked to SLO 5.3)
5. List two components of psychosocial support in paediatric oncology. (Linked to SLO 5.3)

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5.3 Prognosis and Complications of Childhood Cancer

5.3.1 factors influencing prognosis

Several factors combine to shape an individual child's outlook

Prognosis in childhood cancer is influenced by a combination of factors discussed throughout this course, including **tumour type** and **biological subtype**, **stage** or **extent of disease** at diagnosis, **response** to initial treatment, and, for several tumours specifically discussed in earlier Series, particular **biological markers**, such as MYCN amplification in neuroblastoma or histological subtype in rhabdomyosarcoma, each contributing to an individual child's overall expected outcome.

Access to timely diagnosis and **appropriate, complete treatment** also meaningfully influences prognosis at a population level, since delayed presentation, incomplete treatment, or limited access to specialist paediatric oncology services can result in considerably poorer outcomes even for tumour types generally considered highly treatable when managed optimally, an important consideration in resource-limited settings including much of Nigeria.

Fill in the blank: Access to timely diagnosis and appropriate, complete treatment meaningfully influences prognosis at a population _____.

5.3.2 complications of childhood cancer and its treatment

Complications of childhood cancer itself can include direct effects of **tumour mass** or infiltration on surrounding structures, **metabolic derangement**, such as tumour lysis syndrome discussed earlier in this course, and, in some cases, **paraneoplastic phenomena**, effects mediated by substances released by the tumour rather than direct tumour infiltration, illustrating the range of ways a malignancy can affect a child beyond the primary tumour site itself.

Treatment-related complications during active treatment include the acute chemotherapy side effects discussed earlier in this Series, together with specific complications of **surgery** or **radiotherapy** where used, and recognising and appropriately managing these complications promptly is an essential, ongoing component of safe, effective childhood cancer treatment throughout the entire treatment course, not solely at the point of initial diagnosis.

Fill in the blank: Paraneoplastic phenomena are effects mediated by substances released by the tumour rather than direct tumour _____.

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5.3.3 the overall outlook in childhood cancer

The overall **outlook** for childhood cancer has improved dramatically over recent decades, with many childhood cancers, including several discussed across this course, now associated with **cure rates exceeding 80 percent** in settings with access to modern, comprehensive treatment, representing one of the genuine success stories of modern medicine, though this improvement has not been **uniformly distributed** globally, with considerably poorer outcomes persisting in many resource-limited settings.

This gap in outcomes reflects differences in **access to diagnosis**, **treatment availability**, and **supportive care capacity** rather than any fundamental difference in tumour biology between settings, meaning continued investment in paediatric oncology services, training, and infrastructure in resource-limited settings, including Nigeria, remains an important, ongoing global health priority to help close this persistent gap in outcomes.

Fill in the blank: Many childhood cancers are now associated with cure rates exceeding _____ percent in settings with modern treatment.

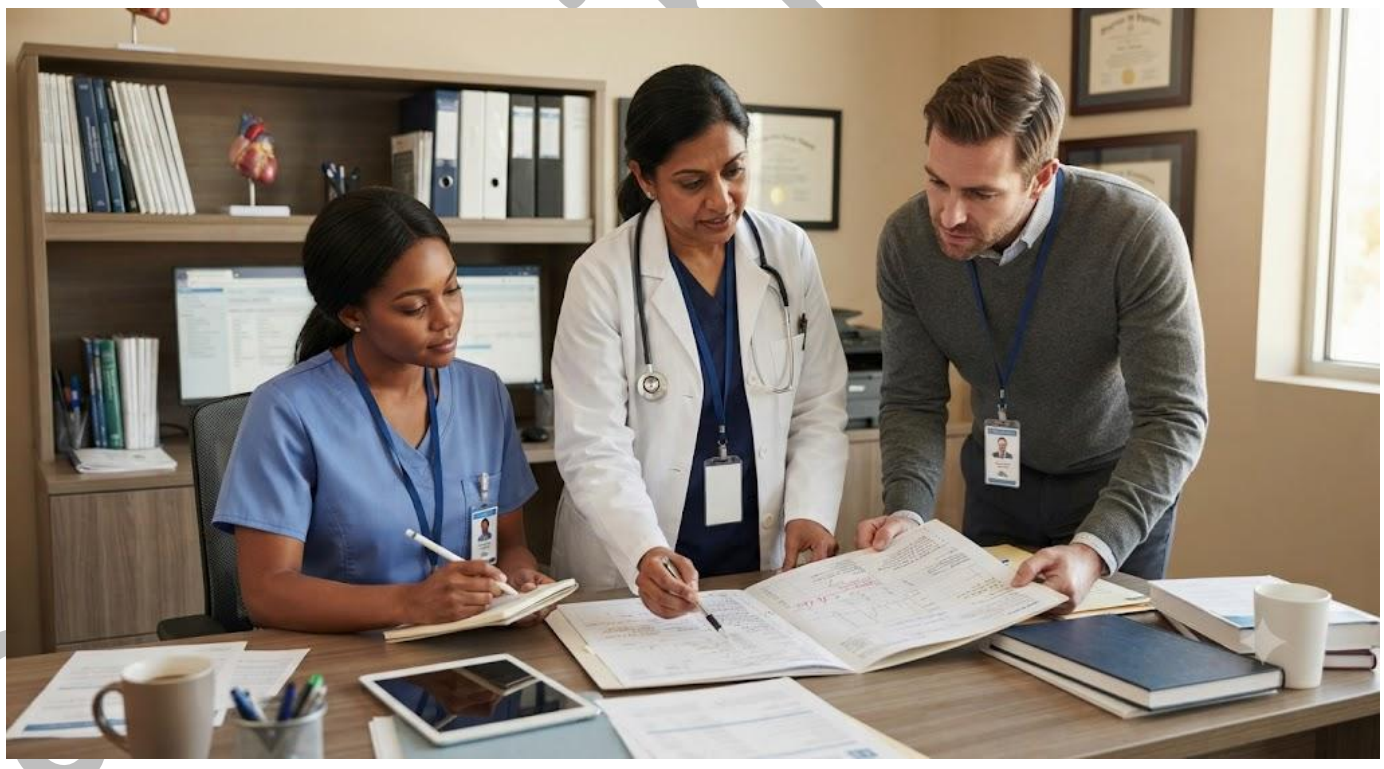

Figure 5.3: A multidisciplinary paediatric oncology team discussing a child's care plan.

Pilot questions 5.3

1. List three factors that influence prognosis in childhood cancer. (Linked to SLO 5.5)
2. Explain why access to timely diagnosis and treatment influences prognosis at a population level. (Linked to SLO 5.5)
3. Describe two types of complications that can arise from childhood cancer or its treatment. (Linked to SLO 5.6)
4. Describe the general improvement in childhood cancer outcomes over recent decades. (Linked to SLO 5.6)
5. Explain why outcomes remain considerably poorer in some resource-limited settings. (Linked to SLO 5.6)

5.4 Late Effects of Childhood Cancer Treatment

5.4.1 defining late effects

Consequences that appear only after successful treatment

Late effects refer to treatment-related complications that become apparent **months to years** after completion of cancer treatment, distinct from the acute, treatment-phase complications discussed earlier in this Series, and reflect the genuine, lasting impact that intensive childhood cancer treatment can have on a still-developing child, even where the treatment itself has been entirely successful in curing the underlying malignancy.

The risk and specific pattern of late effects depends on the **specific treatment received**, including the particular **chemotherapy agents**, **cumulative doses**, whether **radiotherapy** was used and to which body region, and whether **surgery** was performed, meaning the specific late effect surveillance plan for an individual survivor is genuinely **individualised** according to their own specific treatment history rather than following a single, generic protocol applied to every survivor.

Fill in the blank: Late effects refer to treatment-related complications that become apparent months to _____ after completion of treatment.

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5.4.2 organ-specific late effects

Specific **organ-specific late effects** include **cardiotoxicity** from anthracycline chemotherapy, discussed earlier in this Series, presenting as impaired cardiac function that may not become clinically apparent for years, **growth and endocrine effects**, particularly following radiotherapy affecting the growth plates or endocrine glands, **neurocognitive effects**, particularly relevant following treatment involving the central nervous system, and **fertility impairment**, a particular concern for survivors and their families given its significant long-term life impact.

Renal and **hepatic** late effects can also occur following certain chemotherapy agents or abdominal radiotherapy, and **secondary malignancy**, discussed earlier in this course in the specific context of hereditary retinoblastoma, represents one of the most serious potential late effects overall, reflecting the genuinely genotoxic mechanism of many chemotherapy agents and the carcinogenic potential of ionising radiation exposure discussed in Series 1 of this course.

Fill in the blank: Cardiotoxicity from anthracycline chemotherapy may not become clinically apparent for _____.

5.4.3 long-term follow up and survivorship care

Long-term follow up for childhood cancer survivors should be **structured** and **individualised**, based on the specific treatment received, and generally includes regular clinical assessment, **targeted screening** for known potential late effects relevant to that survivor's specific treatment history, discussed in the previous sub-Part, and ongoing **psychosocial support**, recognising that the psychological impact of a childhood cancer diagnosis and its treatment can persist well into adulthood for some survivors.

Survivorship care, increasingly recognised as an essential component of comprehensive paediatric oncology services rather than an optional addition, ideally includes clear, structured **communication** with the survivor, and, as they reach an appropriate age, direct involvement of the survivor themselves, about their specific treatment history and associated late effect risks, empowering them to actively participate in their own ongoing health monitoring well into adult life, completing the full spectrum of paediatric oncology care discussed across this course.

Fill in the blank: Survivorship care ideally includes clear, structured communication about treatment history and associated late effect _____.

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Figure 5.4: A young survivor attending a long-term follow-up survivorship clinic visit.

Pilot questions 5.4

1. Define late effects and explain how they differ from acute treatment complications. (Linked to SLO 5.7)
2. Explain why late effect surveillance is individualised for each survivor. (Linked to SLO 5.7)
3. List four organ systems that can be affected by late effects of childhood cancer treatment. (Linked to SLO 5.7)
4. Describe the general components of long-term follow up for childhood cancer survivors. (Linked to SLO 5.8)
5. Explain the importance of involving the survivor themselves in survivorship care as they grow older. (Linked to SLO 5.8)

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Series Summary

This final Series drew together the shared treatment principles that apply across the range of childhood cancers discussed throughout this course, beginning with the **general principles and classes of chemotherapy**, including how combination regimens are designed to maximise tumour cell killing while limiting resistance, and the acute side effects, particularly myelosuppression, that follow predictably from these mechanisms, before turning to the **comprehensive supportive care**, spanning infection prevention, transfusion, nutrition, and psychosocial support, required to help a child safely tolerate intensive treatment.

We then examined the **factors influencing prognosis and the complications** of childhood cancer and its treatment, before concluding with its **late effects** and the structured, individualised approach to long-term survivorship care. Having worked through this Series, and indeed this entire course, you should now be equipped with a comprehensive foundation in paediatric oncology, from epidemiology and risk factors through specific tumour types to the shared principles of treatment, supportive care, and survivorship that underpin comprehensive care for every child with cancer.

Glossary of Terms

1. **Combination chemotherapy:** the use of multiple chemotherapy agents with different mechanisms given together to maximise effectiveness and reduce resistance.
2. **Myelosuppression:** suppression of bone marrow function by chemotherapy, leading to neutropenia, anaemia, and thrombocytopenia.
3. **Nadir:** the point at which blood counts reach their lowest level following chemotherapy.
4. **Febrile neutropenia:** fever in a child with a significantly low neutrophil count, a medical emergency requiring urgent antibiotics.
5. **Child life specialist:** a professional who helps children cope with and understand medical procedures through age-appropriate techniques.
6. **Paraneoplastic phenomenon:** an effect mediated by substances released by a tumour rather than by direct tumour infiltration.
7. **Late effect:** a treatment-related complication becoming apparent months to years after completion of cancer treatment.
8. **Cardiotoxicity:** impaired cardiac function, a recognised late effect of anthracycline chemotherapy.
9. **Secondary malignancy:** a new cancer arising as a late effect of prior cancer treatment.

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10. **Survivorship care:** structured, long-term care for childhood cancer survivors addressing late effects and psychosocial needs.
11. **Alkylating agent:** a class of chemotherapy that directly damages DNA.
12. **Anthracycline:** a class of chemotherapy that intercalates into DNA and inhibits replication enzymes, associated with cardiotoxicity.

Concept Check Questions [Series 5]

Objective questions

- Chemotherapy works principally by targeting rapidly _____ cells.
- Blood counts typically reach their lowest point, or _____, at a predictable interval after chemotherapy.
- Febrile neutropenia requires prompt assessment and immediate empirical broad-spectrum _____ therapy.
- Many childhood cancers are now associated with cure rates exceeding _____ percent in settings with modern treatment.
- Cardiotoxicity from anthracycline chemotherapy may not become clinically apparent for _____.

Short-answer questions

1. List four major classes of chemotherapy agents and their general mechanism.
2. Describe the immediate management of febrile neutropenia.
3. List two components of psychosocial support in paediatric oncology.
4. List three factors that influence prognosis in childhood cancer.
5. List four organ systems that can be affected by late effects of childhood cancer treatment.

Long-answer questions

6. Discuss the general principles, classes, and side effects of chemotherapy in paediatric oncology. (Linked to SLO 5.1, SLO 5.2)
7. Discuss the principles of supportive care in paediatric oncology. (Linked to SLO 5.3, SLO 5.4)
8. Discuss the factors influencing prognosis and the complications of childhood cancer. (Linked to SLO 5.5, SLO 5.6)
9. Discuss the late effects of childhood cancer treatment. (Linked to SLO 5.7)
10. Discuss the approach to long-term follow up and survivorship care. (Linked to SLO 5.8)

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Answers to Concept Check Questions [Series 5]

Objective questions

11. Dividing.
12. Nadir.
13. Antibiotic.
14. 80.
15. Years.

Short-answer questions

16. Alkylating agents damage DNA, antimetabolites interfere with DNA synthesis, anthracyclines inhibit replication enzymes, and vinca alkaloids disrupt microtubules.
17. Prompt assessment, blood cultures, and immediate empirical broad-spectrum antibiotic therapy.
18. Psychology services and child life specialists are components of psychosocial support.
19. Tumour type, stage at diagnosis, and response to initial treatment influence prognosis.
20. The heart, endocrine system, nervous system, and reproductive system can be affected by late effects.

Long-answer questions

21. **Basic response:** Chemotherapy targets rapidly dividing cells using combination regimens from classes including alkylating agents, antimetabolites, anthracyclines, and vinca alkaloids.

Value-added response: Common side effects include myelosuppression, mucositis, and alopecia, with blood counts reaching a predictable nadir after treatment.

22. **Basic response:** Supportive care includes infection prevention and management, transfusion support, nutritional support, and psychosocial support throughout treatment.

Value-added response: Febrile neutropenia is a medical emergency requiring prompt blood cultures and immediate empirical antibiotics given the risk of rapid deterioration.

23. **Basic response:** Prognosis depends on tumour type, stage, treatment response, and access to timely diagnosis and complete treatment.

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Value-added response: Complications include direct tumour effects, metabolic derangement, and treatment-related toxicity, with outcomes improved but unevenly distributed globally.

24. **Basic response:** Late effects, including cardiotoxicity, growth and endocrine effects, neurocognitive effects, and secondary malignancy, become apparent months to years after treatment.

Value-added response: The specific pattern of late effects depends on the treatment received, meaning surveillance is individualised for each survivor.

25. **Basic response:** Long-term follow up includes structured clinical assessment, targeted screening for relevant late effects, and ongoing psychosocial support.

Value-added response: Involving the survivor themselves as they mature empowers active participation in lifelong health monitoring, completing comprehensive survivorship care.

Answers to Pilot Questions [Series 5]

Part 5.1

1. Chemotherapy exploits the high proliferation rate of cancer cells relative to most normal tissue.
2. Combination chemotherapy maximises tumour cell killing through complementary mechanisms and reduces resistance risk.
3. Alkylating agents damage DNA, antimetabolites mimic building blocks, anthracyclines inhibit replication enzymes, and vinca alkaloids disrupt microtubules.
4. Nausea, vomiting, mucositis, and alopecia are common acute side effects.
5. Nadir is the lowest point of blood counts after chemotherapy, guiding anticipatory monitoring for complications.

Part 5.2

6. Immunosuppression from the malignancy and its treatment increases susceptibility to serious infection.
7. Prompt assessment, blood cultures, and immediate empirical broad-spectrum antibiotics are required.

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8. Red cell transfusion is used for significant anaemia; platelet transfusion for significant thrombocytopenia with bleeding risk.
9. Support ranges from dietary advice through nasogastric feeding to parenteral nutrition as needed.
10. Psychology services and child life specialists are examples of psychosocial support.

Part 5.3

11. Tumour type, stage at diagnosis, and response to treatment are factors influencing prognosis.
12. Delayed diagnosis or incomplete treatment can result in poorer outcomes even for treatable tumours.
13. Direct tumour effects and treatment-related toxicity are types of complications that can occur.
14. Outcomes have improved dramatically, with cure rates now exceeding 80 percent in many settings.
15. Differences in access to diagnosis, treatment, and supportive care explain persisting outcome gaps.

Part 5.4

1. Late effects become apparent months to years after treatment, unlike acute, treatment-phase complications.
2. The specific late effect risk depends on the individual treatment received by that survivor.
3. The heart, endocrine system, nervous system, and reproductive system can be affected.
4. Regular clinical assessment, targeted screening, and ongoing psychosocial support are key components.
5. It empowers the survivor to actively participate in their own lifelong health monitoring.

References and Attributions [Series 5]

1. Kliegman, R. M., St Geme, J. W., Blum, N. J., Shah, S. S., Tasker, R. C. and Wilson, K. M. (2020). Nelson Textbook of Pediatrics (21st ed.). Elsevier.
2. Lackner, H. et al. (2021). Supportive care in paediatric oncology. In Nelson Textbook of Pediatrics (21st ed.). Elsevier.

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3. Children's Oncology Group (2018). Long-Term Follow-Up Guidelines for Survivors of Childhood, Adolescent, and Young Adult Cancers.
4. Robison, L. L. and Hudson, M. M. (2014). Survivors of childhood and adolescent cancer: life-long risks and responsibilities. Nature Reviews Cancer, 14(1), 61 to 70.

Figures, Plates, Tables, and Boxes

1. Figure 5.1: A nurse preparing and checking chemotherapy medication before administration. AI-generated using the prompt: "A professional clinical illustration of a nurse in protective equipment carefully checking a chemotherapy infusion bag against a prescription chart in a hospital pharmacy area. Single clean medical illustration, clinical lighting, no text overlays, no multiple panels, accurate and professional depiction."
2. Table 5.2: Key components of supportive care in paediatric oncology. AI-generated using the prompt: "Create a clean reference table titled Key Components of Supportive Care in Paediatric Oncology, listing component and key focus. Simple clinical reference table style with outside border."
3. Figure 5.3: A multidisciplinary paediatric oncology team discussing a child's care plan. AI-generated using the prompt: "A professional clinical illustration of a small multidisciplinary team of two or three healthcare professionals reviewing a chart together in a hospital office setting. Single clean medical illustration, professional lighting, no text overlays, no multiple panels, accurate and professional depiction."
4. Figure 5.4: A young survivor attending a long-term follow-up survivorship clinic visit. AI-generated using the prompt: "A warm, professional clinical illustration of a clinician sitting with a young person and a parent, reviewing a folder of health records together in a calm clinic office. Single clean medical illustration, soft natural lighting, no text overlays, no multiple panels, respectful and accurate depiction."

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