Basic principles and challenges in paediatric Radiotherapy and Chemotherapy

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Roadmap

- Magnitude of problem
- Unique challenges of pediatric radiation oncology
- Personnel and equipment required in an ideal setting
- What best can be done in a resource constrained setting
- Key issues of chemotherapy
- Psychosocial support and rehabilitation

CHILDREN ARE NOT LITTLE ADULTS

1. Different and unique exposures
2. Dynamic developmental physiology
3. Longer life expectancy
4. Politically powerless

Cancer in Childhood: Key Facts

- **Approximately 300,000** children aged 0 to 19 years old are diagnosed with cancer each year.[1]

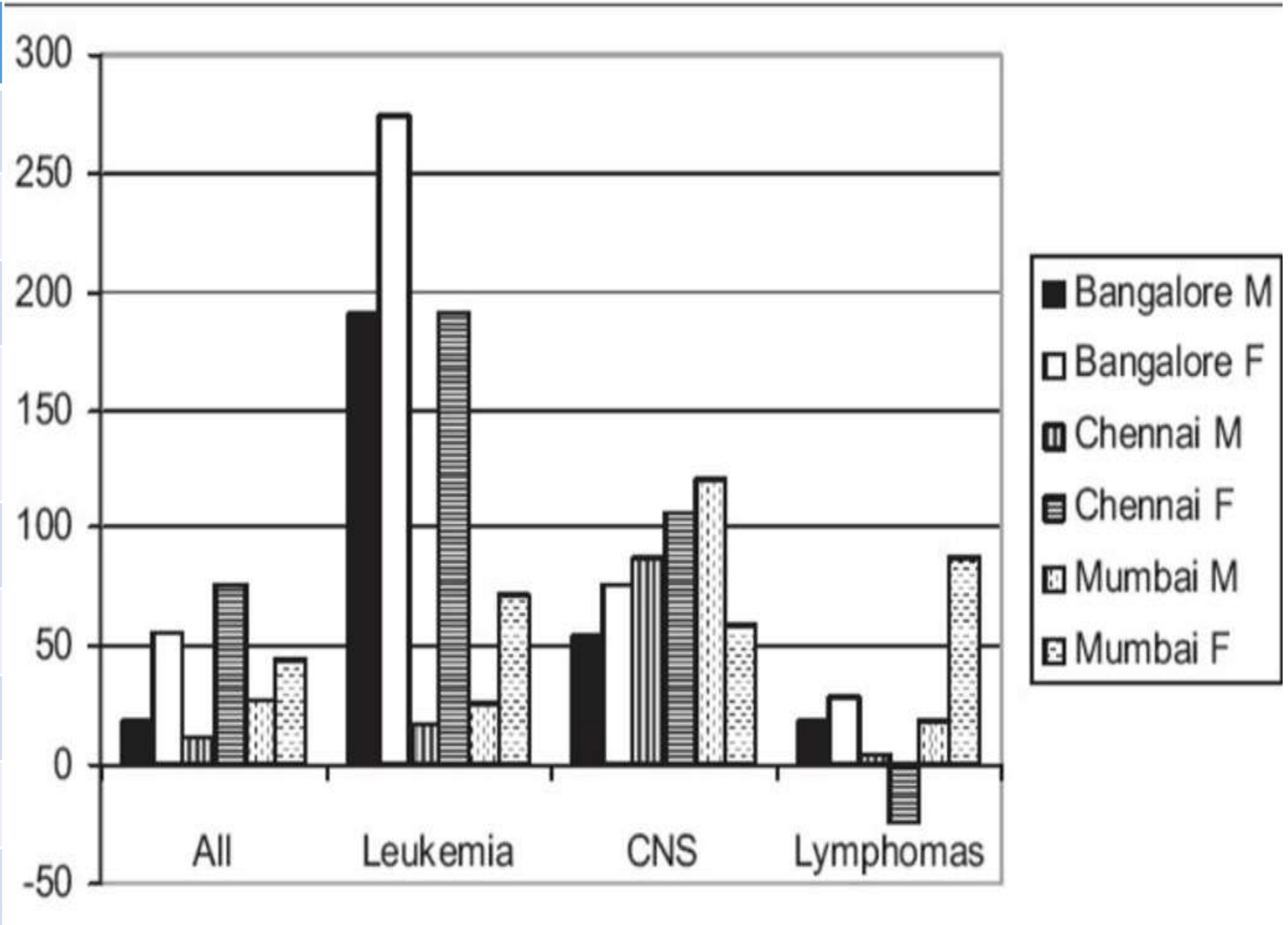
- In high-income countries more than 80% of children with cancer are cured, but in many **low- and middle-income countries (LMICs) only about 20% are cured**.

- Childhood cancer generally cannot be prevented or screened. Improving outcomes for children with cancer requires early and accurate diagnosis followed by effective treatment

- Avoidable deaths from childhood cancers in LMICs result from **lack of diagnosis, misdiagnosis or delayed diagnosis, obstacles to accessing care, abandonment of treatment, death from toxicity, and higher rates of relapse**

Incidence

Cancer	Incidence
Leukemias	32%
CNS tumors	18%
Lymphoma	13%
Bone and soft tissue	12%
Neuroblastoma	8%
Wilms	6%
Retinoblastomas	3%
Hepatic	1%
Germ cell & others	7%



Childhood Cancer Incidence in India

- The overall incidence of pediatric cancer has risen compared to the previous reviews, but the proportion of childhood cancer relative to cancers in all age groups have marginally reduced

- The reported incidence of childhood cancer in males (4-556 pm) is higher than in females (2-309 pm); the ratio being 1.6:1, which is higher than in the developed world (1.2:1), possibly reflecting gender bias in seeking healthcare

- Leukemia remains the most common pediatric cancer for both sexes, followed by lymphoma and CNS tumours in males. However, CNS tumours exceed lymphomas in females.

Das, S., Paul, D.K., Anshu, K. et al. Indian Pediatr (2017) 54: 1033.

Causes for Rising Pediatric Cancer Incidence

- Rapid industrialization and urbanization
- Acquired genetic mutations due to pollution, industrial disasters, rampant insecticides use in the agricultural sector
- Tobacco and gutka addiction among child labourers from lower socio-economic class
- Ozone layer depletion

Global Initiative for Childhood Cancer: WHO Response

- In 2018, WHO launched the Global Initiative for Childhood Cancer with partners to provide leadership and technical assistance to support governments in building and sustaining high-quality childhood cancer programmes

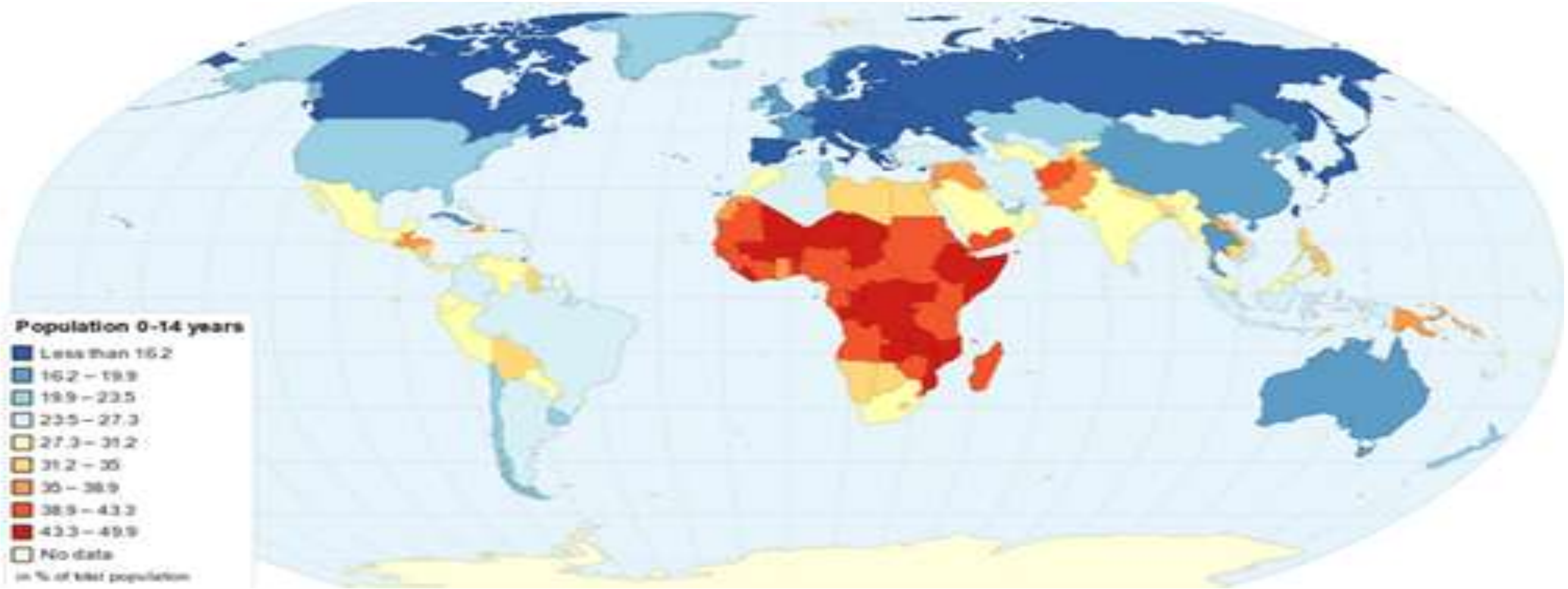
- The goal is to achieve at least 60% survival for all children with cancer globally by 2030

- This represents an approximate doubling of the current cure rate and will save an additional one million lives over the next decade

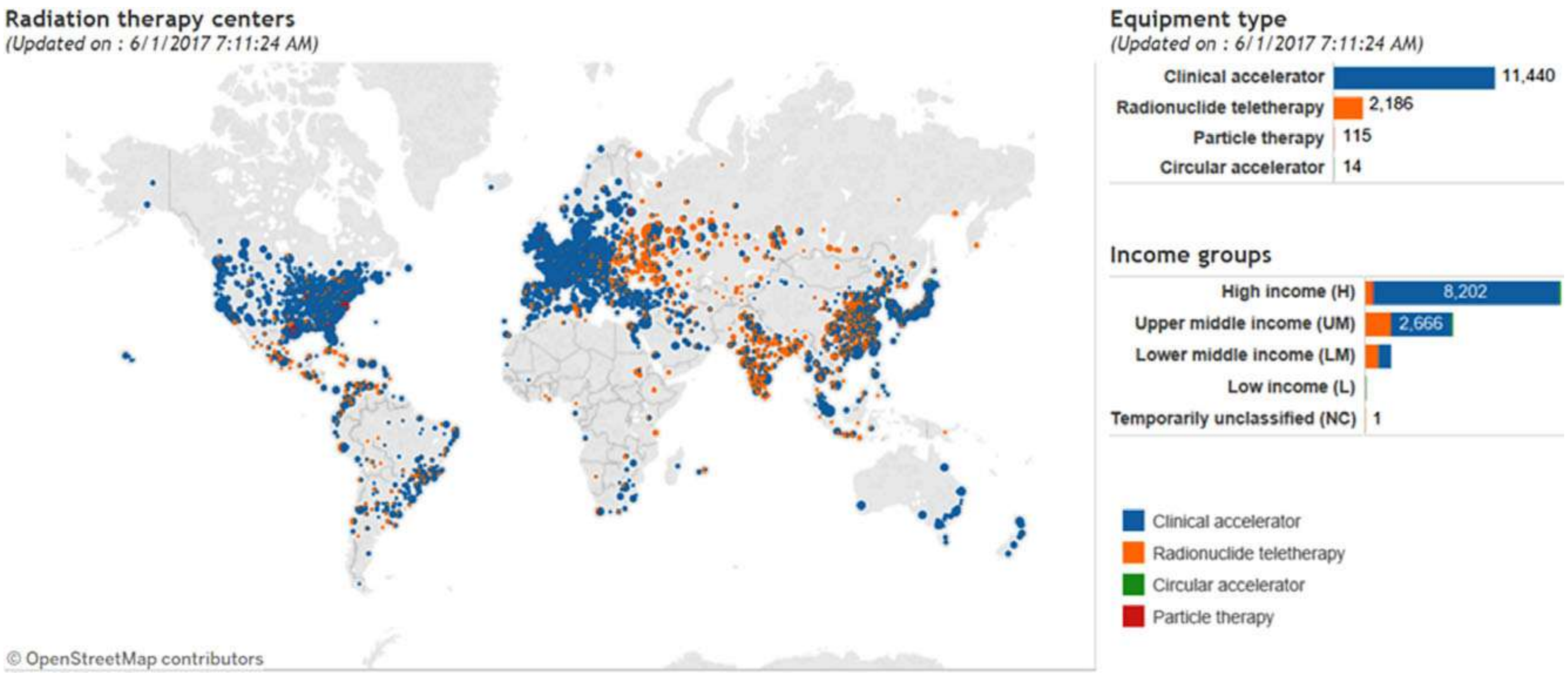
- The objectives are to:

  - Increase capacity of countries to deliver best practices in childhood cancer care
  - Prioritize childhood cancer and increase available funding at the national and global levels

Recommendations for the treatment of children with radiotherapy in low- and middle-income countries (LMIC): A position paper from the Pediatric Radiation Oncology Society (PROS-LMIC) and Pediatric Oncology in Developing Countries (PODC) working groups of the International Society of Pediatric Oncology (SIOP)



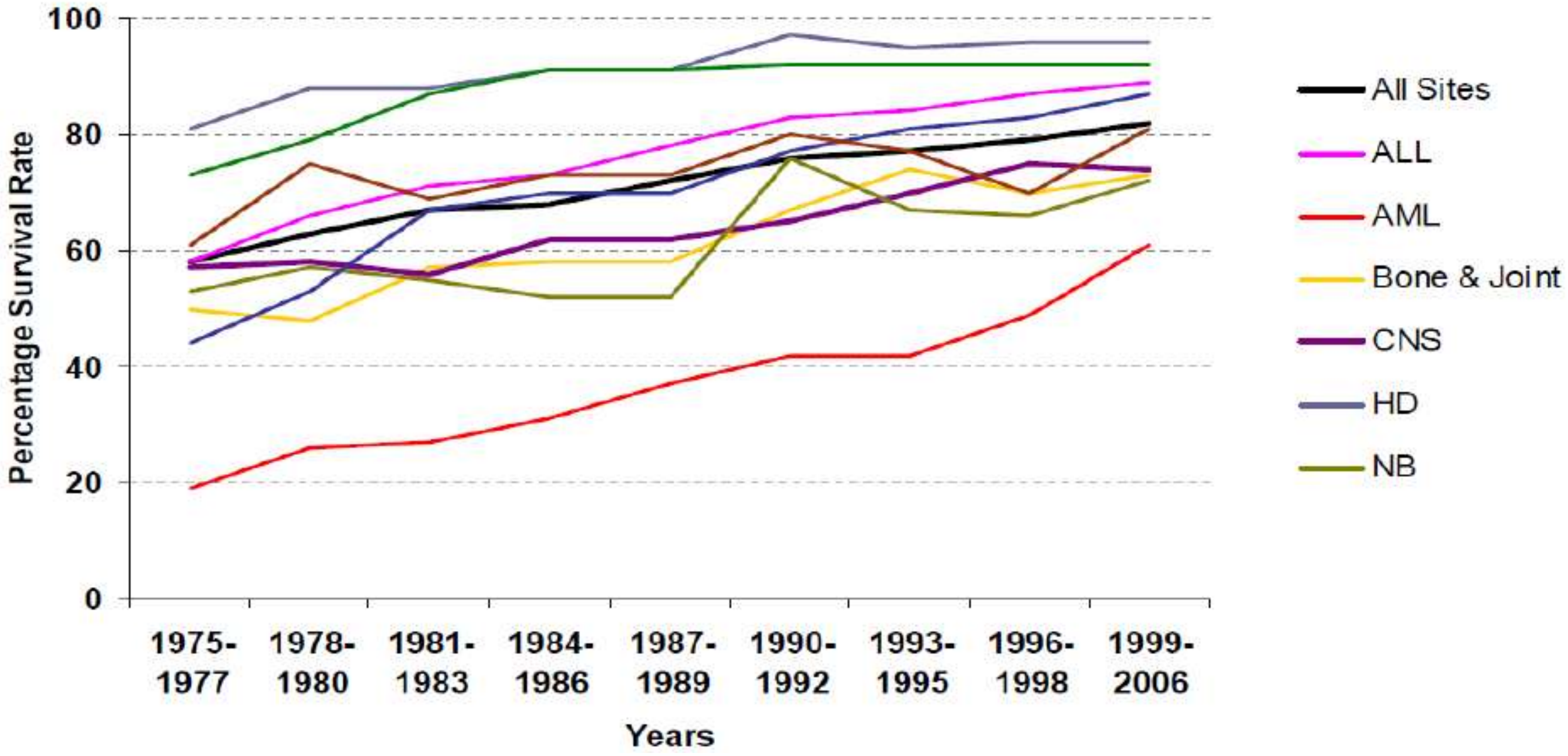
Pediatric Blood & Cancer, Volume: 64, Issue: S5, First published: 03 January 2018, DOI: (10.1002/pbc.26903)



Simple radiotherapy	Complex radiotherapy
Wilms tumor	Rhabdomyosarcoma
Neuroblastoma(low dose)	Neuroblastoma
Leukemia	Brain tumors
Palliative RT	Ewings Sarcoma
Hodgkin Lymphoma (simple field, 2D planning)	Hodgkins Lymphoma(optimal fields3CRT)

	Cobalt	Linac
Energy	Lower than linac, inferior in treating deep seated tumors Minimal electricity requirement for mechanics and control panel	Higher than cobalt, dual energy linacs with a range of electrons can access tumors throughout the body Massive electricity requirement
Dose rate and QA	Dose rate reduces with time due to radioactive decay Monthly calibration No daily checks required	Dose rate is constant Strict daily QA required
Capital cost	Machine cost lower than linac Infrastructure cost less. Shielding requirement and machine footprint much less	Machine cost much higher than cobalt Infrastructure cost much higher. Shielding (especially for high energy beam) is much greater and footprint of machine is much larger
Maintenance and running costs	Expensive source needs to be replaced every 5 years Other costs are much lower than linac	Heat, humidity, electricity, and other conditions affect performance of linac Maintenance and repairs are more difficult and more expensive than cobalt
Safety	Radioactive source poses a problem in the case of an accident Radioactive source may pose a security threat	No risk of radioactive leakage Linacs have several safety control features No radioactive source
Skin dose	40–50%	15–25%
Precision	Larger penumbra, considerable dose reduction near the field edge requiring wider margin	Smaller penumbra. Smaller margins required

Pediatric cancer survival is increasing



Pediatric Radiation Oncology

Pediatric tumors usually develop in a shorter period of time.

The treatment is limited by the fast-growing normal tissues, which are widely susceptible to radiotherapy and chemotherapy, can cause secondary malignancies

Isaac Gordon

First pediatric patient treated for retinoblastoma linear accelerator in 1957

From a radiation perspective…
How do children differ from adults?

- Different diseases
- Survive longer
- Severity of late effects
- Techniques of radiotherapy
- Anesthesia
- Time

Strategies to minimise long term effects of treatment

- Avoidance of radiotherapy altogether (e.g., in patients with low-grade astrocytoma [LGA] for whom surgery alone may be a good option).
- Delay of radiotherapy for young children (i.e., those younger than age 3 to 8)by the use of chemotherapy.
- Use of daily anesthesia, improved immobilization techniques (e.g., rigid casts or a stereotactic frame), and/or daily pretreatment image verification, all of which allow the use of reduced safety margins.
- Use of image-based treatment planning using computed tomography (CT)–MRI or CT–MRI–functional imaging coregistration
- Better treatment planning and delivery techniques

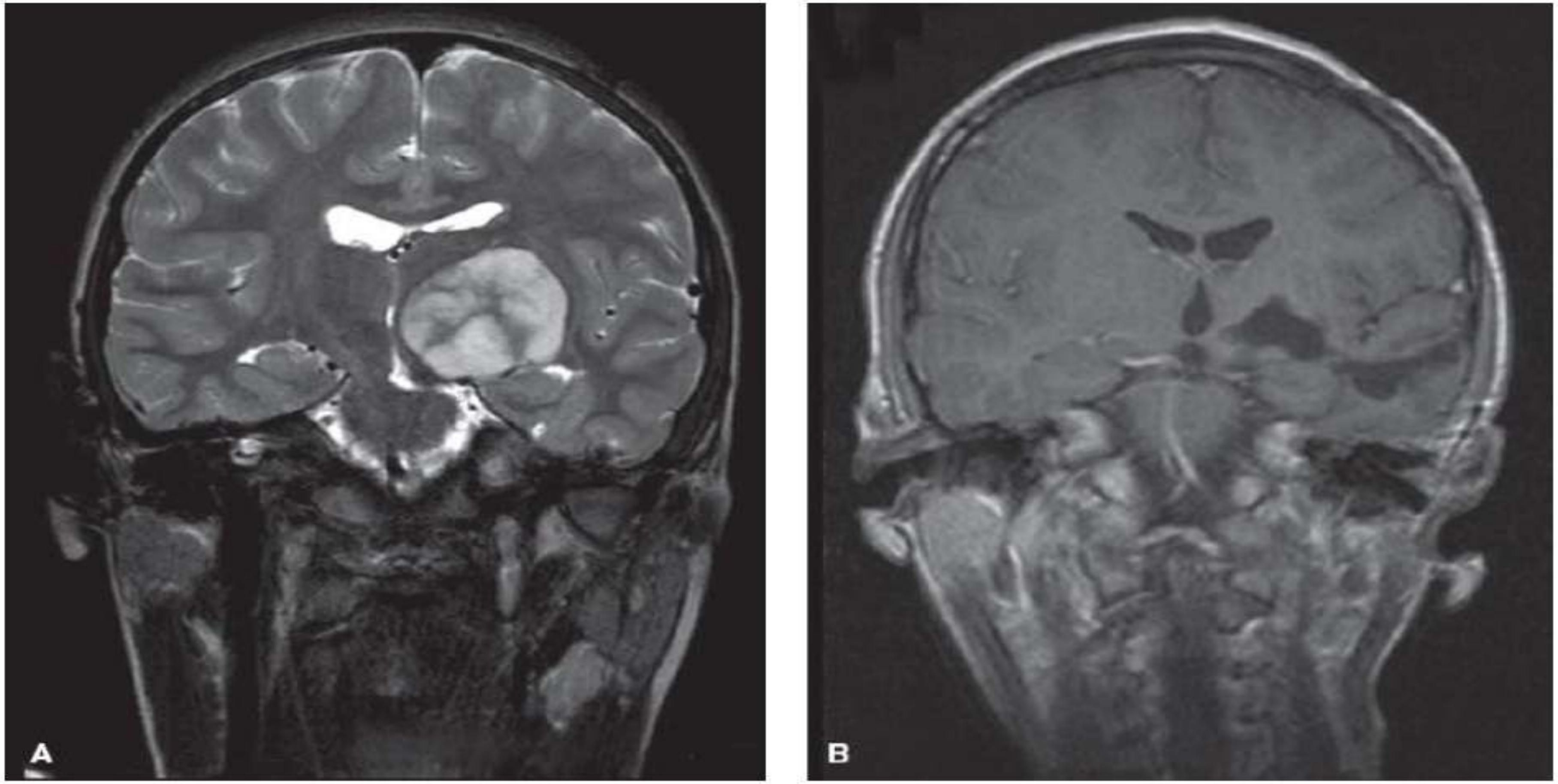
Strategies to minimise long term effects of treatment (cont..)

- Significant increase in the proportion of children with CNS tumors treated by proton therapy.
- Use of reduced radiotherapy target volumes when it is shown safe to do so (e.g., tumor bed rather than whole posterior fossa for the boost in standard-risk medulloblastoma).
- Reduction of radiotherapy dose (e.g., in young patients with standard-risk medulloblastoma for whom in the North American studies the dose for craniospinal irradiation [CSI] has been reduced progressively from 35 to 36 Gy to 23.4 Gy and, in current studies, to 18 Gy for children younger than 8).
- Use of smaller fraction sizes where appropriate (e.g., 1.5 Gy/day for patients with radiosensitive tumors such as germinoma).
- Use of hyperfractionated radiotherapy (HFRT) (e.g., as in the current European studies for standard-risk medulloblastoma).
- Delivering dose with fewer non-coplanar beams could be better.

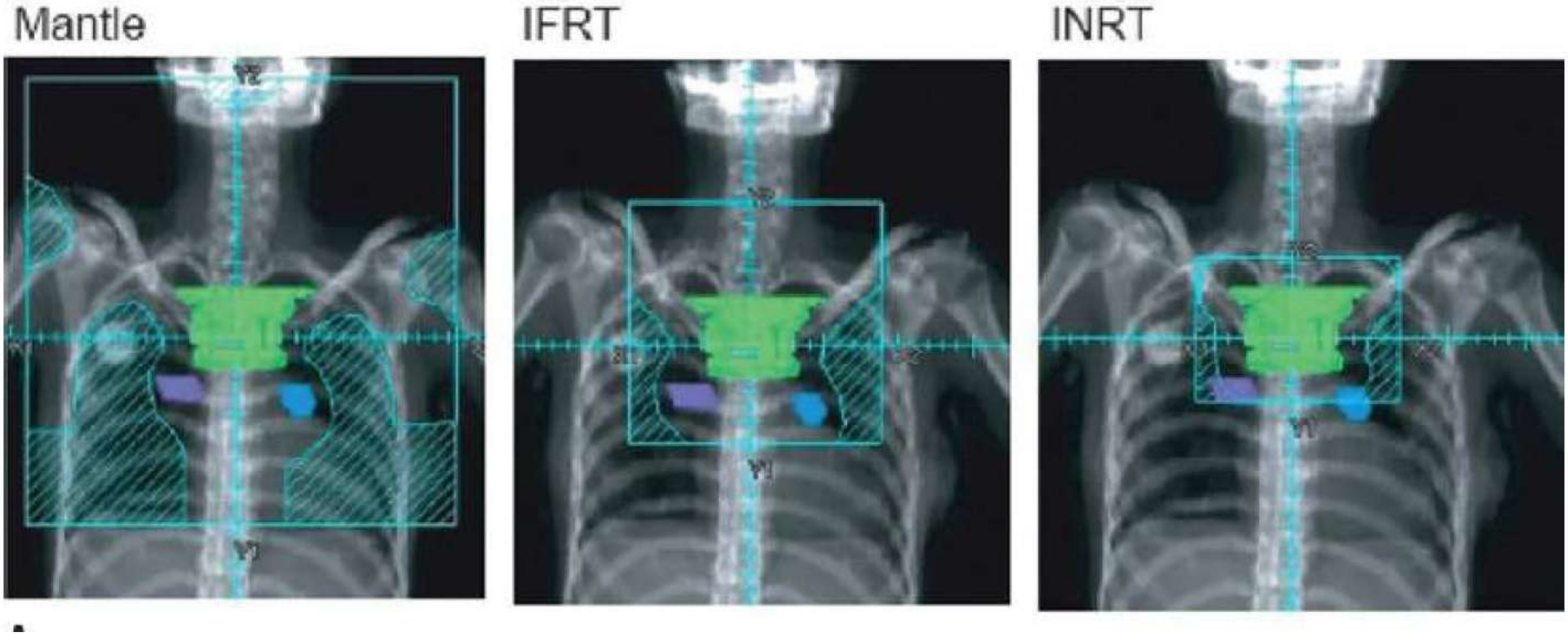
Treatment intensification / deescalation

- The challenge is to optimally balance treatment intensity with its attendant toxicity
- Focus on intensification of therapy in children with unfavorable prognosis, refine and even deescalate treatment in children with a favorable prognosis.
- Early response to therapy as a tool to identify patients with more sensitive disease in whom therapy can be reduced.
- Modern imaging techniques, effective use of chemotherapy allow a more restrictive role for radiotherapy.
- Recognition of the long-term sequelae of therapy has led to the refinement of both chemotherapy and radiation therapy (RT) strategies.

JPA In a 12 Year Old Treated with Chemotherapy Followed by Complete Resection



Perez and Brady 7th edition



Girl with stage I hodgkins lymphoma. DRR shows reduced dose to bilateral lungs and breasts with evolution of RT

Perez and Brady 7th edition

Multidisciplinary Teams

- **Diagnosis :**
  - Oncologist.
  - Radiologist
  - Pathologist

- **Treatment** :
  - A dedicated oncology team comprising radiation, medical, surgical oncologist,consultant anaesthetic , anaesthetic staff radiotherapy physics staff, therapeutic radiographer,dietician and oncology nurse experienced in handling pediatric cancer patients

- **Psychosocial support:**
  - Treating oncologist.
  - Play specialist, activity coordinator/ youth worker, psychological service specialist/ social worker

Multi disciplinary team

- Planning and delivery of radiotherapy for children with tumors are technically challenging and labor intensive for the entire team.

- The expertise of specialist personnel such as pediatric nurses and play therapists can be pivotal in encouraging a young for immobilization and treatment.

- For children younger than age 4 or 5 years, daily anesthesia will almost always be necessary, and this will require a skilled pediatric anesthetist

Pediatric Radiation Oncology

Definitions of clinical states of sedation, proposed by the American Society of Anesthesiologists

Sedation Level	Characteristics
Minimum level of sedation/anxiolysis	Drug-induced state during which patients respond normally to verbal commands. Cognitive function and coordination may be affected. Ventilatory and cardiovascular functions are unaffected
Moderate sedation / analgesia	Decreased consciousness induced by drugs, during which patients respond purposefully to verbal, either alone or accompanied by tactile stimulation. No interventions are required to maintain a patent airway, and spontaneous ventilation is adequate. Cardiovascular function is usually maintained.
Deep sedation / analgesia	Decreased consciousness induced by drugs, during which patients cannot be easily aroused, responding to repeated or painful stimulation. The ability to independently maintain ventilatory function may be impaired. Patients may need help maintaining a patent airway, and spontaneous ventilation may be inadequate. Cardiovascular function is usually maintained.
General Anesthesia	Loss of consciousness induced by drugs during which the patients are not excitable, even by painful stimuli. The ability to independently maintain ventilatory function is affected. Patients often need help maintaining airway and positive pressure ventilation may be required because of depressed spontaneous ventilation or depression drug induced neuromuscular function. Cardiovascular function may be affected.

Sedation vs. Anesthesia

- Who needs it?
  - Anyone who can’t lie still!
    - Almost all kids < 5 years old
    - Most kids 5-6 yrs old
    - A few kids > 6 yrs
- Maximum sedation is necessary for cast making/planning
- Less sedation may be possible at subsequent treatment dates.
- Anesthesia is seldom easily available
- Better idea to use short acting agents such as propofol

Challenge in Pediatric Radiation Oncology: Immobilization

- The child's cooperation depends on several factors: age, previous experience, understanding, position during treatment and duration

- Some children require sedation/general anesthesia for simulation and treatment

- Qualified personnel, equipment and areas to do it properly

- Extensive pretreatment counseling and demonstration of the treatment procedure ensuring comfort may lead to avoidance of sedation / anaesthesia

Personal vacuum filled mattress

Treatment with thermoplastic mask

Quality of Radiotherapy Determines the Quality of Life for Long Term Survivors

- Evidence based protocols
- Quality management program
- Audit outcomes
- Referral

Key areas in discussing late effects

1. Effects on sexual and reproductive function (ways to mitigate these)
2. Neurocognitive defects
3. Hormonal deficiencies and the need for hormone replacement therapy
4. Effect on bone and soft tissue growth
5. Effect on vision and hearing
6. Risk of second malignancies
7. Risk of vascular complications

Principles of chemotherapy

- Combination chemotherapy either alone or in combination with surgery and radiotherapy
- Improvements in the outcomes for childhood cancer
- Dose intensity and the optimisation of supportive care
- Targeted anti-cancer drugs+/- conventional agents

Pediatric Patients at Risk For Fever in Chemotherapy Induced Neutropenia

- Febrile neutropenia (FN) is the most frequent potentially life-threatening complication of chemotherapy in children and adolescents with cancer

- 50% patients- at least one FN episode

- prophylactic antibiotics and granulocyte colony-stimulating factor

- The current standard therapy for FN includes emergency hospitalization and empirical administration of intravenous broad-spectrum antibiotics

Metabolic Changes in Children that Received Chemotherapy

- depend on the patient characteristics, type of chemotherapy and cumulative dose

- Chemotherapy drugs may injure endocrine cells and glandular functions deregulated, interact with receptors or second messengers, can compete for binding sites on carrier proteins.

- may lead to hormone deficiencies, changes in insulin sensitivity, lipid metabolism, inflammatory mediators, and adipokines

- The long-term effects that have been described are reduced growth, obesity, decreased fertility, high blood pressure, cardiovascular diseases, impaired glucose, and another form of cancer, endocrine deficiencies and organ dysfunction

Pediatric chemotherapy induced peripheral neuropathy

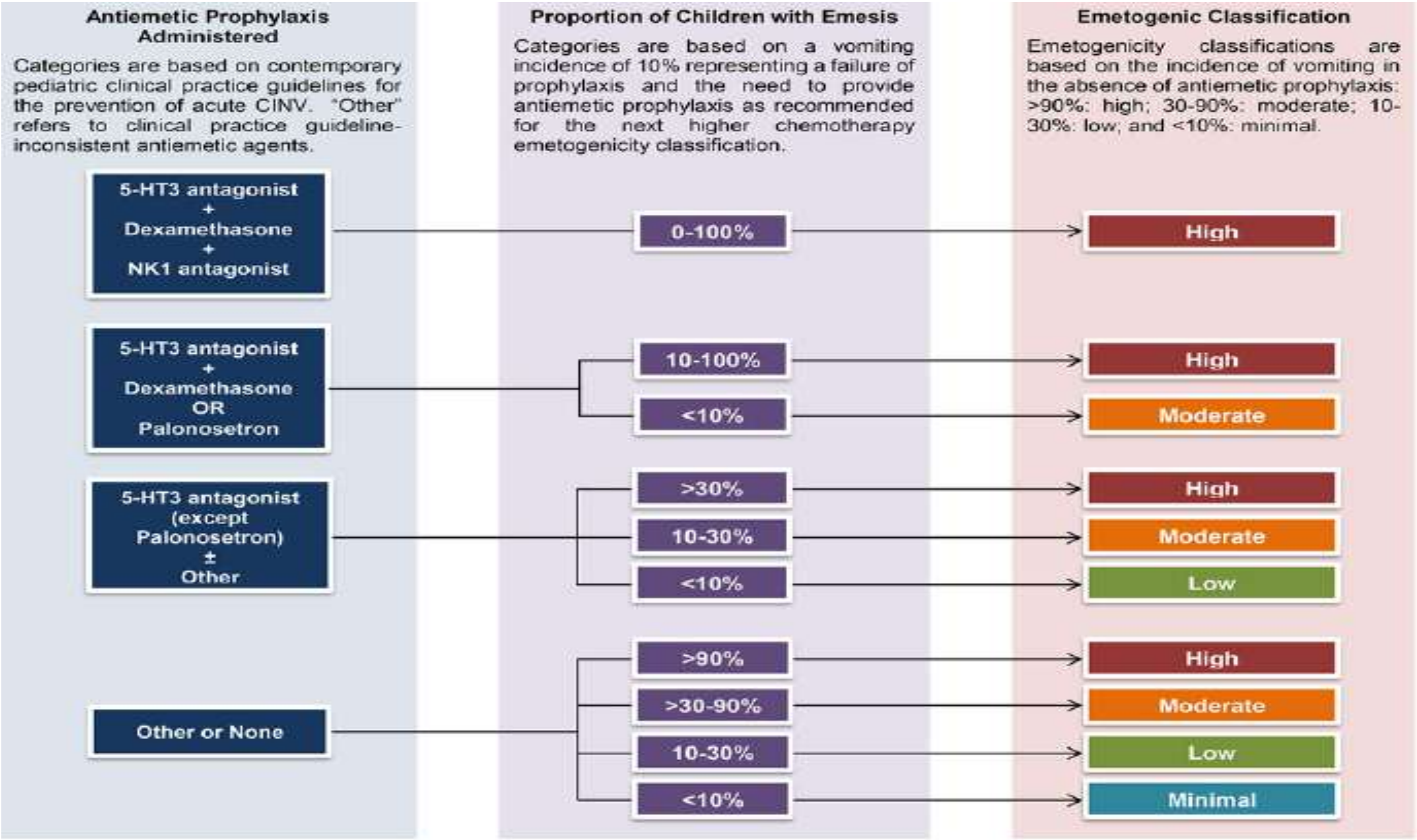
- CIPN is common and can be long lasting.
- Characteristics and natural history of neuropathy are specific to the chemotherapy agent..
- Risk factors for CIPN may be disease, treatment or patient related

Chemotherapy-induced nausea and vomiting (CINV)

- Chemotherapy-induced nausea and vomiting (CINV) remain clinically important treatment-related adverse effects for children and adolescents with cancer

- For chemotherapy-naïve pediatric patients, the inherent emetogenicity of the chemotherapy deciding factor for the CINV prophylaxis recommended in modern guidelines

Chemotherapy Emetogenicity Classification Algorithm



Collins’ Law

- Pertains to maximum length of follow up needed for pediatric patients
- Period of risk for recurrence (age at diagnosis + 9 months[gestational period])
- If tumor was present in utero, then age at diagnosis + 9 months determines rate of growth for it to become clinically evident.
- Residual disease should become evident in the same time frame.

Sure U, Clin Neurol neurosurg 1997

Most beautiful smile!

Thank you