Follow Up in Pediatric Patient

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Follow Up in Pediatric Patients

- For children and adolescents, focusing on the cure of cancer cannot be the only end-point today.
- Because of their young age and life-expectancy, the late sequelae of therapies will probably have effects on their lives and families.
- Health care providers must educate and follow these survivors to ensure a better quality of life.
• CHILDHOOD CANCERS ARE 1-2% OF ALL CANCERS
  ➢ 50% of childhood and adolescent cancers are acute leukemia and cancers of CNS
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- **0-2 yrs**: neuroblastoma, nephroblastoma, retinoblastoma
- **3-5 yrs**: acute leukemia, soft tissues sarcomas
- **5-9 yrs**: central nervous system cancers and lymphomas
- **10-15 yrs**: Hodgkin’s lymphoma, bone sarcomas and soft tissue sarcomas that are still present in adolescents and young adults

More in: J Adolesc Health 2003; 32:405-415
Figure 5: Age-adjusted incidence rates for childhood cancer by ICCC group, age <20, all races both sexes, SEER, 1975-95

*Adjusted to the 1970 US standard population
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Distinct subgroups with respect to:

- cancer type
- biological features
- response to treatment
- long term outcomes
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- Over the past 30 years the survival rate has improved, despite the fact that cancer still remains the most common cause of disease-related mortality

- 5 yrs SURVIVAL
  - 65 % in 1983-85
  - 75 % in 1992-1994

Gatta G, JCO 23; 3742-375
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Currently about 80% of children and adolescents will survive ≥5 year beyond their diagnosis and this group will become “long-term survivors”
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- 1 out of 350 people under the age of 20 years has cancer

- 80% are cured

- 1 out of 700 people is a childhood cancer survivor
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- At present there are approximately 300,000 to 500,000 survivors of childhood cancer in Europe.
- For some survivors follow up and medical care are life-long.
- For others there is little long-term risk.
• The vast majority of these cancer survivors will have at least one chronic health condition by the age of 40 yrs

• Survivorship studies conducted have provided us information on long-term intellectual function, organ toxicity, reproductive outcomes, second cancers, late mortality, and disparities in outcomes
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- 45 years from diagnosis:
  - the risk of death is 3 time greater compared to general population
  - the risk increases with ageing without reaching a plateau

Mertens 2008
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- 60 - 75% of survivors have at least one late effect
- 20 - 30% have a severe/life threatening late effects

- Many studies show that screening identifies a substantial proportion of survivors with previously unrecognized treatment-related complications
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Some of these undiscovered late sequelae may benefit from treatment or preventive interventions

- i.e. heart valve disorders or hypothyroidism
The goal of the follow up is to decrease the morbidity related to cancer treatment, and improve the overall quality of life, so that cancer survivors can successfully integrate back into society and lead productive lives.
St Jude Lifetime cohort: the estimated cumulative prevalence among 1713 adult survivors who completed a 2-3 days evaluations:

- 95% would develop at least one chronic health condition by 45 yrs of age
- 80% would develop a serious or life threatening health condition by 45 yrs of age
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- The data suggested a premature ageing as a consequence of therapies that are used to cure childhood cancer.
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- Survivors have a high risk of **early mortality** from subsequent cancers, cardiac events and pulmonary conditions.
  
  - Only 35% of survivors are aware of their risk.
  - Only 20% have a regular follow up and screening.
The ideal approach to survivors’ care involves a risk-based model that incorporates routine health care and a personalized plan of surveillance and prevention.
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Specific interventions may include social, behavioural and/or pharmacological approaches

- **Changes** in health behaviours (diet, exercise, tobacco use, compliance with recommended screening)

- **Amelioration** of adverse health outcomes

- **Promotion** of positive social and quality of life outcome (education, employment...)
Optimal health screening has not been defined yet

- When to initiate?
- Frequency?
- The most and cost-effective modality?
- The overall risk-benefit?
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- CONTROLLED POPULATION
- HUGE BENEFITS
- HIGH COSTS
- TO BE INCLUDED IN THE HEALING “BUDGET
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WHO SHOULD SHOULDER THE BURDEN OF DIAGNOSIS AND TREATMENT?
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- Potential **barriers** can affect survivors’ access to follow-up

- **Barrieres related to survivors, health care providers or environment**
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- **Survivors**: lack of knowledge regarding cancer treatment history and its associated long term risk

  - Educational process for survivors:
    - definition of the effective and efficient methods of health risk counselling
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- **Providers:** lack of knowledge regarding late effect and the need of follow up
  - Education and training programmes related to survivorship care for health professionals,
  - Dissemination of recommendations and guidelines,
  - Communication between pediatric oncologists and GPs
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- **Environment**: survivorship has not yet recognized as a potential health disorder
  - Who pay for?
  - Who has the responsibility of their follow up and screening?
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- The first generation of childhood cancer survivors is now aging into their fourth and fifth decades of life.
- The problem of transition from a model of care pediatric-based to a medical care adult-based.
  - Who is the referring physician?
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- Pediatric cancer survivors are rare in primary care practices
- Most GPs lack knowledge about their complications
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- Improve communication between the cancer center that provided acute care for the patient and the GPs or community follow-up care.
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- Despite the fact that causes may be multifactorial, it is treatment-specific factors that determine the risk of late effects.
- Characterizing highest-risk survivors and targeting them for intervention-strategies is essential.
# RADIOTHERAPY and LATE EFFECTS

## Table 1 | Selected examples of established radiation-associated late effects

<table>
<thead>
<tr>
<th>Radiation exposure</th>
<th>Established late effects</th>
<th>Refs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular</td>
<td>* Cardiomyopathy&lt;br&gt;  * Carotid and subclavian artery disease&lt;br&gt;  * Coronary artery disease&lt;br&gt;  * Dyssrhythmias and conduction disorders&lt;br&gt;  * Heart valve abnormalities&lt;br&gt;  * Pericardial fibrosis and pericarditis</td>
<td>26–29</td>
</tr>
<tr>
<td>Central nervous system</td>
<td>* Neurocognitive deficits, including learning deficits and diminished intelligence quotient, executive function, sustained attention, memory processing speed and visual–motor integration&lt;br&gt;  * Cerebrovascular disease, including stroke, moyamoya and occlusive cerebral vasculopathy&lt;br&gt;  * Clinical leukoencephalopathy, which causes spasticity, ataxia, dysarthria, dysphagia, hemiparesis and seizures&lt;br&gt;  * Neurological and neurosensory deficits</td>
<td>30–32, 56–61</td>
</tr>
<tr>
<td>Endocrine</td>
<td>* Pituitary dysfunction, including altered pubertal timing; growth hormone, TSH, ACTH, LH and FSH deficiency; altered body composition (reduced lean muscle mass, overweight and obesity); metabolic syndrome&lt;br&gt;  * Thyroid abnormalities, including hypothyroid, hyperthyroid and thyroid nodules&lt;br&gt;  * Diabetes mellitus</td>
<td>33–38</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>* Oesophageal stricture&lt;br&gt;  * Chronic enterocolitis&lt;br&gt;  * Bowel obstruction&lt;br&gt;  * Gastrointestinal fistula or stricture</td>
<td>39</td>
</tr>
<tr>
<td>Reproductive system (females)</td>
<td>* Uterine vascular insufficiency that predisposes to spontaneous abortion, neonatal death, infants who have low birth weights, foetal malposition and premature labour&lt;br&gt;  * Ovarian dysfunction that results in delayed or arrested puberty, premature menopause and infertility</td>
<td>15, 42–44</td>
</tr>
<tr>
<td>System</td>
<td>Late Effects</td>
<td>References</td>
</tr>
<tr>
<td>-------------------------------</td>
<td>-------------------------------------------------------------------------------------------------</td>
<td>------------</td>
</tr>
<tr>
<td>Reproductive system (males)</td>
<td>- Leydig cell dysfunction that results in delayed or arrested puberty and androgen insufficiency</td>
<td></td>
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<tr>
<td></td>
<td>- Germ cell failure, oligospermia, azoospermia and infertility</td>
<td>40,41</td>
</tr>
<tr>
<td>Hepatobiliary</td>
<td>- Hepatic fibrosis</td>
<td>45</td>
</tr>
<tr>
<td>Musculoskeletal</td>
<td>- Hypoplasia and fibrosis</td>
<td>53–55</td>
</tr>
<tr>
<td></td>
<td>- Reduced or uneven growth (resulting in shortened trunk height, limb length discrepancy and kyphoscoliosis)</td>
<td></td>
</tr>
<tr>
<td>Pulmonary</td>
<td>- Pulmonary fibrosis</td>
<td>46–49</td>
</tr>
<tr>
<td></td>
<td>- Interstitial pneumonitis</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Restrictive lung disease</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Obstructive lung disease</td>
<td></td>
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<tr>
<td>Urinary tract</td>
<td>- Bladder fibrosis</td>
<td>50–52</td>
</tr>
<tr>
<td></td>
<td>- Dysfunctional voiding</td>
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<tr>
<td></td>
<td>- Vesicoureteral reflux</td>
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<td></td>
<td>- Hydronephrosis</td>
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<tr>
<td></td>
<td>- Renal insufficiency</td>
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<td></td>
<td>- Hypertension</td>
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<tr>
<td>Any organ system</td>
<td>Subsequent neoplasms, including those of the skin (predominantly basal cell carcinoma), breast, thyroid, bone and brain. Increasing amounts of data indicate a risk of radiation-associated colorectal cancers</td>
<td>62–73, 75,76</td>
</tr>
</tbody>
</table>

ACTH, adrenocorticotropic hormone; FSH, follicle-stimulating hormone; LH, leutinizing hormone; TSH, thyroid-stimulating hormone.
# CHEMOTHERAPY and LATE EFFECTS

<table>
<thead>
<tr>
<th>Class of chemotherapy</th>
<th>Chemotherapeutic agents</th>
<th>Established late effects</th>
<th>Refs</th>
</tr>
</thead>
</table>
| Alkylating agents     | Busulfan, carboplatin, carmustine, chlorambucil, cisplatin, cyclophosphamide, ifosfamide, lomustine, mechlorethamine, melphalan, procarbazine and thiopeta; plus the non-classical alkylators decarbazine and temozolomide | * Secondary myelodysplasia or acute myeloid leukaemia  
* Gonadal dysfunction and infertility  
* Pulmonary fibrosis (after exposure to busulfan, carmustine or lomustine)  
* Urinary tract abnormalities (after exposure to cyclophosphamide or ifosfamide)  
* Renal dysfunction (after exposure to cisplatin, carboplatin and ifosfamide)  
* Ototoxicity (after exposure to cisplatin or very high doses of carboplatin)  
* Dyslipidemia (after exposure to cisplatin) | 41,42, 46,51, 52, 84–87 |
| Anthracyclines        | Daunorubicin, doxorubicin, epirubicin and idarubicin | * Left ventricular dysfunction  
* Cardiomyopathy  
* Dysrhythmias | 29,88, 89 |
| Corticosteroids       | Dexamethasone and prednisone | * Reduced bone mineral density  
* Osteonecrosis  
* Cataracts | 60,90, 91 |
| Vinca alkaloids       | Vinoreistine and vinblastine | Peripheral sensory and motor neuropathy | 92,93 |
| Antimetabolites       | Methotrexate | * Neurocognitive impairment  
* Leukoencephalopathy  
* Liver dysfunction  
* Renal toxicity  
* Decreased bone mineral density | 45,51, 61,90 |
| Epipodophyllotoxins   | Etoposide and teniposide | Acute myeloid leukaemia | 86 |
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- Metabolic syndrome
- Oral and dental late effects
- Haesthetic and cosmetic effects
Psychological and quality of life outcomes

- Educational and occupational attainments, probability of marriage, depression, anxiety, somatic distress, post-traumatic distress, fatigue, pain

- Care providers should consider not only medical effects but also psychological sequelae and mental health
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- Knowledge of long-term adverse effects associated with RT and CT has greatly increased
- RT\(\rightarrow\) Radiation source, cumulative dose, volume and fractionation, sex and age, genetic predisposition
- CT\(\rightarrow\) cumulative dose, scheduling, route of administration, sex and age, genetic predisposition
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- Even Surgery could have a role in long-term adverse effects
  - demolitive surgery, neurocognitive and neuroendocrine or motor sensory deficits, scarring and disfigurement
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• Variable latency of Late Effects and timely preventive and remedial interventions
  ➢ risk of Breast cancer after chest RT with a median time to diagnosis of 15-20 yrs, depending on dose and age and volume
  ➢ recommendations for early BC surveillance
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- Variable latency of Late Effects and timely preventive and remedial interventions
  - cisplatin hearing loss toxicity develops soon after treatment, depending on age, cumulative dose and combination RT
  - monitor of hearing during treatment, modify treatment-strategy, act with remedial interventions to optimize language development and academic achievement
The current knowledge is based on “old” treatment modalities that are modified during the years.
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- Use of **reduction or omission** of cumulative doses of CT and RT
  - i.e. ↓ CNS RT in ALL, ↓ dose and fields of RT in HL, ↓ use of doxorubicin in Wilms Tumor...

- These modifications have **reduced** the treatment burden but **not deleted** the occurrence of life-threatening complications, and their effects on adults have not been established yet

...→ these survivors **still need** follow up
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- Use of treatments’ intensification in selected “High risk group”
  - ie. Ewing S, Neuroblastoma, Anaplastic Wilms Tumor, metastatic Medulloblastoma...
- These modifications have increased the treatment burden, but their effects on adults have not been established yet

... these survivors must have follow up
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... → and further research is needed!!
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• Specific professionals are needed and a team approach should be warranted

• The knowledge of the effects of RT and CT together with previous medical history are essential for professionals
TEAM Approach

Pediatric Onco-hematologist
Psychologists, Psychiatrics
Physiatrics and Ortopedics
Endocrinologists, gynecologist
Radiotherapists and Medical Oncologist
FOLLOW UP
Neuroradiologist, Neurologist
Surgeons
Endocrinologists, gynecologist
Dentists
Cardiologists
Pneumologists
Social workers
mod.da A. Albanese
<table>
<thead>
<tr>
<th>DOSE (Gy)</th>
<th>Endocrine damage</th>
</tr>
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<tbody>
<tr>
<td>&gt;55-70</td>
<td>Increase of PRL Panhypopituitarism</td>
</tr>
<tr>
<td>30-55</td>
<td>Gonadotrophin -releasing hormones deficit</td>
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<tr>
<td>18-24</td>
<td>Neurosecretory disfunction Gonadotropin-Rh Deficit during puberty Precocious puberty GH Deficit</td>
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<tr>
<td>10-15</td>
<td>Neurosecretory disfunctions GH deficit during adulthood</td>
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<tr>
<td>Neurocognitive Domain</td>
<td>Assessment Tools</td>
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<td>---------------------------------------</td>
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<tr>
<td>Global cognitive functioning (IQ)</td>
<td>Griffiths Mental Development Scales (0-8 years)</td>
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<tr>
<td></td>
<td>WPPSI III (2,6-7,3 years);</td>
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<td>WISC III (6-16 years);</td>
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<td></td>
<td>WAIS-R (&gt; 16 years)</td>
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<tr>
<td>Attention</td>
<td>CPT-II</td>
</tr>
<tr>
<td>Memory</td>
<td>Rey-O Memory</td>
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<tr>
<td>Processing speed</td>
<td>WISC III Coding/Symbol Search</td>
</tr>
<tr>
<td>Executive functioning</td>
<td>WCST/MCST</td>
</tr>
<tr>
<td>Psychomotor skills</td>
<td>VMI; Rey-O Copy</td>
</tr>
<tr>
<td>Fine-motor abilities</td>
<td>PPB</td>
</tr>
<tr>
<td>Academic achievement</td>
<td>In English: WIAT-III; WRAT-IV; WJ-III</td>
</tr>
<tr>
<td></td>
<td>In Italian: MT battery for reading, writing and mathematical abilities.</td>
</tr>
<tr>
<td>Function</td>
<td>CHC-Factor</td>
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<tr>
<td>Mental development</td>
<td>G</td>
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<tr>
<td>Fluid intelligence</td>
<td>Gf</td>
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<td></td>
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<tr>
<td>Crystallised intelligence</td>
<td>Gc</td>
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<tr>
<td>Working memory</td>
<td>Gsm</td>
</tr>
<tr>
<td>Visuomotor</td>
<td>Gv</td>
</tr>
<tr>
<td>Attention (selective)</td>
<td>Gs (Gsm)</td>
</tr>
<tr>
<td>Fine motor / Dexterity</td>
<td>Gp</td>
</tr>
<tr>
<td>Total time</td>
<td></td>
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</tbody>
</table>


2 Can be explained in terms of general intelligence.
NEW CONCERNS:

✓ risk of over-medicalization

IMPORTANT: avoid creating anxiety, and, unless within research projects, stick to directions based on scientific evidence
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Children’s Oncology Group …”avoid over-testing, address potential anxieties, and provide a comprehensive evaluation of the survivor’s health status…”
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- Improvement in survival after childhood cancer has resulted in a growing population of childhood cancer survivors

- There is now the recognition of the need to reduce treatment-related sequelae and optimize the quality of life of children treated for cancer

- The medical community would provide appropriate care to the survivors, and address issues related to the etiology and prevention of long-term sequelae of cancer and its treatment.
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- Several issues need to be improved, such as education of survivors and healthcare providers regarding potential late effects.

- Provision of standardized guidelines for appropriate follow-up of survivors in a setting that is feasible and practical for the cancer survivor.
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The screening and surveillance of at-risk treatment groups can facilitate early detection and timely intervention
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- Devastating aesthetic results do not impact on the mortality of survivors, but surely on their social and emotional lives.

- We need to take care of these aspects.
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Thanks for your attention!