Diagnosing children’s cancers

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Outline

• Introduction
• Epidemiology
• Outcomes
• Leukaemia
• Lymphoma
• Solid tumours
  o CNS tumours
  o Other solid tumours
    • Red Flags
    • Conclusions
Introduction

• **Cancer in childhood is rare:**
  (<1% of all cancers < 15 years; 1% in teenagers/TYA)
  - 1 in 500 children < 15 years (UK); 1 in 285 TYA
  - **BUT** most common cause of death < 15 years (West)

• **Improved prognosis for paediatric malignancies:**
  >80% cure overall:
  – Earlier diagnosis & recognition, including of emergencies.
  – Centralisation of care in specialist tertiary centres.
  – Multicentre / international collaboration; randomised controlled clinical trials; now new drugs: targeted agents; immunotherapy.
  – Improved supportive and intensive care.
  – More effective treatment regimens.
  – Survivorship, long term surveillance & care.
UK CCLG Tertiary Paediatric Oncology Centres

- Aberdeen: Royal Aberdeen Children's Hospital
- Edinburgh: Royal Hospital for Sick Children
- Newcastle-Upon-Tyne: Royal Victoria Infirmary
- Leeds: St. James's University Hospital
- Sheffield: Sheffield Children’s Hospital
- Nottingham: Queen's Medical Centre
- Cambridge: Addenbrooke’s Hospital
- Leicester: Leicester Royal Infirmary
- London: Great Ormond Street Children’s Hospital
- Sutton: Royal Marsden Hospital
- Southampton: Southampton General Hospital

- Cardiff: Children's Hospital of Wales
- Bristol: Royal Hospital for Sick Children
Improvement in UK Survival Outcomes (1971-2010)

- Wilms tumour outcomes in UK lag behind northern and western Europe (OS 83 v 89%)
- Overall Mortality rates from childhood cancer in UK less good than for some other northern European countries (Bosetti et al Eur J Cancer 48 (2010))
- Causes may be multifactorial - Early diagnosis important contributor
KEY FINDINGS

- Over half of young people (52%) and almost half of parents (49%) surveyed visited their GP at least three times before their cancer was diagnosed. A quarter of young people (24%) and one in five parents (18%) told us they required five visits or more to obtain a diagnosis.

- A third of parents (34%) and just over half of young people (53%) reported that they felt their diagnosis was delayed. Of those, almost half felt that this perceived delay impacted on their prognosis. They also reported losing trust in their GP.

- For young people and parents who reported a delayed diagnosis, the most common reasons cited were the GP misdiagnosing symptoms and having to visit the GP many times.

- Nearly half of the young people surveyed (44%) said that they felt their GP did not take their concerns seriously.

- Just over a third (34%) felt that their GP did not have time to listen to them talk about their symptoms.

- A quarter of parents (25%) felt that their GP did not have time to listen to them talk about their child's symptoms.

- Two out of five parents (42%) reported that they felt their GP did not take their concerns seriously. A third (36%) thought that their GP did not take into account their knowledge of their child.

- Nearly one in five parents (16%) felt that their child's ability to cope with their illness had been affected by their experience of the health system before diagnosis. Around the same proportion (14%) said that their own ability to cope had been affected. Just under a third of young people (31%) believed that their ability to cope with their illness had been affected by their experience of the health system.

- Nearly half of UK GPs polled (46%) ranked lack of training available as one of their top three barriers to identifying cancer in children and young people.

- When asked what additional support or advice would be beneficial in helping to identify the possible symptoms of cancer in children and young people, more than half of UK GPs polled (57%) said discussions about specific cases with experts, such as paediatric specialists, would help.
Cancer Incidence: 0-14 years (1700/year)

CRUK: Number of New Cases per Year, Great Britain, 2006-2008
Cancer Incidence: 15-24 years (2300/year)

CRUK: Number of New Cases per Year, Great Britain, 2000-2009
Cancer Incidence:

Age-Adjusted and Age-Specific Cancer Incidence Rates for Patients 0-19 Years of Age (SEER 2005-2009)

0-14 Years
- 31.1% Leukemia
- 25.4% CNS
- 10.0% Lymphomas
- 6.6% Soft tissue
- 4.4% Bone tumors
- 4.0% Carcinomas and Melanoma
- 3.4% Germ cell
- 0.3% Other
- 6.1% Neuroblastoma
- 2.5% Retinoblastoma
- 1.5% Hepatic

15-19 Years
- 20.7% Lymphomas
- 13.8% Leukemia
- 18.7% CNS
- 12.3% Germ cell
- 6.8% Soft tissue
- 6.2% Bone tumors
- 0.6% Hepatic
- 0.7% Renal
- 0.4% Neuroblastoma
Aren’t children just little adults?

Leukaemia
Leukaemia: Clinical Features

- **Anaemia** - fatigue, pallor, breathlessness
- **Infection** - fever
- **Bleeding** - petecchiae, purpura, mucosal bleeding
- **Bone & joint pain/limp** – masquerades as arthropathy
- **Organ infiltration** - bone & joint pain, hepatosplenomegaly, lymph node enlargement, gum hypertrophy, mediastinal mass (Beware the ‘new asthmatic’ – risk of tumour lysis syndrome with corticosteroids)
Leukaemia: Differential Diagnoses

- Aplastic anaemia
- Rheumatic disease
- Osteomyelitis
- Bone marrow infiltration from other malignancy, eg neuroblastoma, rhabdomyosarcoma
- Myelodysplastic syndrome
- Viral infection eg EBV, CMV
- Leukaemoid reaction eg pertussis, sepsis (meningococcus)
- Acute erythroblastopaenia of childhood
- ITP
- ‘Failure to thrive’ diagnoses
Leukaemia: NICE Guidance 2015

• Refer children and young people for immediate specialist assessment for leukaemia if they have unexplained petechiae or hepatosplenomegaly or if the results of a full blood count are suggestive of leukaemia

• Offer a very urgent full blood count (within 48 hours) to assess for leukaemia in children and young people with any of the following:
  o pallor
  o persistent fatigue
  o unexplained fever
  o unexplained persistent infection
  o generalised lymphadenopathy
  o persistent or unexplained bone pain
  o unexplained bruising or bleeding

Use the pan-London suspected paediatric cancer referral form
Leukaemia: Diagnostic Work-up

- FBC & Blood Film – What is the WBC? ALL or AML? (CML?)
- U&Es, Ca, PO4, Urate – Are there signs of Tumour Lysis?
- LFTs, LDH
- Coagulation Screen – Is there a coagulopathy?
- Group & Save
- Viral screen – EBV/Monospot, VZV, CMV, Hep B/C
- CXR – Does the child have a mediastinal mass?
- Peripheral blood immunophenotype (BM, CSF + Intrathecal later)
Leukaemia: Initial Management in Hospital

- Iv fluids – 3L/m². Caution if large mediastinal mass ± pleural effusion/SVC obstruction
- Allopurinol or urate oxidase (rasburicase) if high WBC (>75) &/or bulky disease
- Broad spectrum iv antibiotics – if signs of sepsis
- Blood/Platelet Transfusion – caution with RBC if WBC>100 complications of hyperleucocytosis; 5ml/kg slowly after platelets/clotting factors
- FFP/Cryoprecipitate – especially in high count AML
- Monitor biochem q6h
- Discussion with family re: possible diagnosis
- Prognosis:
  - ALL = >80% cure; 2-3 years of treatment
  - AML = 60-70% cure; 6 months of (intensive) treatment
Lymphoma: Demographics

- Hodgkin’s (30-40%) vs Non-Hodgkin’s (60-70%)
- Hodgkin’s common in TYA; prognosis: > 90%
- NHL – all ages; most common 7-10 years
- NHL Pathology: usually high grade & clinically aggressive but most have good prognosis >90%
  - Burkitt’s and atypical Burkitt’s (35-50%)
  - Lymphoblastic lymphoma (35-40%)
  - Diffuse large B-cell lymphoma (15-25%)
  - Anaplastic large cell lymphoma (5-10%)
  - Lymphoproliferative disease

Starry Sky Appearance in Burkitt's Lymphoma
Lymphoma: Clinical Features

• Duration of symptoms may give clues
• Unexplained fevers, weight loss, night sweats
• Lymph node enlargement, especially cervical, supraclavicular
• Respiratory – mediastinal mass, breathlessness
• Extranodal disease more common in children: abdomen;
• rarely bone, skin, thyroid, orbit, eyelid , and kidney.
• Abdominal pain/distension – intussusception, ‘appendicitis’
• Nasopharyngeal or tonsillar – snoring/’sleep apnoea, persistent nasal discharge
Lymphoma: Clinical Features
### Aren’t children just little adults?

<table>
<thead>
<tr>
<th></th>
<th>Childhood</th>
<th>Adulthood</th>
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<tbody>
<tr>
<td><strong>Frequency</strong></td>
<td>Rare (1%)</td>
<td>Common (99%)</td>
</tr>
<tr>
<td><strong>Cell of origin</strong></td>
<td>Usually non-epithelial (embryonal/developmental)</td>
<td>Usually epithelial (carcinomas)</td>
</tr>
<tr>
<td><strong>Latency period</strong></td>
<td>Short</td>
<td>Long</td>
</tr>
<tr>
<td><strong>Environmental factors</strong></td>
<td>Unclear; familial syndromes (rare)</td>
<td>Strong relationship eg smoking</td>
</tr>
<tr>
<td><strong>Disease extent</strong></td>
<td>80% metastatic</td>
<td>Varies</td>
</tr>
<tr>
<td><strong>Response to treatment</strong></td>
<td>Very good (5 year survival &gt; 80%)</td>
<td>Variable, survival (&lt; 60%)</td>
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**Solid tumours**
Paediatric & Adolescent Solid Tumours

• **Central Nervous System Tumours:**
  - Medulloblastoma
  - Glioma – Low Grade, High Grade, Pontine (DIPG)
  - Ependymoma
  - Germ cell tumours
  - Craniopharyngioma
  - [Other: Atypical Teratoid Rhabdoid Tumours; Rare tumours]

• **Most Common Other Solid tumours:**
  - Neuroblastoma, Wilm’s Tumour
  - Sarcoma: Rhabdomyosarcoma & Ewing Sarcoma; Osteosarcoma
  - [Other: Hepatoblastoma; Retinoblastoma; Rare tumours]
## CNS Tumours: Symptoms & Signs

<table>
<thead>
<tr>
<th>Raised ICP</th>
<th>Focal Signs</th>
<th>Focal Signs:</th>
</tr>
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<tbody>
<tr>
<td><strong>General:</strong></td>
<td></td>
<td><strong>Hemispheric</strong></td>
</tr>
<tr>
<td>Headache</td>
<td>Ataxia</td>
<td>Seizures</td>
</tr>
<tr>
<td>Vomiting</td>
<td>Nystagmus</td>
<td>Spasticity</td>
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<tr>
<td>Behavioural change</td>
<td>Diplopia</td>
<td>Memory deficits</td>
</tr>
<tr>
<td>Consciousness level</td>
<td></td>
<td>Behavioural change</td>
</tr>
<tr>
<td>Papilloedema</td>
<td></td>
<td></td>
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<tr>
<td>VI nerve palsy</td>
<td>Facial weakness</td>
<td></td>
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<tr>
<td>Reduced Vision</td>
<td>Dysphagia</td>
<td></td>
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<tr>
<td>Head tilt</td>
<td>Ocular palsies</td>
<td></td>
</tr>
<tr>
<td>Infant: irritability</td>
<td>Spasticity</td>
<td></td>
</tr>
<tr>
<td>Head circumference</td>
<td>Behavioural change</td>
<td></td>
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</tbody>
</table>

**Posterior Fossa:**
- Headache
- Ataxia
- Nystagmus
- Diplopia
- Behavioural change

**Brainstem:**
- Facial weakness
- Dysphagia
- Ocular palsies
- Spasticity
- Behavioural change

**Mid-line:**
- Growth deficits
- Visual deficits
- Appetite/Weight
- Endocrine; DI
- School performance
Head Smart Campaign

**Under 5 Preschool**
- Brain tumours happen...
- Symptoms include:
  - Persistent / recurrent vomiting
  - Balance / co-ordination / walking problems
  - Abnormal eye movements
  - Behaviour change, particularly lethargy
  - Fits or seizures (not with a fever)
  - Abnormal head position such as wry neck, head tilt or stiff neck

If your child has one of these, see your doctor
If two or more, ask for an “urgent referral”

**5 - 11 Children**
- Brain tumours happen...
- Symptoms include:
  - Persistent / recurrent headache
  - Persistent / recurrent vomiting
  - Balance / co-ordination / walking problems
  - Abnormal eye movements
  - Blurred or double vision
  - Behaviour change
  - Fits or seizures
  - Abnormal head position such as wry neck, head tilt or stiff neck

If your child has one of these, see your doctor
If two or more, ask for an “urgent referral”

**12 - 18 Young People**
- Brain tumours happen...
- Symptoms include:
  - Persistent / recurrent headache
  - Persistent / recurrent vomiting
  - Balance / co-ordination / walking problems
  - Abnormal eye movements
  - Blurred or double vision
  - Behaviour change
  - Fits or seizures
  - Delayed or arrested puberty, slow growth

If your child has one of these, see your doctor
If two or more, ask for an “urgent referral”
Especially if growth or puberty is slow

www.headsmart.org.uk
Consider a referral for a same-day assessment (within 24 hours) for suspected brain or central nervous system cancer in children and young people with newly abnormal cerebellar or other central neurological function.
Raised Intracranial Pressure

- Obstruction of CSF flow by tumour – hydrocephalus
- Direct pressure effect from tumour /bleed – cerebral oedema
- Does the child have a VP shunt in-situ?
**Medulloblastoma**

- Posterior fossa tumour: cerebellar signs or raised ICP
- Risk group and prognosis depends on Chang staging (& now molecular subtype)
- Prognosis 80% 5 year survival for standard risk medulloblastoma
- Treatment is intensive:
  - CSF diversion & resection
  - Craniospinal radiotherapy
  - Chemotherapy: Packer regimen – vincristine, cisplatin, CCNU
- Late effects common
- Metastatic disease: curable
- Relapsed disease: poor prognosis

<table>
<thead>
<tr>
<th>M0</th>
<th>No evidence of subarachnoid or hematogenous metastasis</th>
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<tbody>
<tr>
<td>M1</td>
<td>Tumor cells found in cerebrospinal fluid</td>
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<tr>
<td>M2</td>
<td>Intracranial tumor beyond primary site</td>
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<td>M3</td>
<td>Gross nodular seeding in spinal subarachnoid space</td>
</tr>
<tr>
<td>M4</td>
<td>Metastasis outside the cerebrospinal axis (especially to bone marrow, bone)</td>
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Glioma

- WHO Classification of Glioma (Grade I-IV) - 2007
- Malignant transformation from LGG to HGG: common in adults but rare in paediatrics (Gilbertson et al, JCO)
  - **Low-grade**: (prognosis >80% 5yr OS)
    - I - Pilocytic astrocytoma
    - II- Diffuse/Fibrillary astrocytoma
  - **High-grade**: (prognosis <25% AA/10% 5yr OS)
    - III - Anaplastic astrocytoma (AA)
    - IV - Glioblastoma multiforme (GBM)
- **Diffuse intrinsic Pontine Glioma (DIPG)**: (prognosis average 9 months) OS)
WHO Classification of CNS Tumours

5th edition, 2016

Integrated diagnosis and classification assigned based on histopathological AND molecular features
Age-related grade differences in astrocytoma (glioma)

**Adult Astrocytoma**

Grade distribution

Age at diagnosis

**Paediatric Astrocytoma**

Grade distribution

Age at diagnosis

Modified from Gerges et al, Genome Medicine 2013
Pilocytic astrocytoma

Surgery +/- Radiotherapy or chemotherapy (depends on age & NF1 status); LGG: Vincristine & carboplatin; 2nd line Vinblastine; excellent prognosis

• Tumour of cerebellum, often partly solid with cyst;
• Biphasic, Rosenthal fibres, piloid cells
• KIAA1549-BRAF Fusion diagnostic
Glioblastoma

- Present with hemispheric signs and symptoms; seizures, raised ICP
- Prognosis affected by degree of surgical resection
- Surgery, Radiotherapy and temozolomide (Stupp regimen)
- Novel therapies eg anti-angiogenic agents, BRAFV600 inhibitors for a few
- Very poor prognosis
Building on this:

**Dabrafenib:** BRAFV600E inhibitor (BRAFV600)

**Trametinib:** MAP Kinase inhibitor (BRAF fusions)

**Combination** – improve efficacy; overcome resistance
DIPG

- Not resectable; biopsy rarely done; only radiotherapy is of (transient) benefit; re-irradiation may be possible
- Risks to cranial nerves – airway, swallow – GA for radiotherapy as usually aged < 7 years
Anatomical distribution, incidence and clinical correlates of histone H3F3A and HIST1H3B mutations in pHGG

Modified from Jones, Nature Reviews Cancer 2014.
Neuroblastoma:

- Commonest extra-cranial solid tumour in children (8% of childhood cancers) & most common malignancy of infancy
- Tumour of sympathetic nervous system; primary may arise anywhere from neck to pelvis

**Symptoms and signs:**
- Localised (primary; lump)
- Metastatic – bone, bone marrow, liver, skin, CNS
  - Catecholamine secretion: hypertension – risk at GA – hypertensive crisis
  - Opsoclonus-myoclonus syndrome
  - Other: vasoactive intestinal peptides-flushing, sweating, watery diarrhoea

**Prognosis:** age (18months), stage, biology
Neuroblastoma: a spectrum of diverse biology & clinical behaviour

- Undifferentiated neuroblastoma
- Differentiating neuroblastoma
- Ganglioneuroma

Degree of malignancy/aggressive biological features
MYCN in neuroblastoma:
A major determinant of outcome

- Proto-oncogene on chromosome 2p24.3 identified in 1999
- 4-fold number of MYCN FISH signals compared to the reference probe
- MYCN amplification in 25% of all neuroblastoma, 50% of high risk patients
- MYCN amplification in infants – especially powerful as a prognostic factor:
  10% versus 85% survival
- Other molecular features, eg ALK status

Dual-coloured FISH

Overall Survival in Neuroblastoma

Years From Diagnosis
Standard treatment of high risk neuroblastoma

- **Induction Chemotherapy**
- **Surgical Resection**
- **Myeloablation & Autologous Stem Cell Rescue**
- **Radiotherapy**
- **Minimal Residual Disease Therapy (Differentiation; Immunotherapy)**

###chemotherapy regimens

- Carboplatin
- Etoposide
- Vincristine
- Cisplatin
- Cyclophosphamide

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<th>Days</th>
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<td>50</td>
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<td>60</td>
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<td>70</td>
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*Days*
Wilm’s Tumour (nephroblastoma)

- Presentation is usually with an abdominal mass – may be asymptomatic, or have abdominal pain. May be acute if spontaneous tumour rupture or haemorrhage
- May have hypertension – control essential prior to biopsy/surgery
- May have coagulopathy
- European vs US treatment strategy:
  - EU = Biopsy – now only if atypical features; Pre-operative chemotherapy; Definitive surgery (nephrectomy) – risk group assigned – further treatment with chemotherapy +/- radiotherapy (flank and/or pulmonary).
  - US = Primary nephrectomy then adjuvant.
- Prognosis is excellent (>80%); most patients salvageable at relapse
Wilm’s Tumour

Renal mass – pressure symptoms, hypertension, +/- respiratory symptoms
Rhabdomyosarcoma

- Embryonal tumour of muscle: smooth/skeletal
- Prognosis: age of the patient, site of origin, tumour size, resectability, presence & number of metastatic sites or tissues involved, presence or absence of regional lymph node involvement, histopathologic subtype (alveolar vs. embryonal)
- Localised disease: 70% 5yr survival
- Metastatic ARMS: < 30%
- Primary sites with more favourable prognoses include: orbit and non-parameningeal, head and neck, paratestis, vulva, vagina, uterus (nonbladder, nonprostate genitourinary tract), biliary tract.
- Chemo +/- Surgery +/- Radiotherapy
Ewing’s sarcoma

- Signs & Symptoms:
  - Bony pain/swelling
  - Fever (a third)
  - Diaphysial tumour
  - Pelvis, femur, humerus, ribs
• Consider urgent referral (for an appointment within 2 weeks) for ophthalmological assessment for retinoblastoma in children with an absent red reflex.
Red Flags

- Persistent swollen glands
- Persistent back pain
- Persistent headaches
- Nocturnal pain waking patient
- Frequent bruising
- Constant tiredness
- Unexplained fits (seizures) or changes in vision or behaviour
- An unexplained lump (anywhere)
- Abdominal pain or swelling
- Unexplained GIT symptoms
- Unexplained sweating or fever
- Changes in appearance of the eye/unusual appearance in photos
- Frequent infections or flu-like symptoms
- Repeat visits to GP or A & E
- Parental concern
GP Roles in Childhood Cancer

- **Key** role in early diagnosis and referral
- **Key** role in providing ongoing support through treatment (holistic, family)
- **Key** role in survivorship follow-up
- **Key** role in bereavement follow-up