PET/CT in Paediatric Oncology
Hybrid Imaging PET/CT & PET MRI

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Discipline of Medical Imaging, Sydney Medical School
University of Sydney

iPET 2015 Vienna
The Children’s Hospital at Westmead

(Royal Alexandra Hospital for Children)

- Bed capacity: 340
- Inpatients 2014: 31,833
- Outpatients 2014: 734,030
- Tertiary/Quaternary hospital
- Dept Nuclear Medicine
  - 4203 studies
  - NM, PET/CT, BMD, body composition
  - Therapy: I131, MIBG
PET/CT

June 2006 – Dec 2014: >4,500 PET/CT studies
80% Oncology, 15% neurology / neuro-oncology, 5% Infection / PUO

Oncology Whole Body PET/CT Scans

- Lymphoma 39%
- Primary Bone Tumours 18%
- Soft Tissue Sarcomas 10%
- Wilms 1%
- Neuroblastoma 1%
- Other 31%

Other – adrenocorticocarcinoma, NPC, Germ Cell tumours, neuroendocrine tumours, melanoma, thyroid carcinoma, hepatoblastoma, HCC, LCH, NF1, PTLD etc.

Siemens PET mCT 128
Hybrid Imaging in Paediatric Oncology

PET/CT & PET/MR or PET/CT & MR?

- Lymphoma
- Sarcoma – bone, soft tissue
- Neurofibromatosis type 1
- Neuroendocrine
PET/CT Oncology 2015

• Common Paediatric Malignancy
• PET/CT – ‘Standard of Diagnostic Care’
  – Stage
  – Response to Treatment
  – Detection residual & recurrent cancer
  – End of treatment stage
  – Surveillance
PET/CT Oncology 2015

**Definite role in management**

- **Lymphoma**
  - Hodgkins lymphoma
  - Non-Hodgkins lymphoma

- **Sarcoma**
  - Primary bone
  - Soft tissue
    - Rhabdomyosarcoma 55%
    - Non rhabdomyosarcoma 45%
Less well defined role

• Other & rare solid tumours
  – Malignant brain tumours
  – Neuroblastoma
  – Hepatoblastoma, hepatocellular carcinoma
  – Langerhan Cell Histiocytosis
  – Germ Cell Tumours
  – Malignant peripheral nerve sheath tumours
  – Neuroendocrine
  – Epithelial Neoplasms & Melanoma
    • Adrenocortical
    • Nasopharyngeal
PET, CT & MRI

• Technologies are rapidly changing and improving
  – MRI: DWI, fMRI and MRSI: anatomy, pathology, bio-physiology and chemistry
  – PET/CT: faster, less radiation, more specific radiopharmaceuticals- biomarkers, metabolism, theranostics
  – PET/MRI or PET/CT & MRI?
Advances in multimodal neuroimaging: Hybrid MR–PET and MR–PET–EEG at 3 T and 9.4T

Strengths of modalities
Diagnostic value of combined 18F-FDG PET & MRI for staging and restaging in paediatric oncology
Pfluger et al Ludwig Maximilians University of Munich

Table 3  Imaging findings of examination-based analysis in primary diagnosis (n=76) and follow-up (n=194)

<table>
<thead>
<tr>
<th>Findings</th>
<th>18F-FDG PET</th>
<th>MRI</th>
<th>18F-FDG PET/MRI image combination</th>
<th>18F-FDG PET/MRI image registration</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PD</td>
<td>F/U</td>
<td>PD</td>
<td>F/U</td>
</tr>
<tr>
<td>True-positive</td>
<td>63</td>
<td>69</td>
<td>64</td>
<td>71</td>
</tr>
<tr>
<td>True-negative</td>
<td>1</td>
<td>96</td>
<td>3</td>
<td>35</td>
</tr>
<tr>
<td>False-positive</td>
<td>11</td>
<td>22</td>
<td>9</td>
<td>83</td>
</tr>
<tr>
<td>False-negative</td>
<td>1</td>
<td>7</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>Sensitivity (%)</td>
<td>98</td>
<td>91</td>
<td>100</td>
<td>93</td>
</tr>
<tr>
<td>Specificity (%)</td>
<td>-</td>
<td>81</td>
<td>-</td>
<td>30</td>
</tr>
<tr>
<td>Pos. likelihood ratio</td>
<td>-</td>
<td>4.8</td>
<td>-</td>
<td>1.3</td>
</tr>
</tbody>
</table>
MRI issues

• Primary Dx: Identifying viable bone/bone marrow tumour lesions due to limited size and/or soft tissue changes e.g. oedema

• False-positive findings - nonspecific inflammatory lymph node enlargement or infectious tissue changes

• Follow-up: MRI low specificity— misinterpretation of post-therapeutic changes.
  o bone marrow appearance in children varies with age, bone marrow oedema, necrotic tissue, contrast enhancement in successfully treated lesions,
  o difficulties in distinguishing between active tumour tissue and residual mass (necrosis or fibrosis on morphological imaging).
  o lymph node enlargement without active tumour was regularly seen on a post-therapeutic MRI scan.
PET- Gold standard for Molecular Imaging

- F^{18}
  - Glucose-FDG
  - Amino acids-FET, DOPA
  - Cell hypoxia-F-MISO
  - Cell proliferation-FLT
  - Choline-CHT

- Ga^{68}
  - SSTR- Dotatate

- C^{11}
- Cu^{64}

Lopci et al. EJNMMI 2015
DOI 10.1007/s00259-014-2971-8
Lymphoma & FDG PET/CT
Children and Adolescents

• Standard of Diagnostic Care
• Valuable technique high sensitivity & specificity
• Essential for staging & impacts on management

<table>
<thead>
<tr>
<th></th>
<th>FDG PET/CT</th>
<th>CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity</td>
<td>95.9%</td>
<td>70.1%</td>
</tr>
<tr>
<td>Specificity</td>
<td>99.7%</td>
<td>96.9%</td>
</tr>
</tbody>
</table>

• PET/CT correct modality in 86% discordant lesions
• PET/CT better specificity for predicting poor response

London et al. 18F-FDG PET/CT in pediatric lymphoma: comparison with conventional imaging EJNMMI 2011;38:274-284
13 yr F: Presented with painful R tibia? Primary bone malignancy Biopsied?
Bx:Hodgkins Disease
Stage IVB
Stage IVB
Rx BEACOPP
**Response**

### Table 2  Deauville criteria for interim PET interpretation [68]

<table>
<thead>
<tr>
<th>Scale level</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>No uptake</td>
</tr>
<tr>
<td>2</td>
<td>Uptake ≤ mediastinum</td>
</tr>
<tr>
<td>3</td>
<td>Uptake &gt; mediastinum ≤ liver</td>
</tr>
<tr>
<td>4</td>
<td>Uptake moderately &gt; liver</td>
</tr>
<tr>
<td>5</td>
<td>Uptake significantly &gt; liver and new disease foci</td>
</tr>
</tbody>
</table>

J Clin Oncol 32:3048-59 2014 Barrington et al
Completion of therapy March 2010 Complete response
Note: abnormal bone on CT but not metabolic.
Remains in remission May 2014
Lymphoma-CI & MRI

• WBMR-high sensitivity 96%
• WBMR with DWI- helps in nodal disease and extranodal involvement
  – Gu et al AJR 2011;197:W384-W391
  – Krohmer S et al Eur J Radiol 2010;256-261
    – Good correlation PET/CT and WBMR (STIR & RARE imaging)
Paediatric HD
Surveillance & Relapse

Texas Childrens Hospital, Baylor College of Medicine, Texas

• 2-17 mths post Tx
• 11 (85%) within 12 mths (mean 5 mths)
• 2 pts at 16 and 17 mths post Tx

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The Children’ Hospital at Westmead, Sydney

• June 2006-June 2013
• Patients: 64
• PET/CT scans 535---- av 8.4
• Relapse: 7.8% 5/64 <12 mths
NHL

- Highly proliferative malignant cells 85-99%
- Cure rates depends on pathological subtype and tumour stage 70-90%

**Histopathology**

1. Burkitt or B cell Acute Lymphoblastic leukemia 40-50%
2. Lymphoblastic lymphoma (80% T cell 20% B cell) 20-25%
3. Anaplastic Large Cell Lymphoma (T cell or null cell) 10-15%
4. Diffuse Large B Cell Lymphoma 10%
5. Primary Mediastinal B cell lymphoma rare
6. Follicular Lymphoma rare
# Major Histopath Categories of Non-Hodgkin’s Lymphoma in Children and Adolescents

<table>
<thead>
<tr>
<th>Category WHO Classification/ Updated REAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lymphoblastic lymphoma, Precursor T/leukemia</td>
</tr>
<tr>
<td>Burkitt’s and Burkitt’s like lymphomas</td>
</tr>
<tr>
<td>Diffuse large B-cell lymphoma</td>
</tr>
<tr>
<td>Anaplastic large cell lymphoma, systemic</td>
</tr>
<tr>
<td>Anaplastic large cell lymphoma, cutaneous</td>
</tr>
</tbody>
</table>

## All Types Positive $^{18}$F-FDG Considered high grade NHL
Stage & Response assessment

7 yr F Anaplastic Large Cell NHL

STAGE III

Very Good Response after 2 cycles chemotherapy
Minimal activity in right axilla
Increased bone marrow activity
- Chemotherapy
- G-CSF
# International Pediatric Non-Hodgkin Lymphoma Response Criteria

John T. Sandlund, R. Paul Guillerman, Sherrie L. Perkins, C. Ross Pinkerton, Angelo Rosolen, †Catherine Patte, Alfred Reiter, and Mitchell S. Cairo

## Table 1. International Pediatric NHL Response Criteria

<table>
<thead>
<tr>
<th>Criterion</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CR</strong></td>
<td>Disappearance of all disease (three designations)</td>
</tr>
</tbody>
</table>
| **CR** | CT or MRI reveals no residual disease or new lesions  
Resected residual mass that is pathologically (morphologically) negative for disease (detection of disease with more sensitive techniques described as supporting data [Table 2])  
BM and CSF morphologically free of disease (detection of disease with more sensitive techniques described as supporting data [Table 2]), with no new lesions by imaging examination |
| **CRb** | Residual mass has no morphologic evidence of disease from limited or core biopsy (detection of disease with more sensitive techniques described as supporting data [Table 2]), with no new lesions by imaging examination  
BM and CSF morphologically free of disease (detection of disease with more sensitive techniques described as supporting data [Table 2])  
No new and/or progressive disease elsewhere |
| **CRu** | Residual mass is negative by FDG-PET, no new lesions by imaging examination  
BM and CSF morphologically free of disease (detection of disease with more sensitive techniques described as supporting data [Table 2])  
No new and/or progressive disease elsewhere |
| **PR** | 50% decrease in SPD on CT or MRI; FDG-PET may be positive (Deauville score 4 or 5 with reduced lesional uptake compared with baseline); no new and/or PD; morphologic evidence of disease may be present in BM or CSF if present at diagnosis (detection of disease with more sensitive techniques described as supporting data [Table 2]); however, there should be 50% reduction in percentage of lymphoma cells |
| **MR** | Decrease in SPD > 25% but < 50% on CT or MRI; no new and/or PD; morphologic evidence of disease may be present in BM or CSF if present at diagnosis (detection of disease with more sensitive techniques described as supporting data [Table 2]); however, there should be 25% to 50% reduction in percentage of lymphoma cells |
| **NR** | For those who do not meet CR, PR, MR, or PD criteria |
| **PD** | For those with > 25% increase in SPD on CT or MRI (Deauville score 4 or 5 on FDG-PET with increase in lesional uptake from baseline, or development of new morphologic evidence of disease in BM or CSF) |

Abbreviations: BM, bone marrow; CR, complete response; CRb, complete response biopsy negative; CRu, complete response unconfirmed; CT, computed tomography; FDG, $^{[18]}$fluordeoxyglucose; MR, minor response; MRI, magnetic resonance imaging; NHL, non-Hodgkin lymphoma; NR, no response; PD, progressive disease; PET, positron emission tomography; PR, partial response; SPD, sum of product of greatest perpendicular diameters.
Sarcomas: Bone and Soft Tissue

- MRI preferred modality for
  - Stage and extent of primary tumour
    - directs protocols, surgery, radiotherapy
  - Response primary +/- other sites
    - residual mass ? viable
  - Post induction pre surgery
  - Surveillance

- Chest CT- pulmonary metastases

- PET/CT
  - Staging- extent of distant disease
  - Response
  - End of treatment
  - Surveillance
15yr male pain left leg
Bx Osteogenic sarcoma

Staging: Pulmonary, bone and bone marrow metastases

$\text{SUV}_{\text{max}} = 7.4$
A. 12 yr M pain in Left femur. Abn X-ray Bx:High grade osteogenic sarcoma

B. 11yr M Pain proximal R tibia Bx:Osteoblastic osteogenic sarcoma

*Growth plate Involvement?
Response 2 cycles chemotherapy
Response to Chemotherapy

A

Poor responder
$SUV_{\text{max}} \ 10.6 \rightarrow 6.1 \ (42\%)$

Surgery: 25% viable cells
Mx changes: more aggressive chemotherapy

B

Very good response
$SUV_{\text{max}} \ 17.8 \rightarrow 2.1 \ (88\%)$

Surgical Resection:
Histopath: no viable cells
Response

- MRI
  - Residual mass? Viable malignant tissue
  - DWI or contrast enhancement may useful for tumour necrosis
    - Uhl et al Invest Radiol 2006;41:618-623
  - Bone marrow
    - Age differences, hyperactive stimulated marrow
    - G-CSF
    - Oedema and tumour infiltration
• Relative reduction in SUVmax rather than the absolute value SUVmax following chemotherapy may be a stronger predictor of tumor response.


<table>
<thead>
<tr>
<th>PET/CT</th>
<th>CI (inc regional MR)</th>
</tr>
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<tbody>
<tr>
<td>Sensitivity</td>
<td>98%</td>
</tr>
<tr>
<td>Specificity</td>
<td>97%</td>
</tr>
</tbody>
</table>
Soft Tissue Sarcomas

- Histopathologically classified according to tissue they resemble.

Rhabdomyosarcoma  55%
Other                    45%
Diagnosis & Staging

- MRI: preferred modality at diagnosis, extent of local involvement
- CT- pulmonary metastases
- Multicentre trial- Pediatric Sarcoma
  - Volker et al J Clin Oncol 2007;25:5435-5441 (Berlin Dusseldorf)
    - Marked added value of FDG PET/CT over CI
      - Lymph node involvement (RMS sens PET 93% c/w CI 36%)
      - Bone metastases
        - OS Sensitivity PET/CT 90% v CI + Bone Scan 90%
        - ES Sensitivity PET/CT 88% v CI+ Bone Scan 37%
Response Soft Tissue Sarcoma

• PET/CT
  – More accurate than sized base criteria for histopathological response
  – Modality of choice
    • Evilevitch et al Clin Cancer Res 2008;14:715-720

• MR + DWI tumour cellularity
  – ? Useful for response assessment
    • Schnapauff et al J Magn Reson Imag 2009;29:1355-1359
6 yr M IDDM Rx insulin
Pain in L leg.
Mass L lower medial leg above knee

MRI: solid+necrotic mass R vastus medialis

Bx. Alveolar Rhabdomyosarcoma
PET CT: Metabolic lesion with central necrosis (SUVmax 3.5)
No regional LNs or distant metastases

FDG coreg MRI- RTx planning
Post 2 cycles of chemotherapy

MR COR STIR
Mild reduction in size

PET MR COREG
SUVmax 2.3 (34%)

Partial response
9 mths post Tx developed pain lower right back
MRI metastatic disease
12 yr F presented with a mass on the right back July 2007
CT and MRI revealed a soft tissue mass with bone destruction and
extension into the spinal canal

Bx: High grade sarcoma Peripheral Nerve Sheath origin
PET/ CT localised tumour
Rx surgery, chemotherapy (ARST0332), radiotherapy

SUVmax 5.3

Co-Registered MR and FDG PET Axial
Follow up PET/CT

Follow up - orthopaedic hardware artifacts
Neurofibromatosis Type 1
8 yr F Multiple Plexiform Neurofibromas 2007

R paravertebral- Mn Peripheral Nerve Sheath Tumour

SUVmax 4.6
SUVmax 2.4

R lower leg Benign PN

SUVmax 4.6
Follow up MRI 2013: enlarging tumours
18F-FDG increased metabolic activity:
Mass soft tissue deep to left 5th intercostal space

*SUVmax*
Grade 1 < 3
Grade 2 >3-<4
Grade 3 >4

*EJNMMI (2010) 37:1309*  
Moharir et al

*SUVmax* 6.2 to 6.8 delay
Histopath: MPNST WHO GrIV
15yr M
NF1
Multiple plexiform Neurofibromas
Rx Imatinib
WBMR STIR
Proximal R tibial lesion
Larger than previous
FDG PET
Other Paediatric Malignancy

- Neuroblastoma
- **Neuroendocrine tumours**
- Neurofibromatosis (NF1)
- Langerhan Cell Histiocytosis
- Hepatoblastoma, Hepatocellular carcinoma
- Adrenocortical carcinoma
- Nasopharyngeal carcinoma
- Germ cell tumours
- Yolk sac tumours
- Wilms’ tumour*
- Retinoblastoma
- Melanoma
- Thyroid carcinoma
Neuroendocrine Tumours

- Previous somatostatin agent $^{111}$In-octreotide
- Replaced by PET agent $^{68}$Ga DOTATATE or DOTATOC
# Management

<table>
<thead>
<tr>
<th></th>
<th>Well-differentiated</th>
<th>Poorly differentiliated</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Grade (ENETS)</strong></td>
<td>Low (G1)</td>
<td>Intermediate (G2)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>High (G3)</td>
</tr>
<tr>
<td><strong>Ki-67 index (%)</strong></td>
<td>≤2</td>
<td>3-20</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&gt;20</td>
</tr>
<tr>
<td><strong>Anatomic imaging</strong></td>
<td></td>
<td>more rapid growth on serial imaging</td>
</tr>
<tr>
<td><strong>Functional imaging</strong></td>
<td></td>
<td>FDG PET +ve</td>
</tr>
<tr>
<td></td>
<td>Octreoscan SPECT</td>
<td></td>
</tr>
<tr>
<td></td>
<td>or SSTR PET +ve</td>
<td></td>
</tr>
<tr>
<td><strong>Prognosis</strong></td>
<td>Indolent (slowly growing)</td>
<td>Aggressive</td>
</tr>
<tr>
<td><strong>Treatment options</strong></td>
<td>Surgery for localised +/- resectable metastatic disease</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Observation</td>
<td>Chemotherapy</td>
</tr>
<tr>
<td></td>
<td>Somatostatin analogues</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Radionuclide therapy</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Everolimus, sunitnib, α-interferon</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Liver metastases: radiofrequency ablation, hepatic embolisation, TACE, SIR-Spheres</td>
<td></td>
</tr>
</tbody>
</table>

**Figure 1.** Classification of neuroendocrine tumor with corresponding imaging features and treatment options. From Hofman et al., 2011. SPECT, single photon emission tomography; PET, positron emission tomography; SSTR, somatostatin receptor; TACE, transarterial chemoembolization.
ES 9 yr F
2007
Hypertension, intermittent headaches, abdominal pain, hot and sweaty episodes

Elevated catecholamines

CT.: 4cm vascular lobulated mass R para-aortic area

$^{123}$I- MIBG Study +ve

**Paraganglioma with lymphatic invasion**

**Succinate Dehydrogenase B (SDH B) mutation**
Represented 13 yrs June 2011 Recent increasing headaches, mass R paravertebral region near renal hilum on MRI.
Ga68 DOTATATE
2x2cm Lesion in hilum of R kidney: high uptake of Ga68
Incidental lesion in 6th R rib

R recurrence
Co-Reg Ga68 & MR T2
PET CT L rib
Surgery
1. R paravertebral mass---- Paraganglioma
2. L 6\textsuperscript{th} Rib--- no abnormal pathology
Routine F/U
30 Aug 2012
$^{68}$Ga DOTATATE

Multiple bone lesions

- 6$^{th}$ L rib
- R pedicle T8
- L1 vertebral body
- L iliac bone
Referred for
Peptide Receptor Radionuclide therapy (PRRT)
$^{177}$Lu DOTATATE (Lutate)

St George Hospital Sydney

Uptake moderate

Completed course
Repeat Ga68 Dotatate- stable disease
16-yr F  R adrenal Phaeochromocytoma (MIBG neg)  
Surgically removed  2010  
Now presents 2012 biopsy proven metastases in the liver.
Nuclear medicine evaluation for biological markers for staging and therapy

$^{123}$I-MIBG

$^{68}$Ga DOTATATE

NEGATIVE
Metastases

- Liver multiple
- R paravert near kidney
- Mid anterior vert L4
Loss of SSR expression indicates poorly differentiated NET

- adverse prognosis
- higher responsiveness to chemotherapy: e.g. carboplatin and etoposide

Other treatments

- Tyrosine kinase antagonists
  - Sunitinib
- Chemotherapy
  - Platinum and etoposide
  - 5-Fluouracil (5-FU)
  - Neo-vascularisation antagonists
    - Avastin
- Radiotherapy bone and soft tissue
- Metastases localised to liver
  - Surgery
  - Inoperable
    - Y-90 microspheres(SIRT)
Conclusion
PET/CT Paediatric Oncology 2015

• PET/CT – ‘Standard of Diagnostic Care’
  – Stage
  – Response to Treatment
  – Detection residual & recurrent cancer
  – End of treatment stage
  – Surveillance

• Is complementary to MRI and other conventional imaging
Conclusion

- PET/CT has become standard of diagnostic care in the common paediatric solid tumours.
- There is a significant but less well defined role in many of the uncommon and rare solid tumours.
- The uptake of FDG relates to the degree of malignancy and cellular differentiation of these cancers.