

PET/CT Imaging of Pediatric Lymphoma: What is the Evidence?

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Pediatric Lymphoma

- 3rd most common pediatric malignancy accounting for 10-15% of pediatric cancers with 1700 new US cases/year
- HD more common > 10 yr
- NHL more common < 10 yr
- NHL is a **group of lymphomas** of various histology
- Excellent prognosis: 5 Yr survival
HD = 91% NHL = 72%

Pediatric Lymphoma: The Literature

- **NHL is a group of lymphomas of various histology**
- **Evolving technologies: dedicated PET/CT**
- **Non-standardized imaging and dosing protocols**
- **Non-standardized interpretive guidelines**
- **Few prospective studies**
- **Small numbers of patients**
- **Tendency to follow the adult literature**

Pediatric Lymphoma

- Treatment is based on histology, symptoms and **extent of disease** at presentation
- Imaging plays a key role in management of lymphoma and can be considered at 4 points:

Staging at Presentation--Risk Adaptive

During Therapy--Response Adaptive

End of Therapy--Response Adaptive

Remission Surveillance-- Recurrence
detection

PET/CT Imaging: Initial Staging

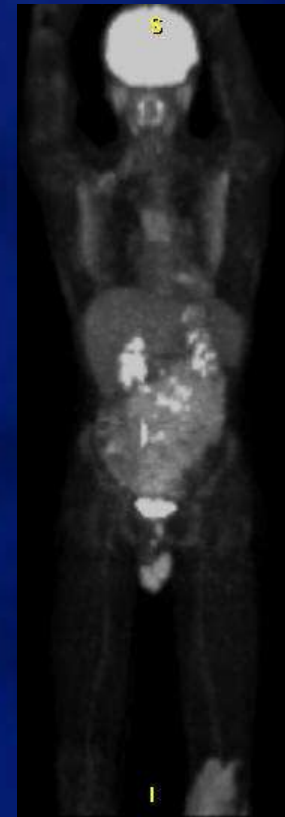
- **What is PET/CT accuracy compared to conventional imaging modalities (CIM)?**
- **Can PET/CT replace CIM?**
- **Upstaging and Downstaging?**
- **Change of therapy?**
- **Can it replace bone marrow aspirate, BMA?**
- **What should be imaged: entire body vs eyes to thighs?**

PET/CT Imaging: Initial Staging

What should be imaged? Frequency and importance of disease beyond thighs or elbows?



Eyes to Thighs



Vertex to Knees

PET/CT Imaging: Initial Staging

What should be imaged?

Baseline: Whole Body

Follow-up: Eyes to thighs if no disease beyond field on baseline study. Include all areas of imaging/clinical concern.

PET/CT Imaging: Initial Staging Accuracy

- Gold Standard typically has been CIM and BMA
- PET/CT will alter staging in 25-33% of patients
 - upstage 12% downstage 15%
- PET/CT will alter therapy in 11-27%^{◦*}
- PET accuracy >95%^{◦◦}

◦ **Riad** 2009 Eur J Nuc Med Mol Imaging

◦ **Hermann** 2005 Nuklearmedizin

•* **Depas** 2005 Eur J Nuc Med Mol Imaging

◦◦ **Kabickova** 2006 Eur J Nuc Med Mol Imaging

PET/CT HD Imaging: PET vs Gallium

- PET more sensitive for staging, early response and at end of therapy; esp. for abdominal, splenic and bone disease.
- Fewer false + at end of therapy.
- PET/CT can have lower radiation dose.
- PET provides same day imaging and results.

Hines-Thomas 2008 *Pediatr Blood Cancer*

Mody 2007 *Leukemia and Lymphoma*

Rini 2005 *Pediatr Radiol*

PET/CT Imaging: Detection of Bone Marrow Involvement

- Occurs in 30% of patients with NHL and 10% of patients with HD
- Bone marrow involvement = Stage IV disease
- Multifocal nature of BM involvement is well established: bilateral BMA has at least a 5-10% increased yield over unilateral BMA.
- Meta-analysis estimated PET sensitivity of 76%, but typically identifies 5-15% more patients with bone/BM lesions than CIM.

PET/CT Imaging: Impact of FN Detection of Bone Marrow Involvement

- **For a PET/CT sensitivity of 76% and a prevalence of 10%, 100 bilateral BMB would be need to be performed, rather than unilateral BMA, to identify 1-2 cases of BM involvement missed with PET/CT**
- **For minimal disease not demonstrable with PET/CT and not upstaged, the impact on overall survival is not known.**

PET/CT Imaging: Detection of BM Involvement-Sensitivity

- **FDG PET/CT identifies all sites of BM lesions demonstrated with CIM/BMA**
- **CT identified 32/193 FDG PET identified lesions**
- **Multifocal BM disease was associated with positive BMA in 12/43 pts**
- **Sampling error inherent with iliac crest BMA**
- **PET/CT upstaged 42% patients with bone lesions WRT staging with CIM/BMA**

Moulin-Romsee 2010 Eur J Nucl Med Mol Im

Schaefer 2007 Eur J Nuc Med Mol Im

PET/CT Imaging: Detection of BM Involvement-Specificity

- **Specificity: 18/18 bone lesions identified with PET were due to lymphoma.**
- **Other authors have found false positive PET scans for BM involvement due to marrow hyperplasia (anemia, cytokine release).**
- **Diffuse uniform uptake due to anemia or reactive changes is usually easily distinguished from multifocal bone involvement from lymphoma.**

PET/CT Imaging: Detection of Bone Marrow Involvement



Reactive

Diffuse Infiltration

Normal

PET/CT Imaging: Detection of BM Involvement-Specificity



19 year old with newly diagnosed HL and anemia due to von Willebrand disease. BMA c/w anemia only.

PET/CT Imaging: Detection of Bone Marrow Involvement

“Prospective studies are now needed to determine whether ^{18}F -FDG PET/CT makes BM biopsy superfluous or whether the two are complimentary.”

Moulin-Rumsee 2010 Eur J Nucl Med Mol Im

PET/CT Imaging: Detection of Splenic Involvement

At initial staging and in the absence of diffuse BM activation, diffusely increased (> liver) or multi-focal splenic uptake is typically due to lymphomatous infiltration rather than hyperplasia.

Salaun 2009 Eur J Nucl Med Mol Im

PET/CT Imaging: Treatment Response

- Can FDG PET/CT define response adaptive therapy?
- When should early response PET/CT be done? After one cycle? Two? Three? End of Treatment?

Nearly all cases of pediatric lymphoma will show some initial treatment response.

CIM: Response Adaptive Therapy

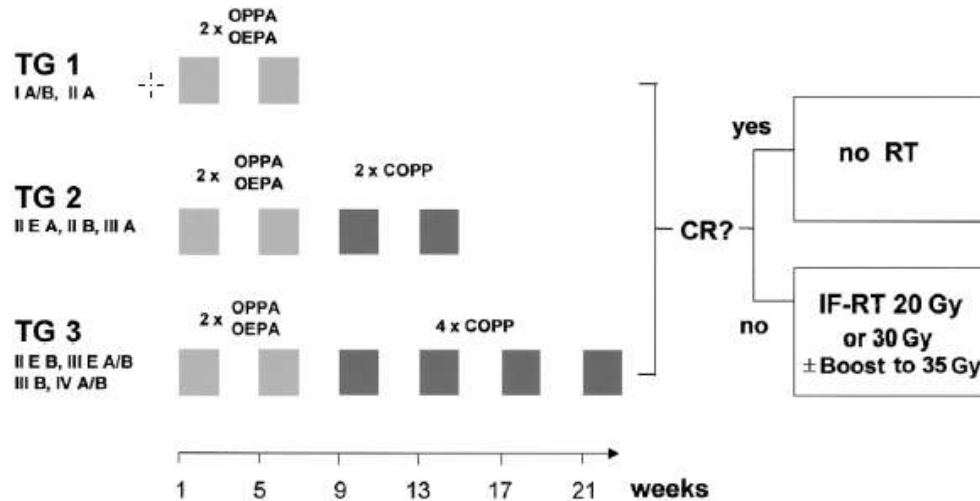
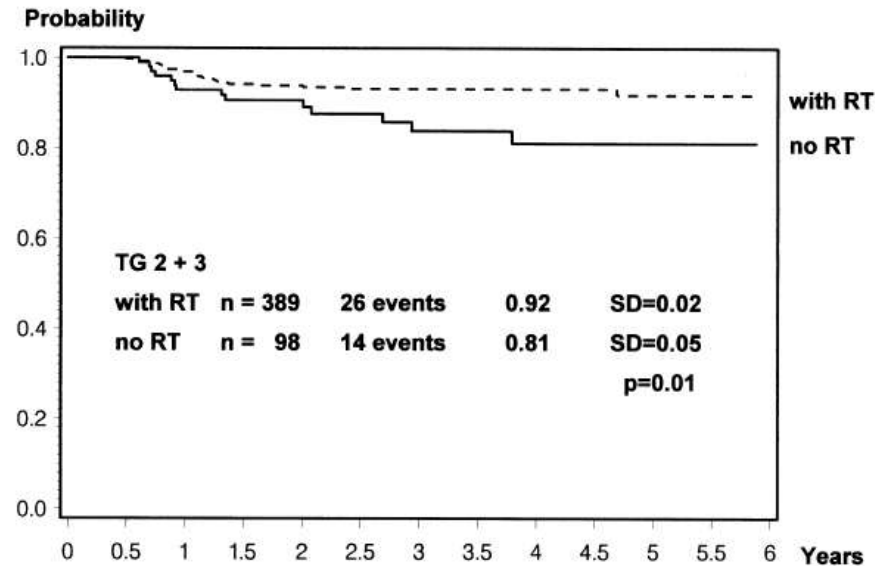


Fig. 1. Protocol schedule GPOH-HD 95.

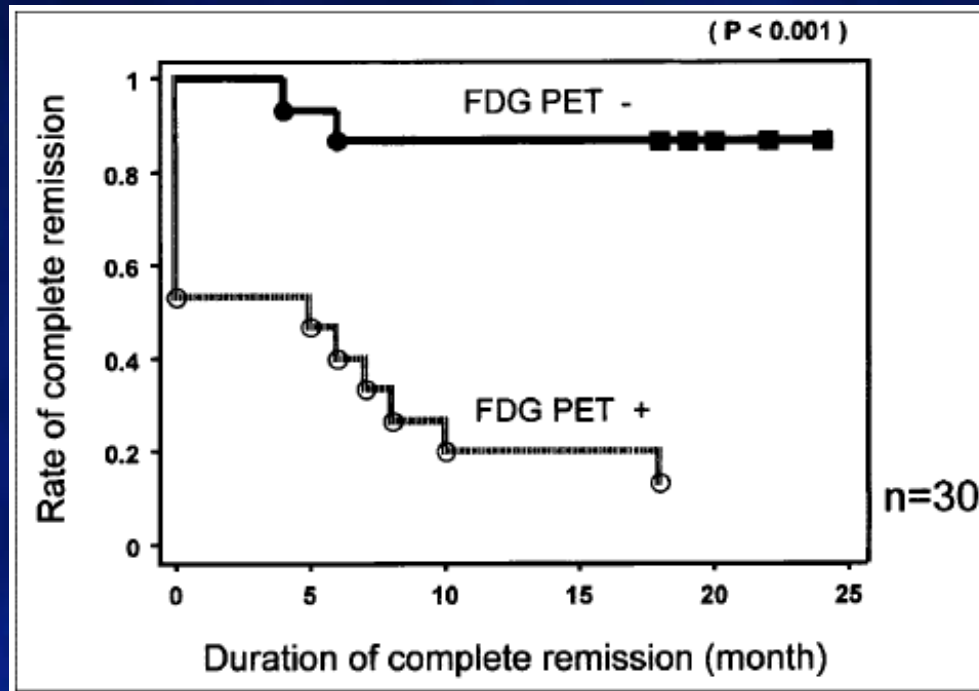


“...omitting radiotherapy for [pediatric] patients with complete response defined by CIMs resulted in decreased EFS rates for advanced stage HL patients.”

PET/CT Imaging: Early Treatment Response

Can PET/CT do better than CIM?

PET/CT Imaging: Early Treatment Response



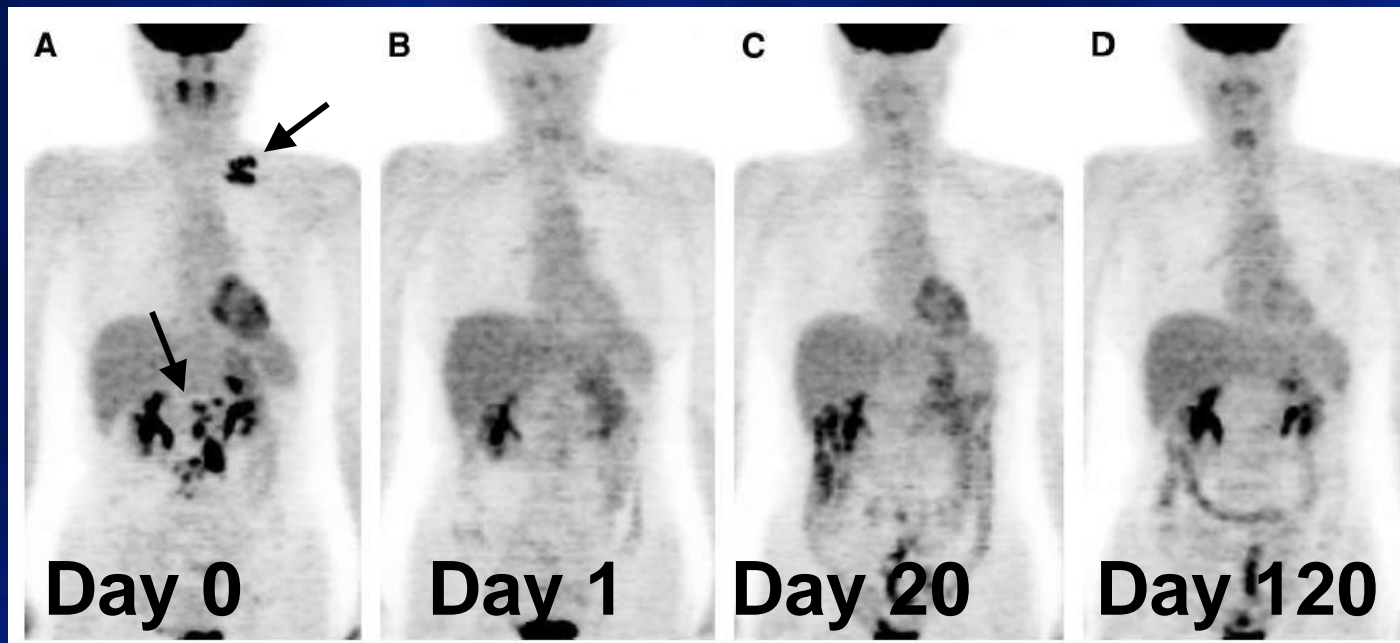
Post 1st Chemo

Early adult study with coincidence PET

Kostakoglu (2002) JNM

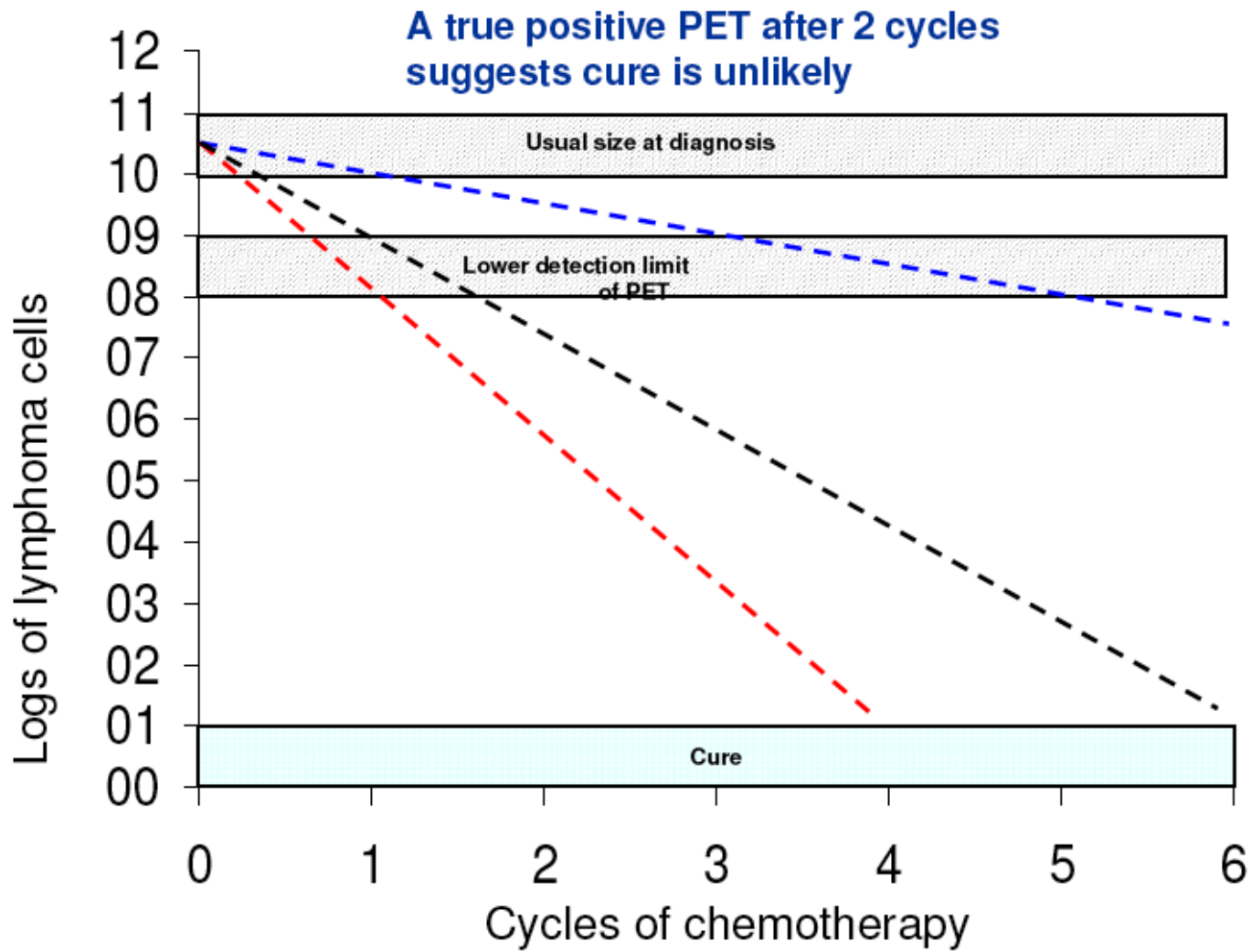
PET/CT Imaging: Early Treatment Response

- Early assessment PET/CT may provide information about **rate of cell kill** that is not available with end of treatment PET/CT.



PET/CT Imaging: When to Image for Evaluation of Treatment Response

- **Nearly all cases of pediatric lymphoma will show some initial treatment response.**
- **Early treatment vs mid-treatment vs. end of treatment vs combination**



Early Therapy Assessment with PET/CT

- Prospective evaluation of 40 pediatric HL pts
- PET at staging, after 2 cycles of chemo and at end of chemo compared with CIMs.
- PET had better sensitivity than CIM for complete response (early 97% vs 3%, end 78% vs 11%)
- Negative PET (early and/or end of therapy) had a 100% NPV for early relapse (mean f/u 4yrs).

Furth 2009 J Clin Onc

PET/CT Imaging: Treatment Response

- PET/CT after first cycle better correlated with PFS than end of treatment PET/CT*
- For HL, a negative PET/CT after 2 cycles of chemotherapy was found to have 97% PPV for complete remission.**

*McManus 2007 Cancer Img

**Gallamini 2006 Haematologica

PET/CT Imaging: End of Treatment Evaluation

- A negative PET/CT at end of treatment is highly predictive of FFP and EFS independent of initial staging and risk assessment.

“We propose that two negative PET scans, one early and the other at the end of chemotherapy, may eliminate the need for involved field radiation therapy, IFRT.”

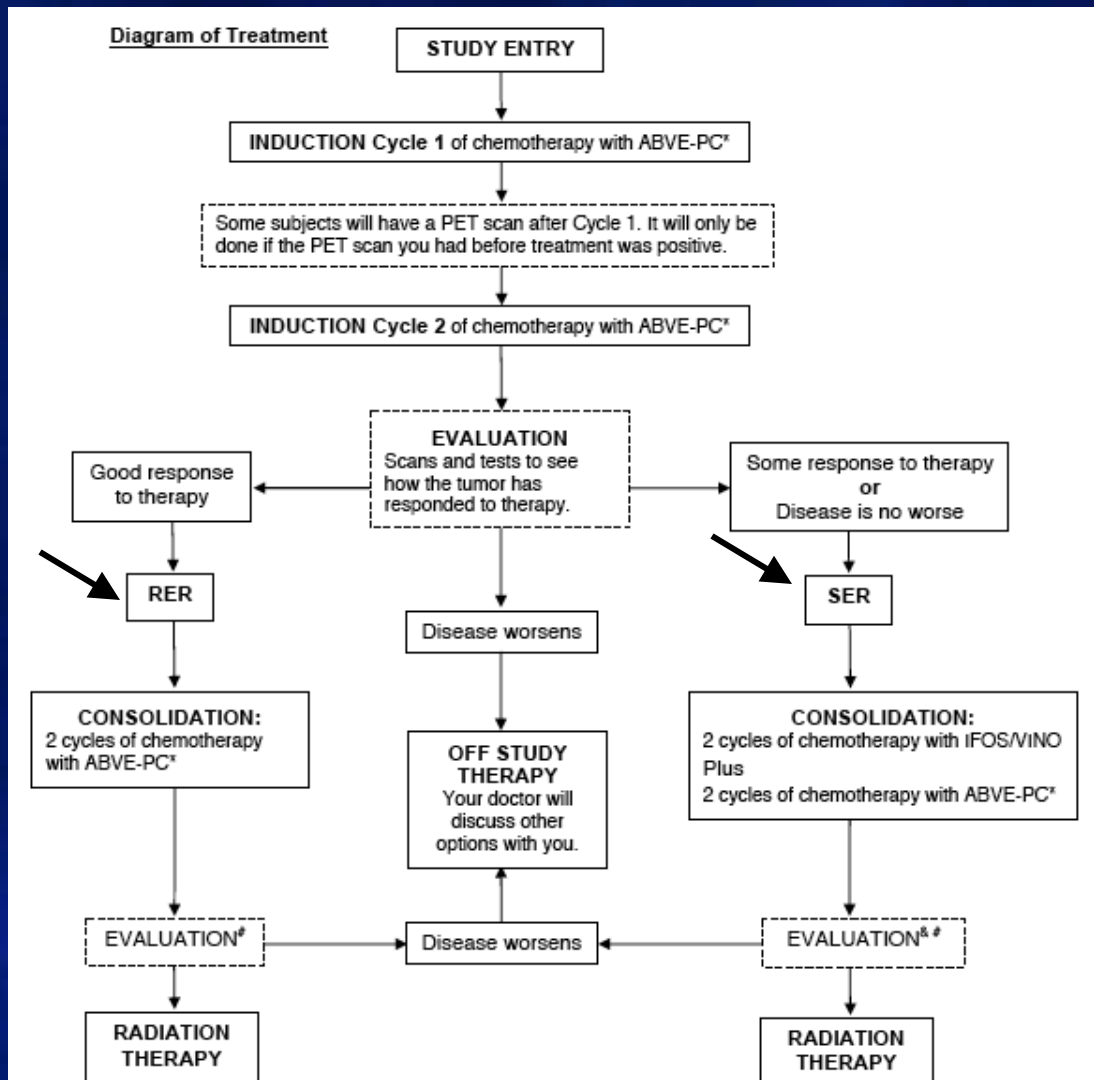
Advani 2007 JCO

Attias 2009 Pediatric Blood Cancer

Early Therapy Assessment with PET/CT

- Larger prospective studies underway to investigate if patients with a rapid early response by PET/CT can be safely treated with fewer cycles of chemotherapy and/or without IFRT.
- Childrens Oncology Group AHOD0831
- EuroNet PHL-C1

PET/CT Imaging: Response Adaptive Chemotherapy



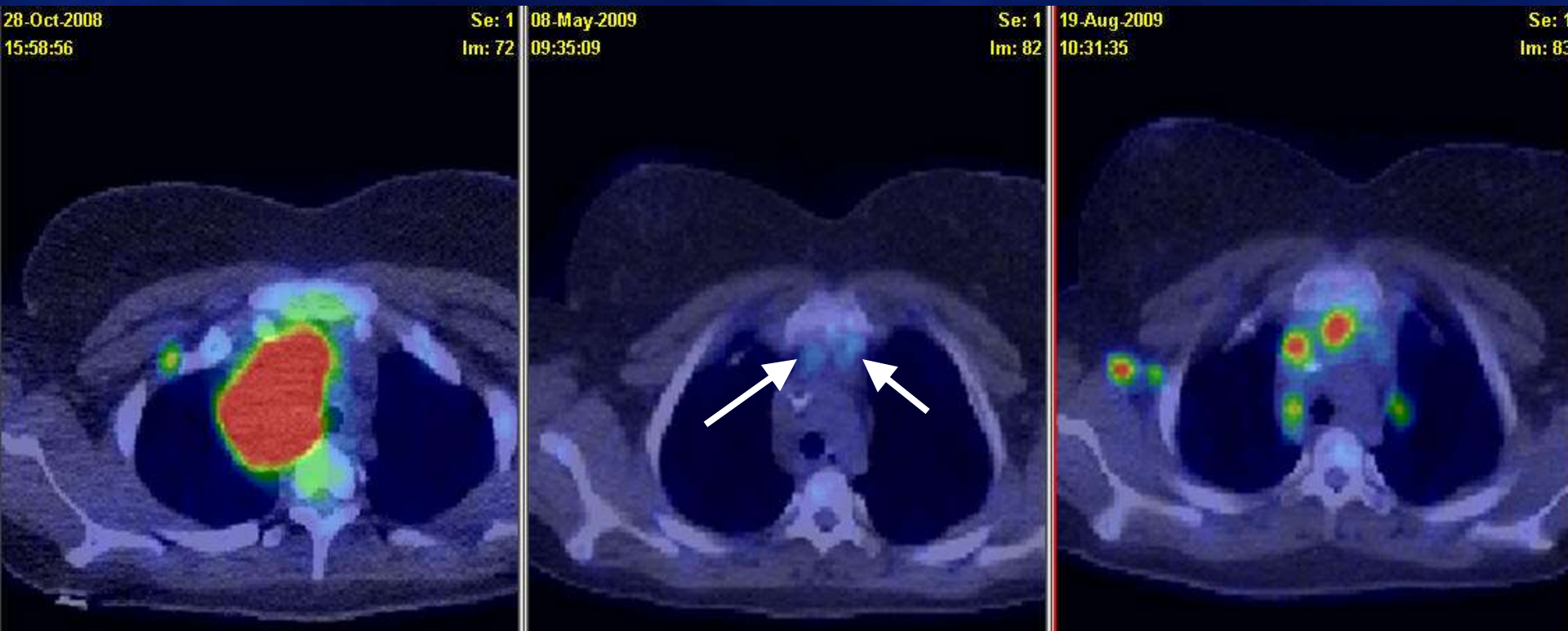
PET/CT Imaging: Early Treatment Complete Response



Initial staging Mid-treatment End of Treatment

17 yr old with PMLBCL, no BMA

PET/CT Imaging: Early Treatment Partial Response w/ Early Recurrence



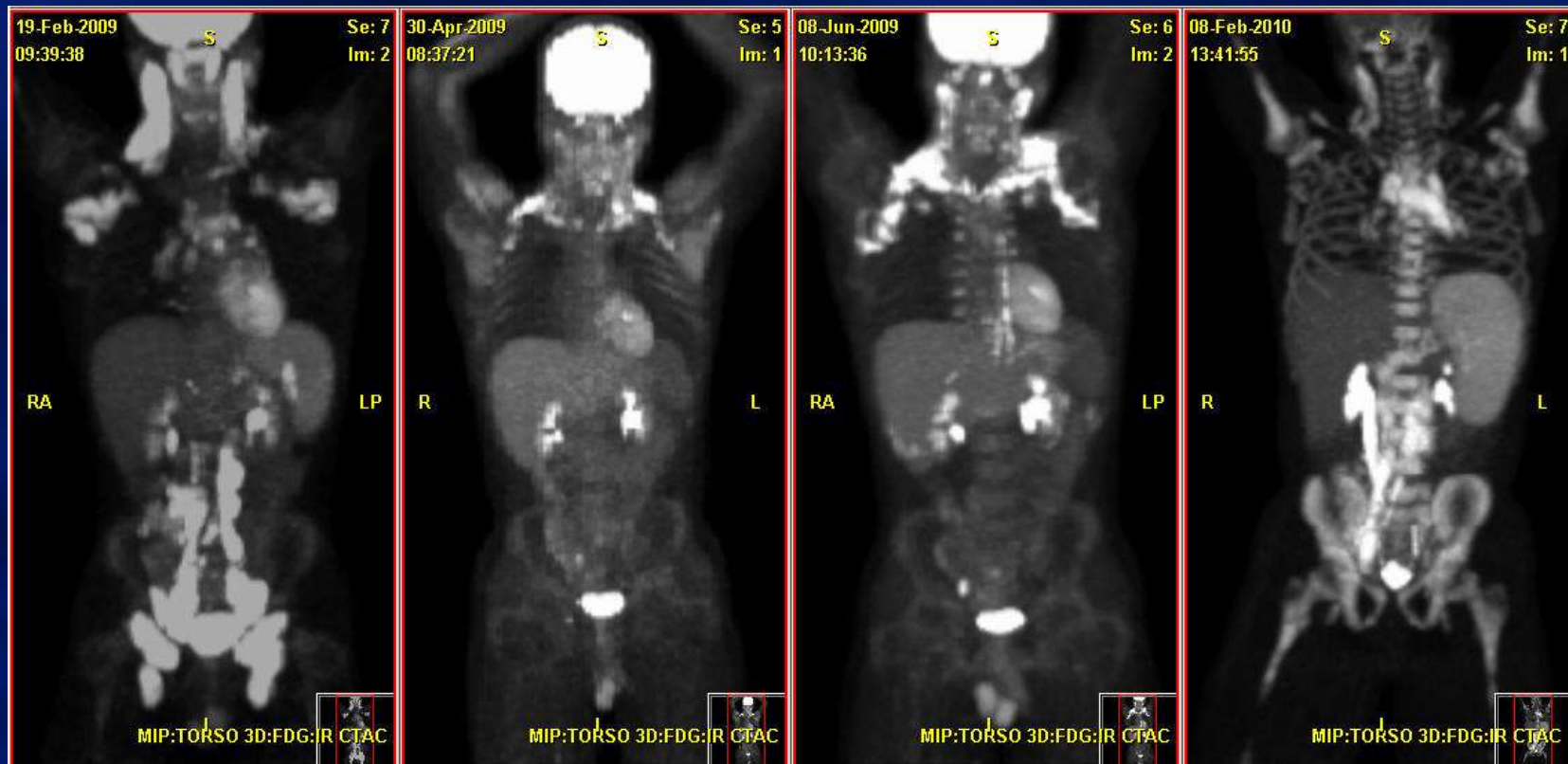
Initial staging

End of Treatment

Early Recurrence

21 yr old with nodular sclerosing HL

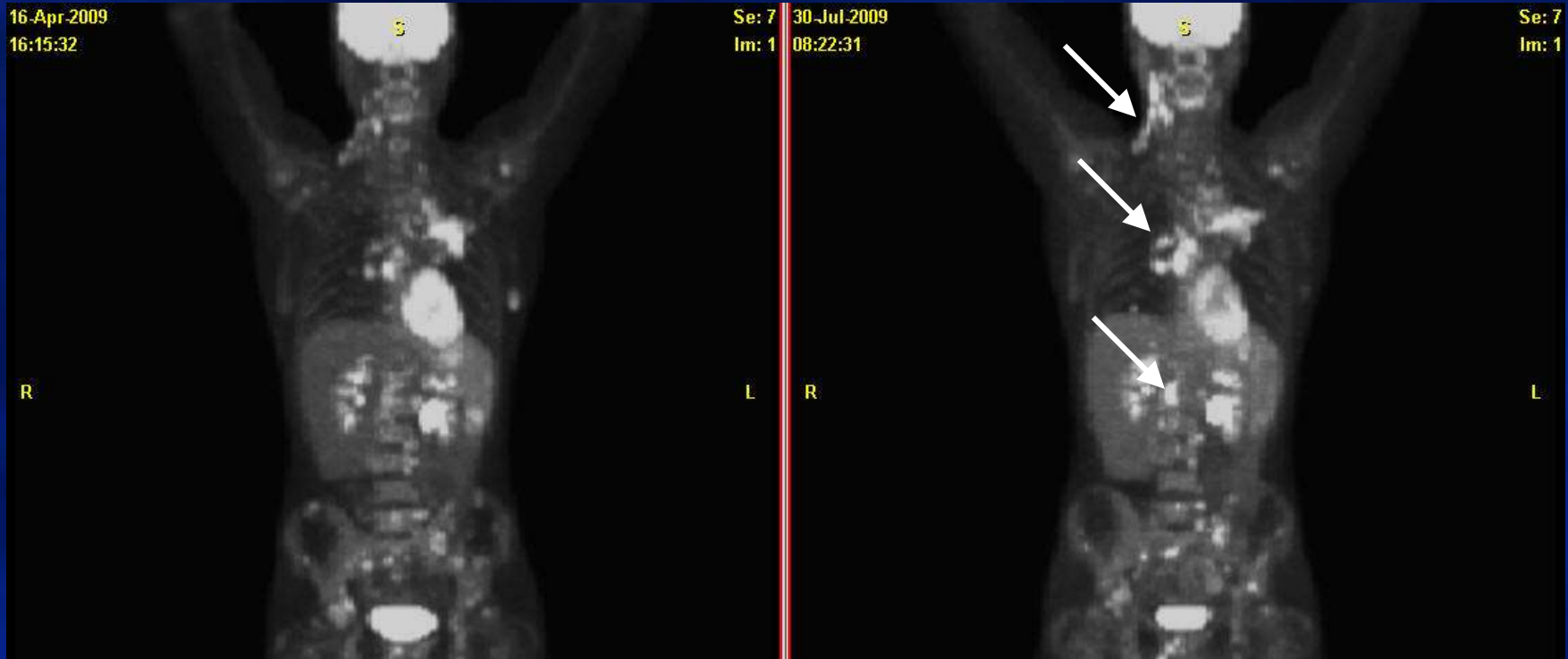
PET/CT Imaging: Early Treatment Partial Response w/ Leukemic Transformation



Initial Early Tx Maintenance T cell L/L

12 yr old with T-cell Lymphoblastic NHL

PET/CT Imaging: Early Treatment Progressive Disease



Initial

Early Post-Tx

19 yr old with Nodular Sclerosing HL

PET/CT Revised Response Criteria for Malignant Lymphoma

- *Visual assessment* is considered adequate...and the use of SUV is not necessary”
- Mediastinal blood pool activity is recommended as the reference background activity for a residual mass > 2 cm in greatest transverse diameter.
- A smaller residual mass or a normal size lymph node (< 1 cm) should be considered positive if its activity is greater than surrounding background.

J Clin Oncol. 2007 Feb 10;25(5):579-86.

Interpretation PET/CT : Lung

- New nodules in patients without established pulmonary involvement and with evidence of CR at all previously known sites should be considered negative regardless of size or uptake
- New lung nodules ≥ 1.5 cm (in patients with previous lung involvement) should be considered suggestive of lymphoma if their uptake exceeds mediastinal blood pool

J Clin Oncol. 2007 Feb 10;25(5):579-86..

Revised response criteria for malignant lymphoma.

Interpretation PET/CT: Liver and Spleen

- Residual lesions > 1.5 cm should be considered positive if their uptake is \geq liver or spleen
- Diffusely increased splenic uptake $>$ liver should be considered positive (unless within 10 days of cytokine treatment)

J Clin Oncol. 2007 Feb 10;25(5):579-86..

Revised response criteria for malignant lymphoma.

Interpretation PET/CT Bone Marrow

- Clearly increased (multi) focal bone marrow uptake should be considered positive for lymphoma
- Diffusely increased bone marrow uptake, even if $>$ liver, is usually due to marrow hyperplasia: anemia or cytokines
- A negative PET in the bone marrow does not exclude bone marrow involvement

J Clin Oncol. 2007 Feb 10;25(5):579-86..

Revised response criteria for malignant lymphoma.

Interpretation PET/CT : New Sites of Suspected Disease

- Increased FDG in a previously unaffected site should only be considered relapsed or progressive disease after confirmation with other modalities

J Clin Oncol. 2007 Feb 10;25(5):579-86..

Revised response criteria for malignant lymphoma.

PET/CT Standardized Response Criteria

Response	Definition	Nodal Masses	Spleen, Liver	Bone Marrow
CR	Disappearance of all evidence of disease	(a) FDG-avid or PET positive prior to therapy; mass of any size permitted if PET negative (b) Variably FDG-avid or PET negative; regression to normal size on CT	Not palpable, nodules disappeared	Infiltrate cleared on repeat biopsy; if indeterminate by morphology, immunohistochemistry should be negative
PR	Regression of measurable disease and no new sites	$\geq 50\%$ decrease in SPD of up to 6 largest dominant masses; no increase in size of other nodes (a) FDG-avid or PET positive prior to therapy; one or more PET positive at previously involved site (b) Variably FDG-avid or PET negative; regression on CT	$\geq 50\%$ decrease in SPD of nodules (for single nodule in greatest transverse diameter); no increase in size of liver or spleen	Irrelevant if positive prior to therapy; cell type should be specified
SD	Failure to attain CR/PR or PD	(a) FDG-avid or PET positive prior to therapy; PET positive at prior sites of disease and no new sites on CT or PET (b) Variably FDG-avid or PET negative; no change in size of previous lesions on CT		
Relapsed disease or PD	Any new lesion or increase by $\geq 50\%$ of previously involved sites from nadir	Appearance of a new lesion(s) > 1.5 cm in any axis, $\geq 50\%$ increase in SPD of more than one node, or $\geq 50\%$ increase in longest diameter of a previously identified node > 1 cm in short axis Lesions PET positive if FDG-avid lymphoma or PET positive prior to therapy	$> 50\%$ increase from nadir in the SPD of any previous lesions	New or recurrent involvement

J Clin Oncol. 2007 Feb 10;25(5):579-86..

Revised response criteria for malignant lymphoma.

PET/CT Standardized Response Criteria: Interobserver Consistency

**Inter-observer consistency crucial for
meaningful future research and clinical
use of PET/CT**

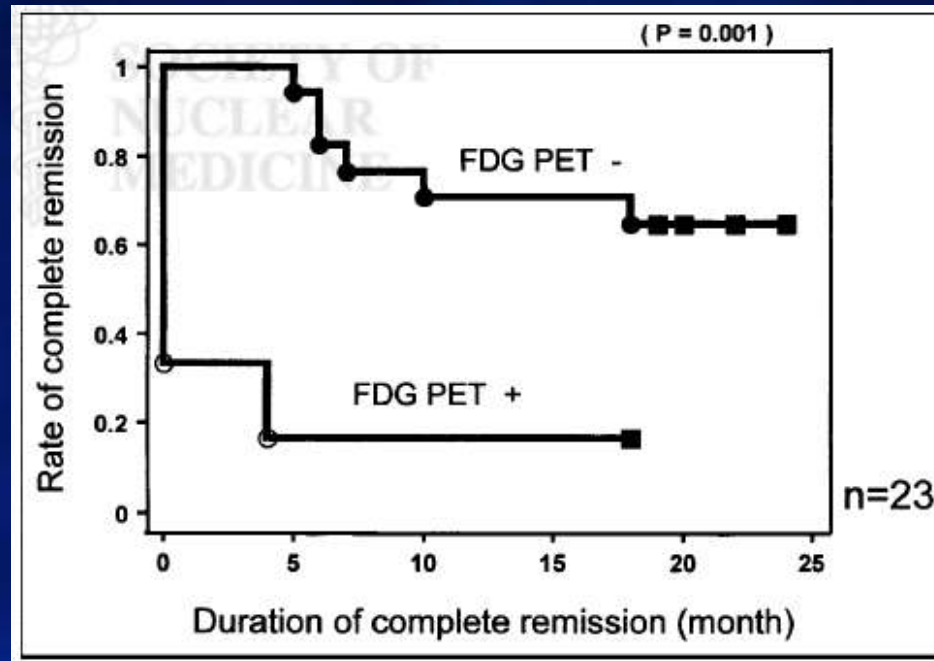
**Agreement rates of 82%-88% achieved
based on “sensitive” and “conservative”
reading guidelines for “positive” or
“negative” scans**

Barrington SF Eur J Nucl Med Mol Imaging. 2010 May 27

PET/CT Imaging: End of Treatment Evaluation

- Does a negative scan indicate a better prognosis?
- Does persistent disease mandate further therapy?
- What is false positive rate with PET/CT at end of therapy?

PET/CT Imaging: End of Treatment Response



End of Chemo

Early adult study with coincidence PET

Kostakoglu (2002) JNM

PET/CT Imaging: End of Treatment Evaluation and FP Findings

- From a clinicians standpoint, an on-going issue is end of treatment FP PET.
- Investigators have reported high incidences of FP (20%) end of treatment PET scans with low PPV (11-25%).

Depas (2005) Eur J Nuc Med Mol Img

Levine (2006) J Ped Hematol Onc

Wong (2007) Mol Img Biol

Ediline (2007) Leukemia Lymphoma

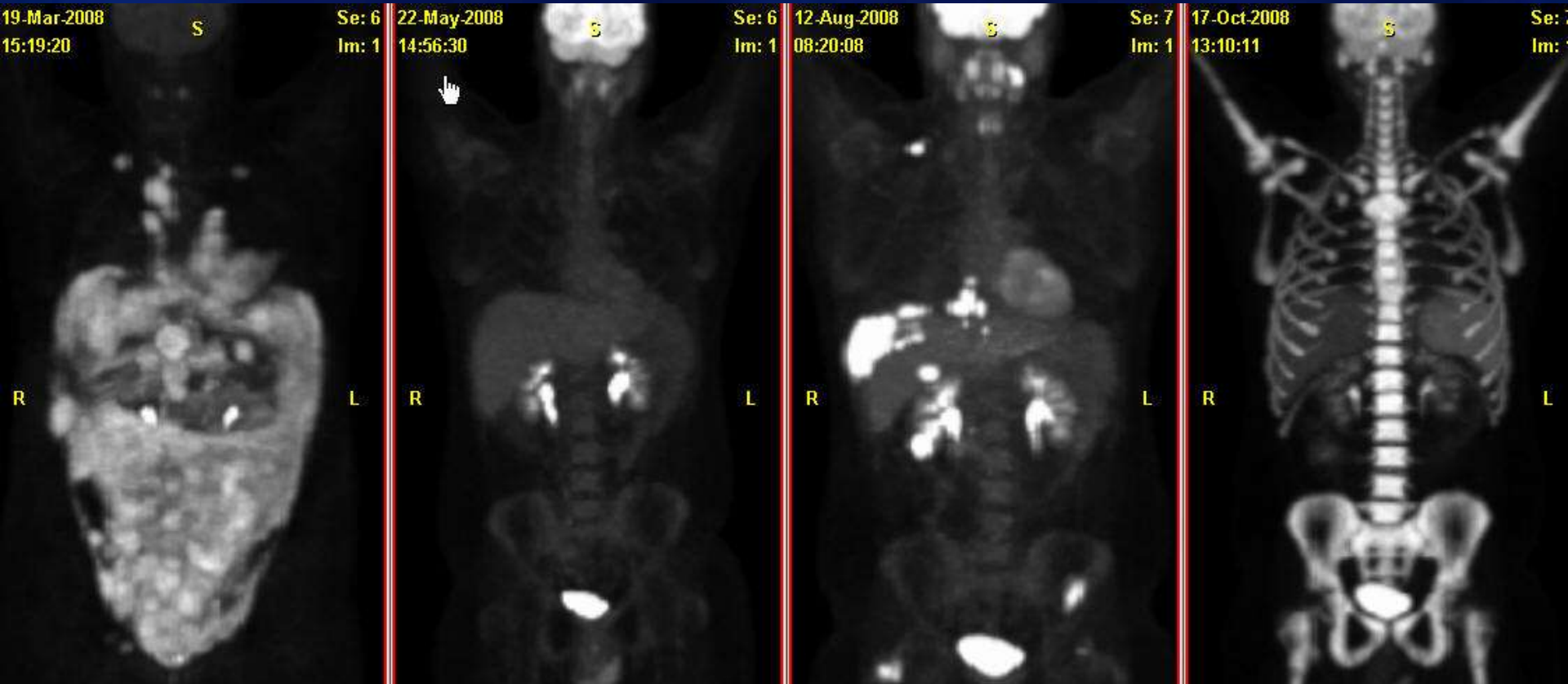
Furth (2009) J Clin Onc

PET/CT Imaging: End of Treatment Evaluation and FP Findings

Comparison to baseline scans, co-localization with CT, quantitation with SUVs and increased experience with brown fat can decrease FP.

Mardis (2007) J Ped Hematol Onc
Ediline (2007) Leukemia Lymphoma

PET/CT Imaging End of Treatment Evaluation: True Positive



Initial

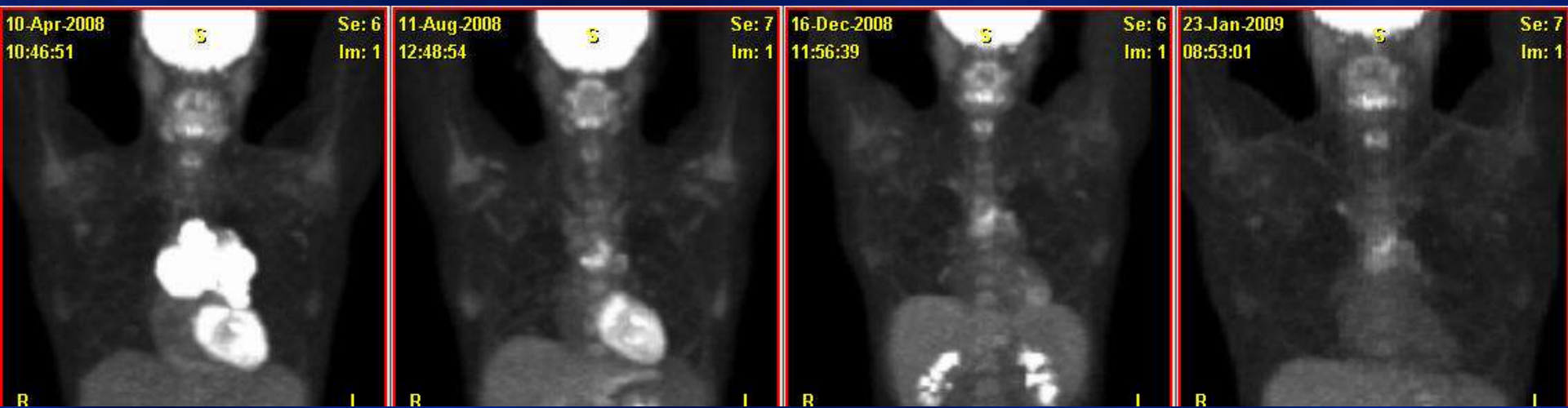
Early Tx

“End of Tx”

2nd CR

16 year old Burkitt Lymphoma

PET/CT Imaging End of Treatment Evaluation: False Positive



Initial

End TX

Surveillance

**17 yr old with B Cell Lymphoma, CT Chest
stable through 12/09**

PET/CT Imaging: Surveillance

- Does surveillance lead to early recurrence detection and improved long-term outcomes?
- If so, what is an appropriate schedule for surveillance?

PET/CT Imaging: Surveillance

25/156 surveillance PET scans were + despite CR in f/u for 1 yr PPV= 11%

Levine (2006) J Hematol Oncol

Only 2/11 + surveillance PET were associated with recurrent lymphoma for PPV = 18%

Meany 2007 Pediatr Blood Cancer

All 5/5 surveillance PET were associated with recurrent lymphoma for PPV = 100%

Riad 2009 Eur J Nucl Med Mol Imag

PET/CT Imaging: Current Guidelines

Histology	Pretreatment	Mid-Treatment	Response Assessment	Post-Treatment Surveillance
Routinely FDG avid				
DLBCL	Yes*	Clinical trial	Yes	No
HL	Yes*	Clinical trial	Yes	No
Follicular NHL	No†	Clinical trial	No†	No
MCL	No†	Clinical trial	No†	No
Variably FDG avid				
Other aggressive NHLs	No†	Clinical trial	No†‡	No
Other indolent NHLs	No†	Clinical trial	No†‡	No

Abbreviations: PET, positron emission tomography; CT, computed tomography; FDG, [¹⁸F]fluorodeoxyglucose; DLBCL, diffuse large B-cell lymphoma; HL, Hodgkin's lymphoma; NHL, non-Hodgkin's lymphoma; MCL, mantle-cell lymphoma; ORR, overall response rate; CR, complete remission.

*Recommended but not required pretreatment.

†Recommended only if ORR/CR is a primary study end point.

‡Recommended only if PET is positive pretreatment.

Cheson (2007) J Clin Oncol

PET/CT Imaging of Pediatric Lymphoma: Summary

- Research has not yet fully established PET/CT in the evaluation of pediatric lymphomas.
- Wide variety of histologies, imaging protocols, imaging schedules and lack of consistent interpretive guidelines has left many questions unanswered.
- PET/CT single best staging study
- PET/CT early in treatment can predict early and late treatment response.

PET/CT Imaging of Pediatric Lymphoma: Summary

- **PET/CT early in treatment may be able to allow for response-adapted therapy.**
- **PET/CT early in and/or at the end of treatment may stratify patients to less invasive therapy; specifically, it may allow for elimination of IFRT with negative effect.**
- **No established role for surveillance.**

PET/CT Imaging of Pediatric Lymphoma: Summary

- PET/CT > CIM, esp Gallium, **may** replace BMA
- PET/CT for response-adaptive therapy is promising but still needs large scale studies for validation
- Role of PET/CT in surveillance?
- Avoid false negatives early and **false positives late**. Biopsy if result changes treatment
- Baseline studies crucial

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