Potential Applications of PET/CT in T-cell Lymphoma

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OUTLINE

- Epidemiology, classification, prognosis
- FDG PET imaging features
- FDG PET/CT in diagnosis and staging
- FDG PET/CT for response assessment and prognosis
- Clinical trials, emerging data, discussion points

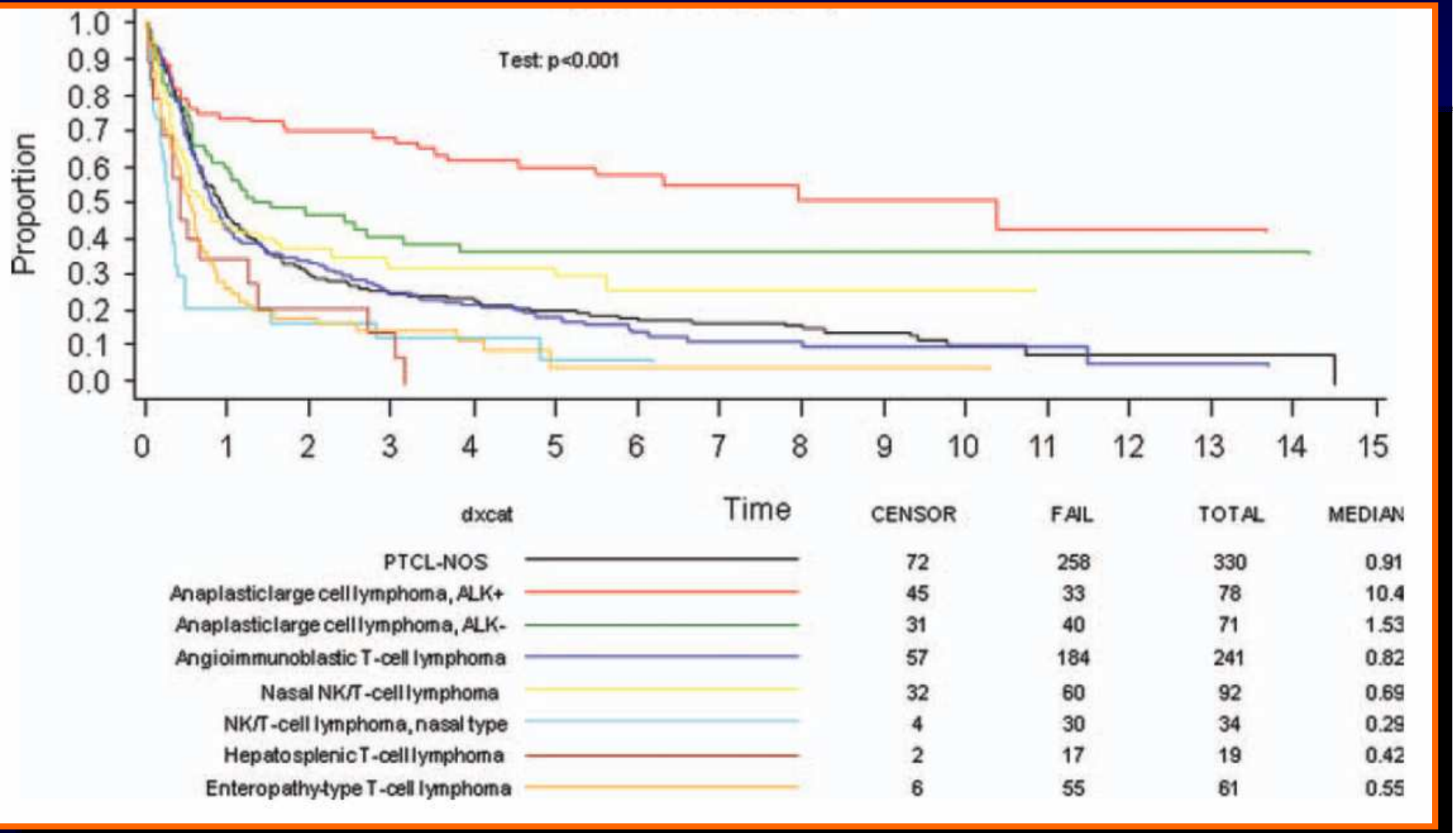
Peripheral T-cell Lymphomas

- Usually indolent with extra-nodal presentation
  - Mycosis fungoides and variants
  - Cutaneous CD30 positive cutaneous lymphoproliferative disorders
    - Lymphomatoid papulosis
    - Cutaneous anaplastic large cell lymphoma
  - Subcutaneous panniculitis-like T-cell lymphoma
  - Primary cutaneous CD4-postive small/medium T-cell lymphoma
- Usually aggressive-typically nodal presentation
  - *Angioimmunoblastic T-cell lymphoma*
  - *Anaplastic large cell lymphoma*
    - *ALK positive*
    - *ALK negative*
  - *Peripheral T-cell lymphoma–not otherwise specified*
  - Adult T-cell lymphoma/leukemia
- Usually aggressive-typically extra-nodal presentation
  - *Extra-nodal NK/T cell lymphoma, nasal type*
  - *Enteropathy type intestinal T-cell lymphoma*
  - *Hepatosplenic T-cell lymphoma*
  - EBV positive lymphoproliferative disorders of childhood
  - Primary cutaneous gamma-delta T-cell lymphoma
  - Primary cutaneous CD-8 positive aggressive epidermotropic cytotoxic T-cell lymphoma
- Typically Leukemic Presentation
  - T-cell prolymphocytic leukemia
  - T-cell large granular lymphocytic leukemia
  - Chronic lymhoproliferative disorders of NK cells
  - Aggressive NK-cell leukemia

10-15% of lymphoid malignancies

Armitage.Am J Hematol 2012

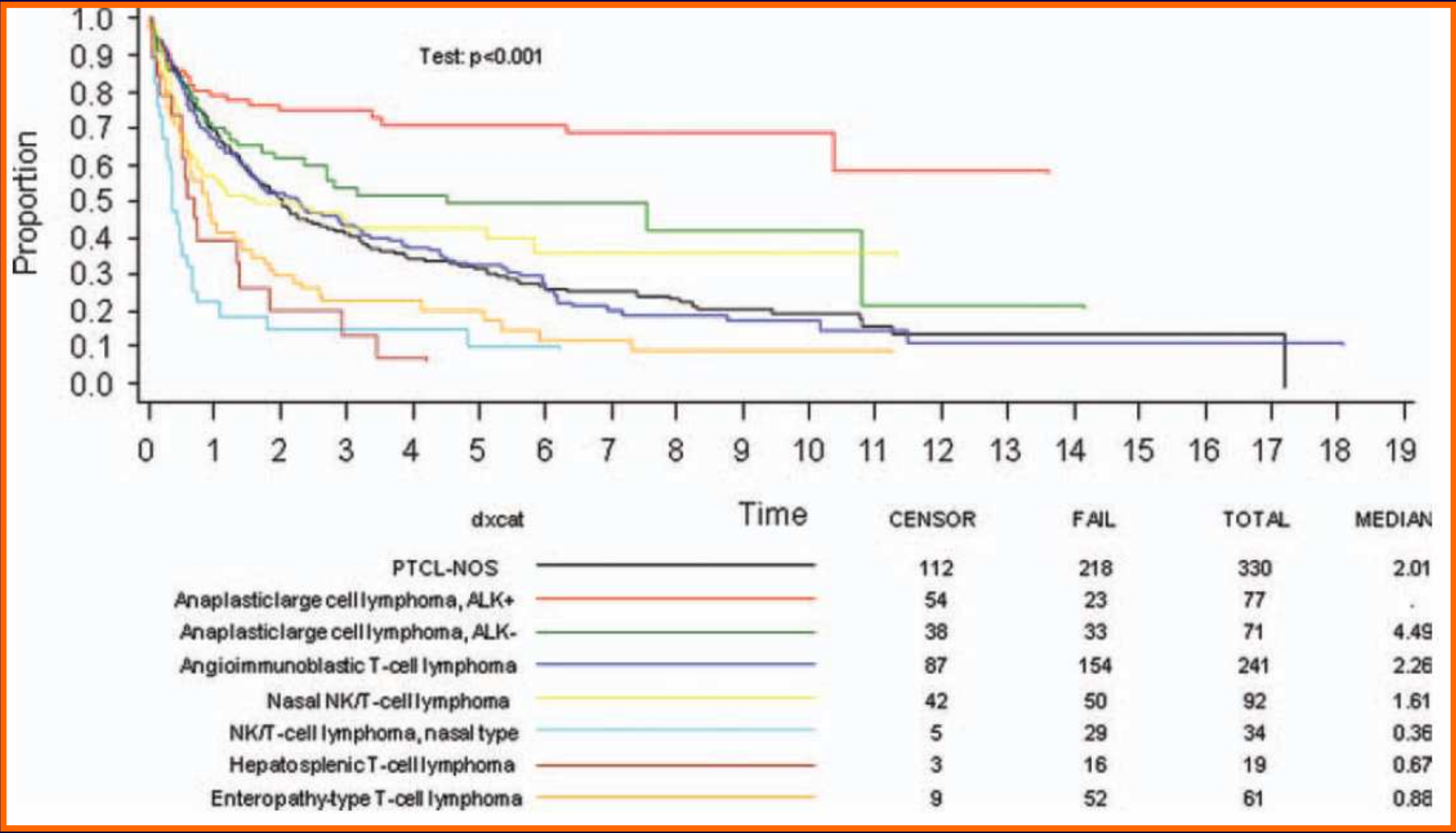
Failure-Free Survival



dxcat	CENSOR	FAIL	TOTAL	MEDIAN
PTCL-NOS	72	258	330	0.91
Anaplastic large cell lymphoma, ALK+	45	33	78	10.4
Anaplastic large cell lymphoma, ALK-	31	40	71	1.53
Angioimmunoblastic T-cell lymphoma	57	184	241	0.82
Nasal NK/T-cell lymphoma	32	60	92	0.69
NK/T-cell lymphoma, nasal type	4	30	34	0.29
Hepatosplenic T-cell lymphoma	2	17	19	0.42
Enteropathy-type T-cell lymphoma	6	55	61	0.55

Armitage.Am J Hematol 2012; Vose et al. J Clin Oncol 2008;26:4124-30

Overall Survival



dxcat	CENSOR	FAIL	TOTAL	MEDIAN
PTCL-NOS	112	218	330	2.01
Anaplastic large cell lymphoma, ALK+	54	23	77	.
Anaplastic large cell lymphoma, ALK-	38	33	71	4.49
Angioimmunoblastic T-cell lymphoma	87	154	241	2.26
Nasal NK/T-cell lymphoma	42	50	92	1.61
NK/T-cell lymphoma, nasal type	5	29	34	0.36
Hepatosplenic T-cell lymphoma	3	16	19	0.67
Enteropathy-type T-cell lymphoma	9	52	61	0.88

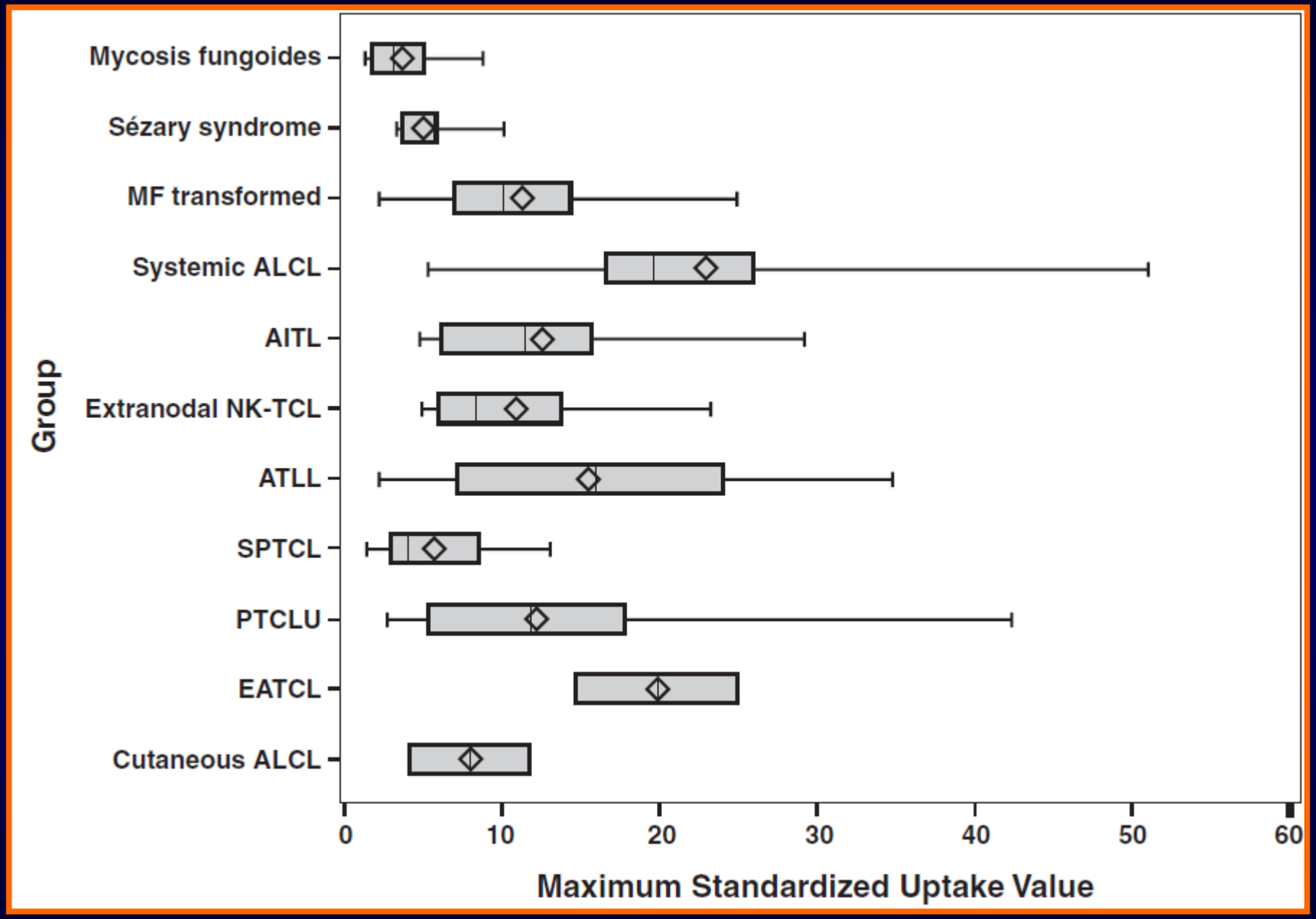
Armitage.Am J Hematol 2012; Vose et al. J Clin Oncol 2008;26:4124-30

PET Imaging Findings

FDG PET in T-cell Lymphomas
Summary of PET Imaging Findings

- 135 pts, 90% with FDG+ disease
- Cannot determine true sen and spec
- Uptake seen in all entities, from 50% (cutaneous ALCL) to 100% of cases
- Interesting features:
  - Field of view should extend from vertex of skull to feet
  - Lower detection rate for cutaneous lesions
  - MF patches not detected; plaques and nodules + ***(need to adjust display settings!)***
  - MF transformation occurs in up to 39% of cases; shows higher SUV's in this study

Feeney et al. AJR 2010;195:333-40



Vertical: mean; diamond: median; box: 25-75th percentile, whiskers 10-90%

Feeney et al. AJR 2010;195:333-40

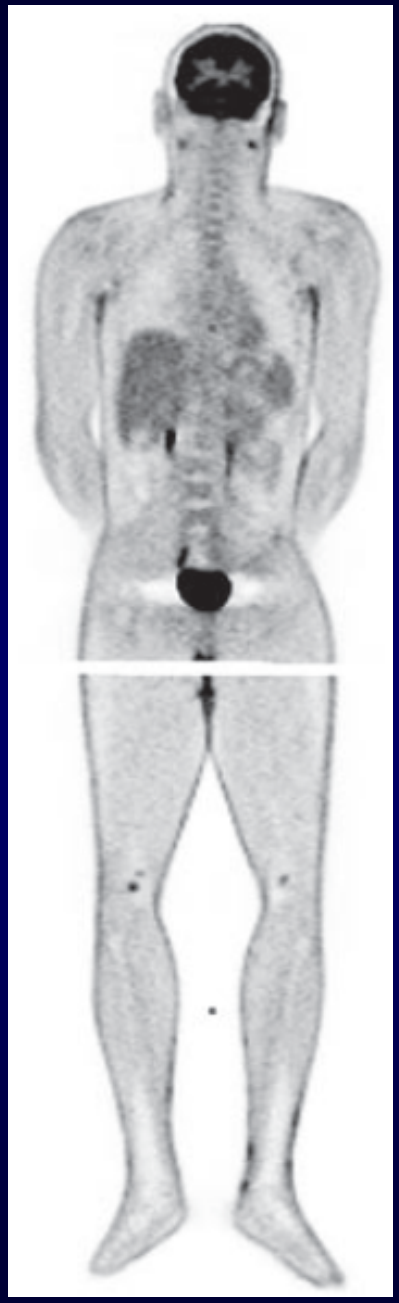
FDG PET in T-cell Lymphomas

Summary of PET Imaging Findings

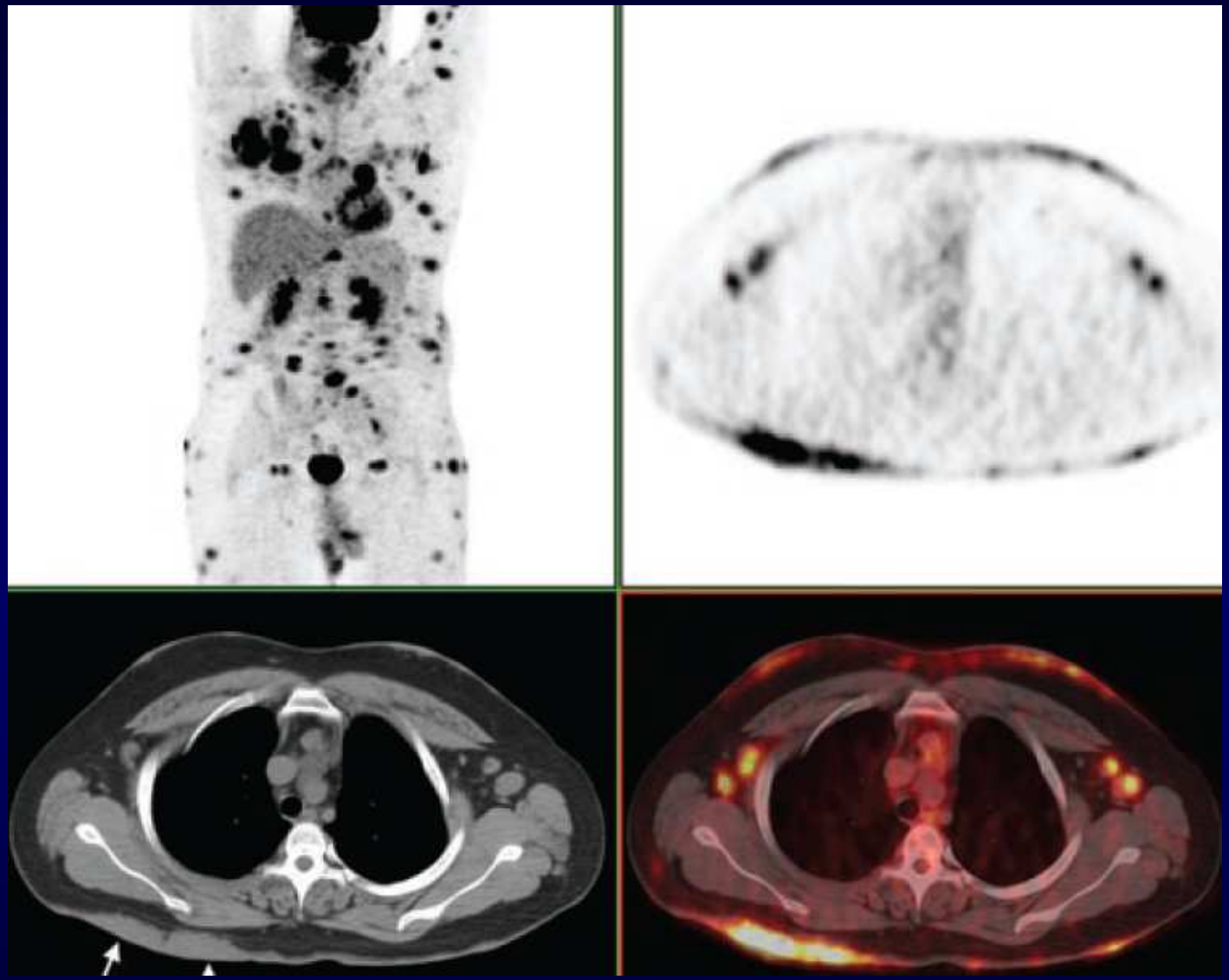
Type of Lymphoma	No. of Patients	Sex, No. of Patients		PET Scan Positive, No. of Patients/ Total (%)	Type of Disease, No. of Patients/Total			Disease Outside Field of View,[a] No. of Patients	Maximum Standardized Uptake Value, Mean (Range)
		Male	Female		Cutaneous	Nodal	Visceral		
PTCLU	34	24	10	33/34 (97)	8/33	29/33	17/33	7	12.3 (2.8–42.3)
Systemic ALCL	16	11	5	15/16 (94)	4/15	15/15	8/15	3	22.9 (5.3–51.0)
AITL	18	7	11	14/18 (78)	0/14	14/14	7/14	0	12.6 (4.8–29.2)
Mycosis fungoides	12	6	6	10/12 (83)	9/10	4/10	0/10	5	3.8 (1.4–8.9)
Sézary syndrome	8	3	5	8/8 (100)	5/8	8/8	1/8	2	5.0 (3.4–10.2)
Transformed mycosis fungoides	11	5	6	10/11 (91)	9/10	8/10	4/10	7	11.3 (2.3–25.0)
Extranodal NK-TCL	12	11	1	10/12 (83)	6/10	6/10	7/10	5	10.8 (4.9–23.3)
SPTCL	9	7	2	9/9 (100)	9/9	1/9	1/9	6	5.7 (1.5–13.1)
ATLL	9	2	7	9/9 (100)	3/9	8/9	6/9	4	15.5 (2.3–34.8)
Cutaneous ALCL	4	3	1	2/4 (50)	2/2	1/2	1/2	0	8.05 (4.2–11.9)
EATCL	2	0	2	2/2 (100)	0/2	1/2	2/2	0	19.9 (14.7–25.0)
Total	135	79	56	122/135 (90)	55/122	95/122	54/122	39	—

Note—AITL = angioimmunoblastic T-cell lymphoma, ALCL = anaplastic large cell lymphoma, ATLL = adult T-cell leukemia lymphoma, EATCL = enteropathy-associated T-cell lymphoma, NK-TCL = extranodal natural killer cell–T-cell lymphoma, PTCLU = peripheral T-cell lymphoma, unclassified, SPTCL = subcutaneous panniculitis-like T-cell lymphoma.

Feeney et al. AJR 2010;195:333-40



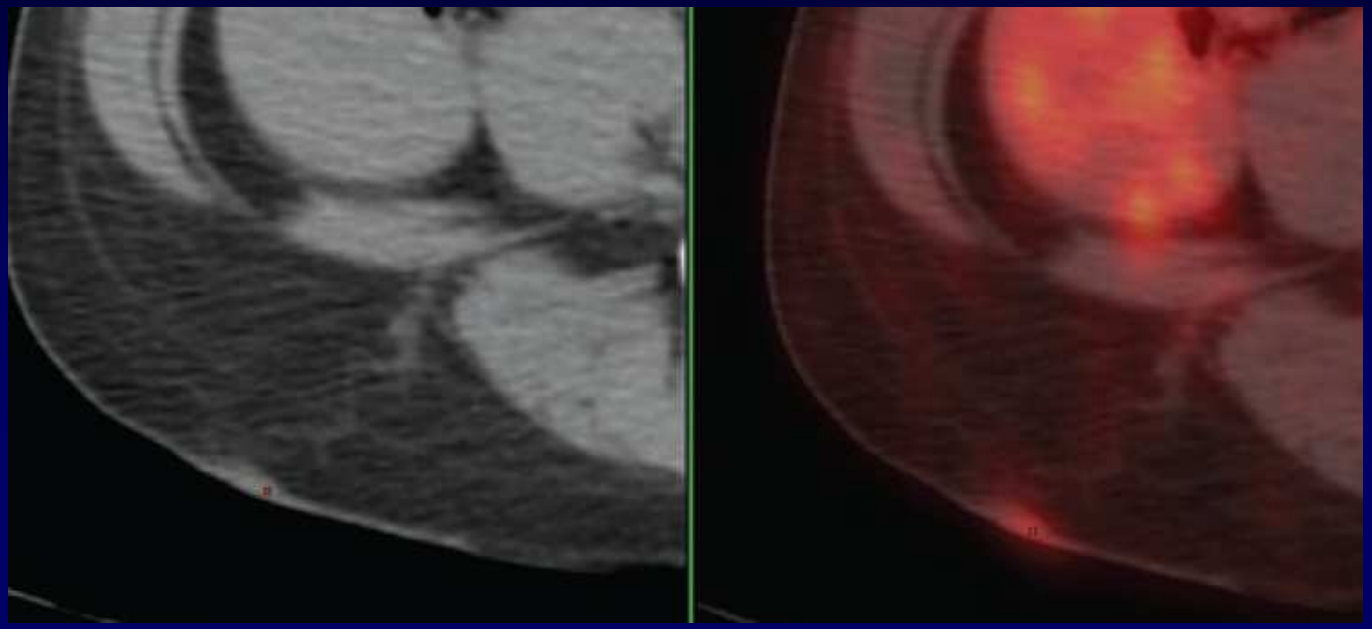
Sezary syndrome



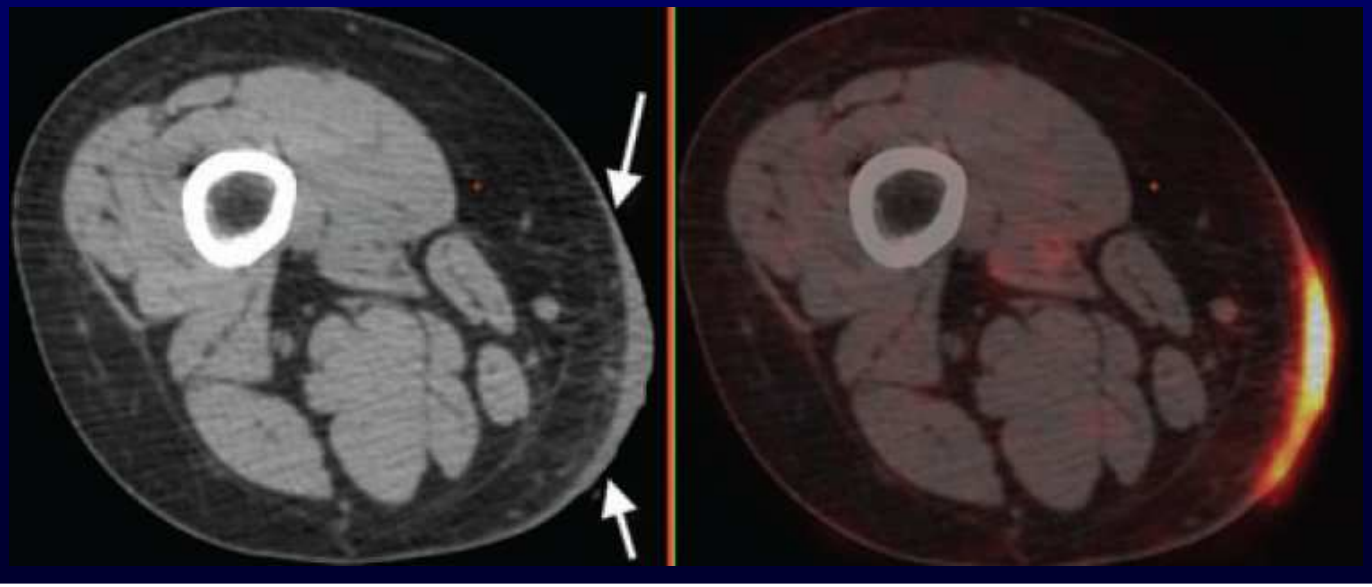
NK/T-cell lymphoma, nasal type

Feeney et al. AJR 2010;195:333-40

MF – Spectrum of Findings



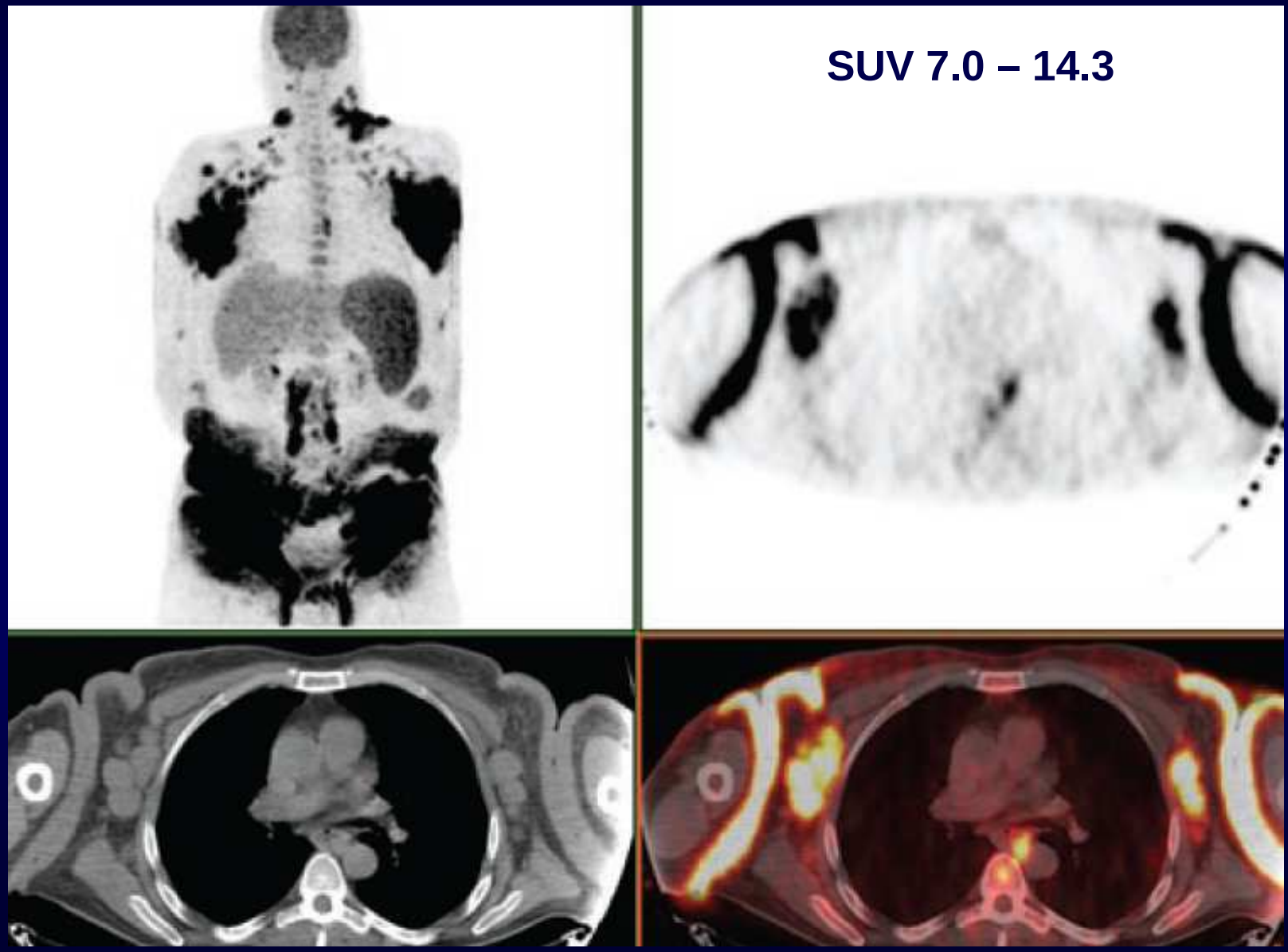
SUV 1.4



SUV 8.9

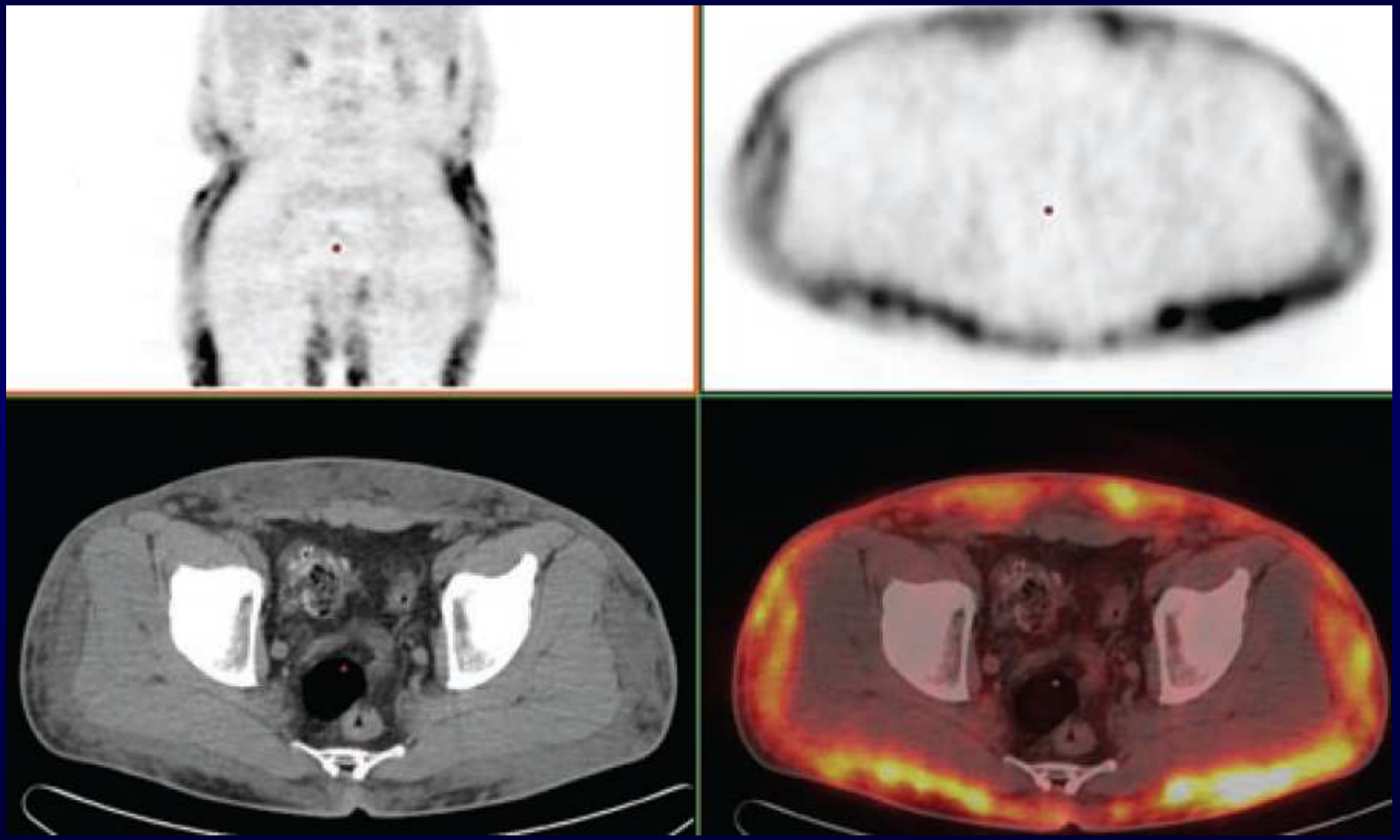
Feeney et al. AJR 2010

MF transformed



Feeney et al. AJR 2010

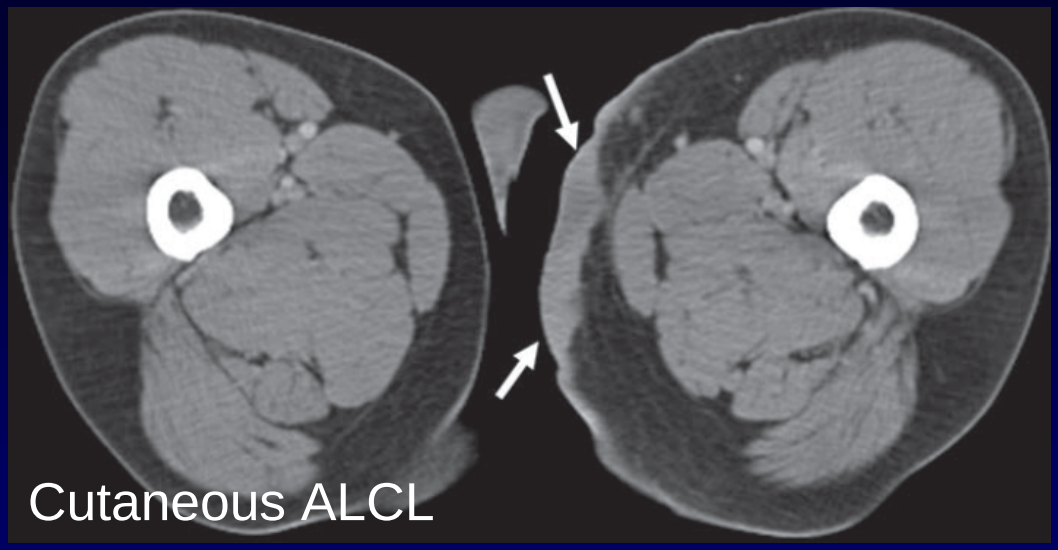
Subcutaneous Panniculitis-like TCL

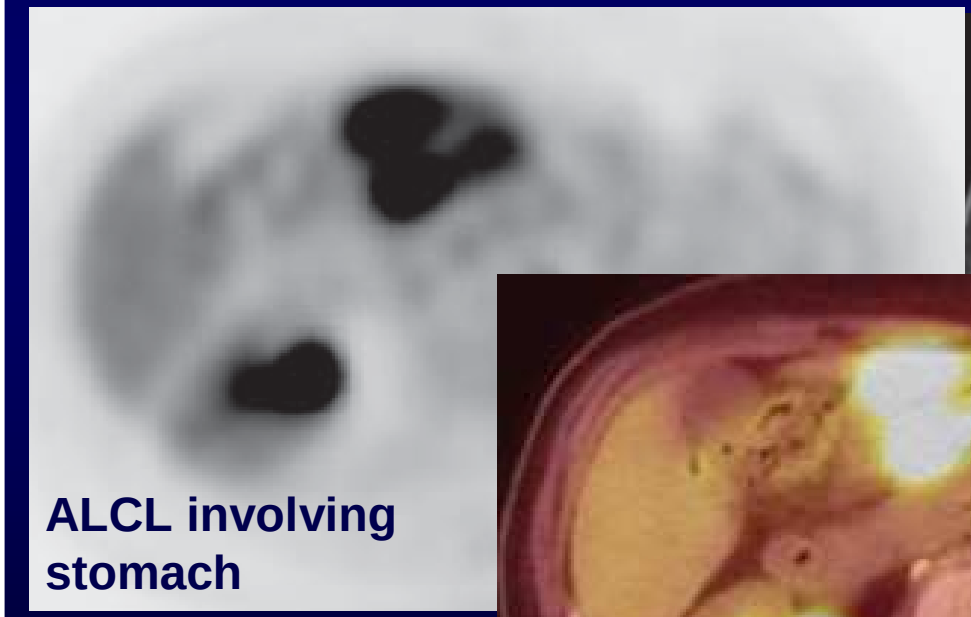


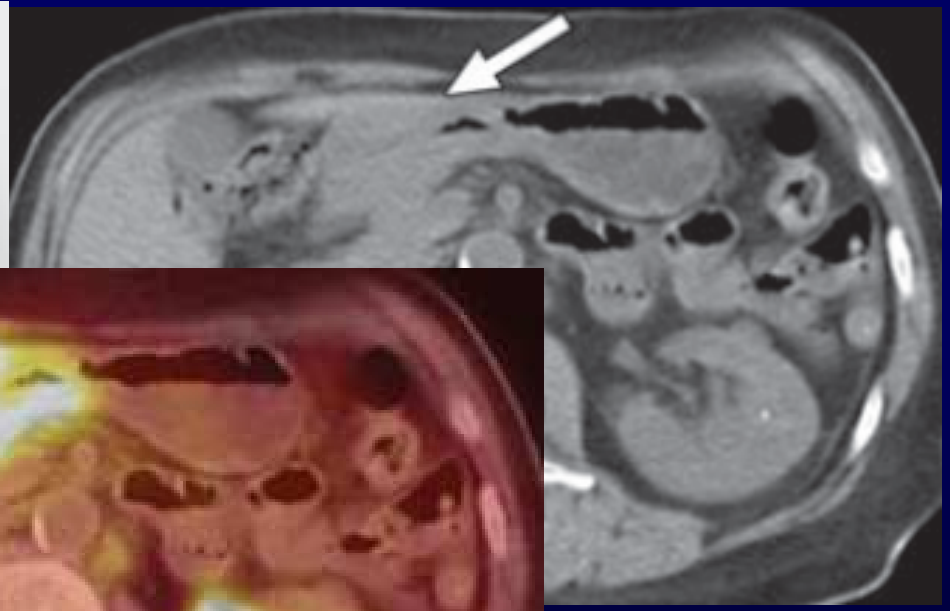
SPL Pat 1: SUV range 5.0 – 13.7

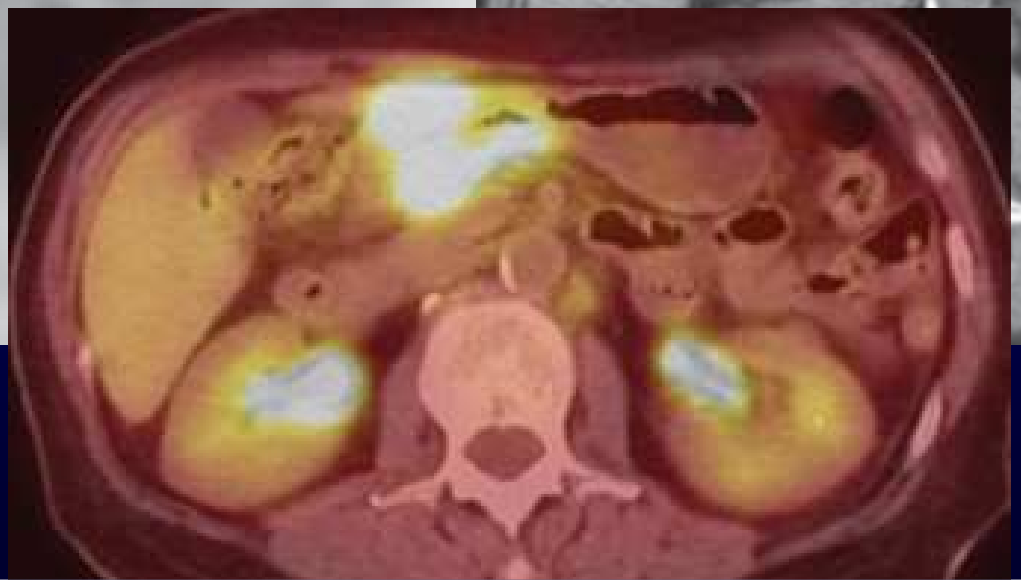
SPL Pat 2

Feeney et al. AJR 2010





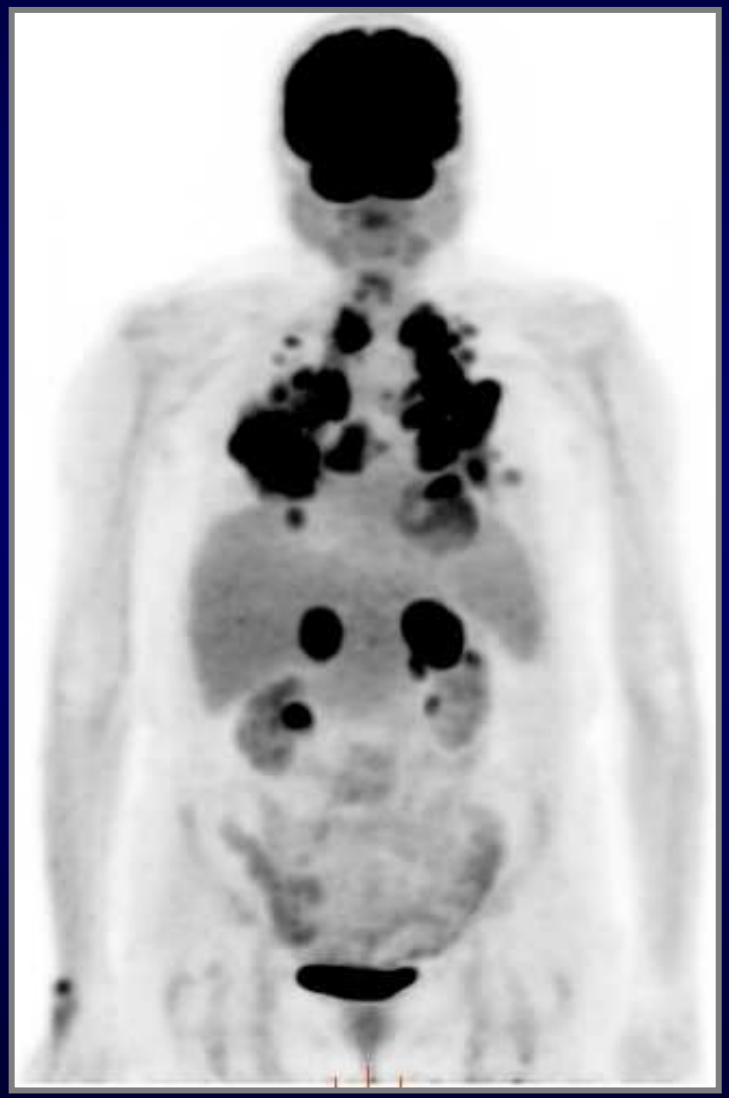




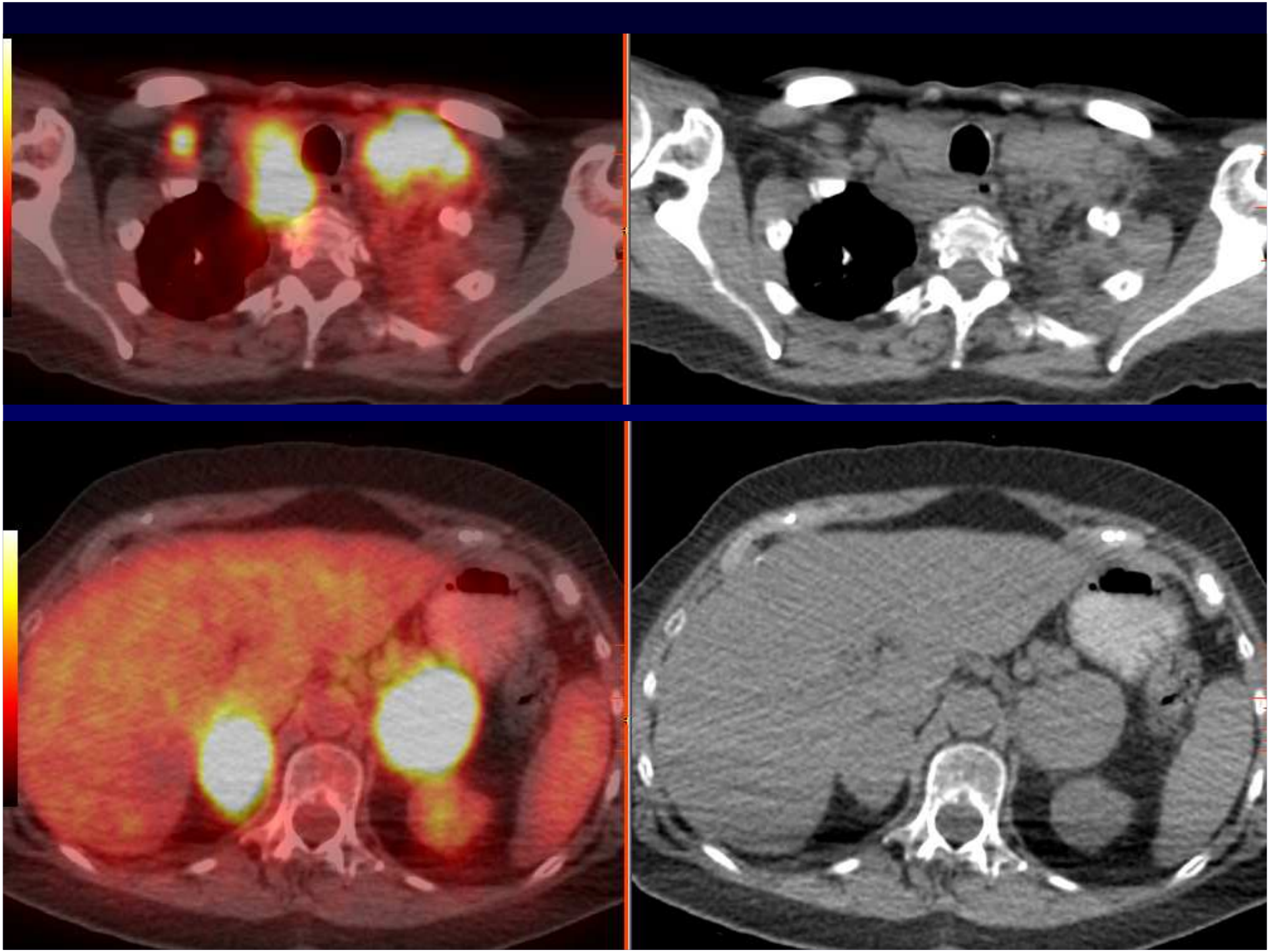
ALCL involving stomach

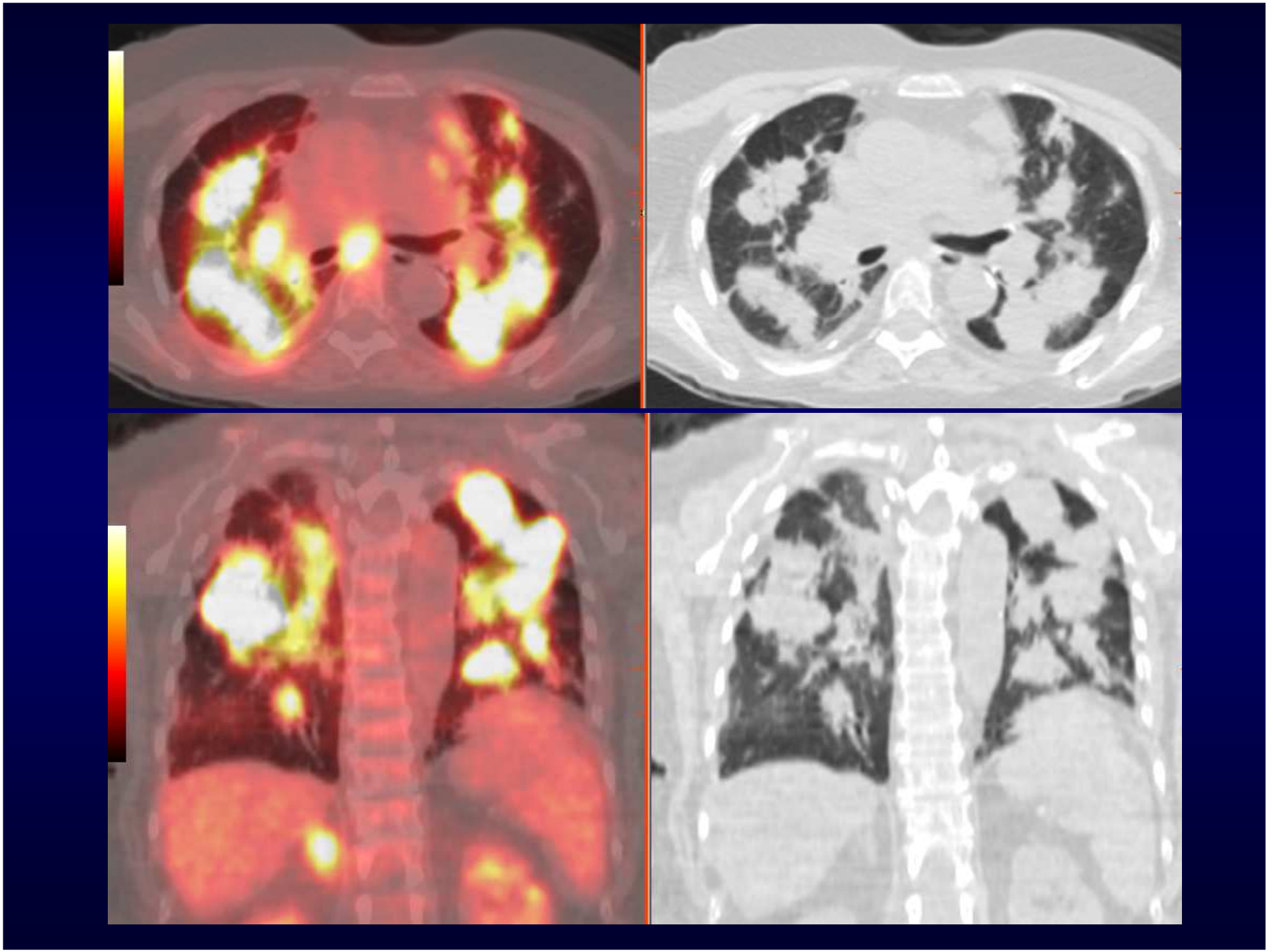
from Otero, AJR 2009

Angioimmunoblastic T-cell Lymphoma



- FDG MIP
- Widespread FDG-avid disease
- Lymph nodes, lungs, adrenal glands
- Progression on brentuximab (adrenals, lung nodules)





FDG PET/CT in Diagnosis and Staging of PTCL

FDG PET for Staging of PTCL

- 94 pts with mature NK/T-cell lymphoma
- Variety of entities; excluded primary cutaneous TCL
- 91/94 pts (97%) of staging scans were PET+
  - SUV 1.1 – 20.5 *(→ careful adjustment of display settings in order to detect small volume disease!)*
  - PET detected additional sites in 25/95
    most common: neck, supraclavicular LN, nasopharynx; 10 bone; 1 incidental HNSCC
- Stage altered in 5.3%* *(because most already had advanced disease; 2 upstaged I > III or II > IV; 3 downstaged)*

**c/w GOELAMS study: 20% upstaged*

Casulo, Horwitz et al. 2012

Extranodal NK/T-Cell Lymphoma

- 19 untreated pts w/ NK/T-cell lymphoma, *nasal type*
- Total of 116 lesions
- PET/CT detected 108/116 lesions

Lesion detection rate	**PET/CT**	**CT only**
Nodes	28/28	26/28
Extra-nodal	84/89	54/89
Cutaneous	31/31	20/31

- Suboptimal for bone marrow involvement
- **Change in stage**

	stage I-II	stage III-IV
CT	53%	47%
PET/CT	42%	58%

Fujiwara et al. Eur J Hematol 2011;87:123-9

Cutaneous Lesions

- PET detection rate is related to lesion size *(nodule > plaque > erythrodermia)* and intensity of uptake

Histology	All lesions				Extracutaneous lesions*			
	Positive FDG+	Negative FDG -	Total	%Pc (95%	Positive	Negative	Total	%Po (95%
PTCLu	10	1	11	91	9	0	9	100 (
ENKL	8	0	8	100	8	0	8	100 (
C-ALCL	3	2	5	60	3	0	3	100 (
AILT	4	0	4	100	4	0	4	100 (
ALCL	3	0	3	100	3	0	3	100 (
MF/SS	1	2	3	33	1	0	1	100 (
Others**	7	0	7	100	6	0	6	100 (
Total	36	5	41	88	34	0	34	100 (

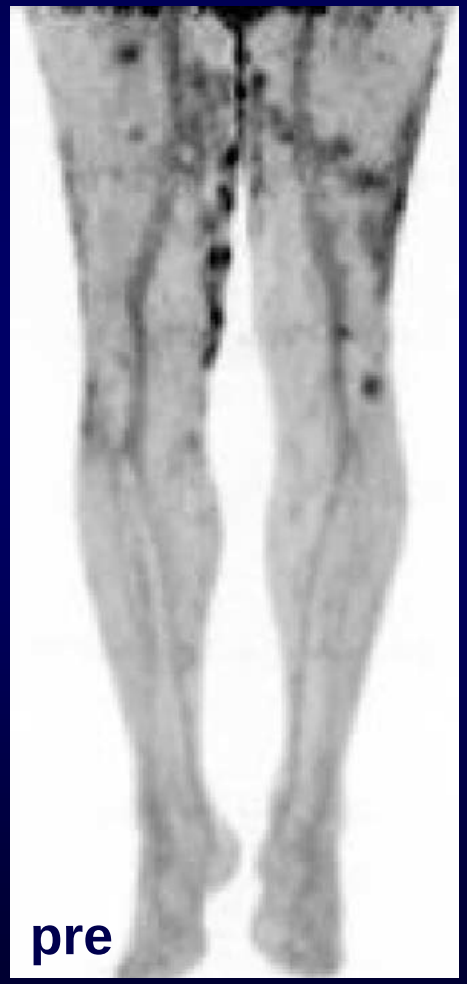
Histology	Positive	Negative	Total	%Positive (95% CI)
PTCLu	2	1	3	67 (9–99)
C-ALCL	2	3	5	40 (5–85)
ENKL	1	0	1	100 (3–100)
ALCL	1	0	1	100 (3–100)
MF/SS*	0	3	3	0 (0–71)
SPTCL	1	0	1	100 (3–100)
Total	7	7	14	50 (23–77)

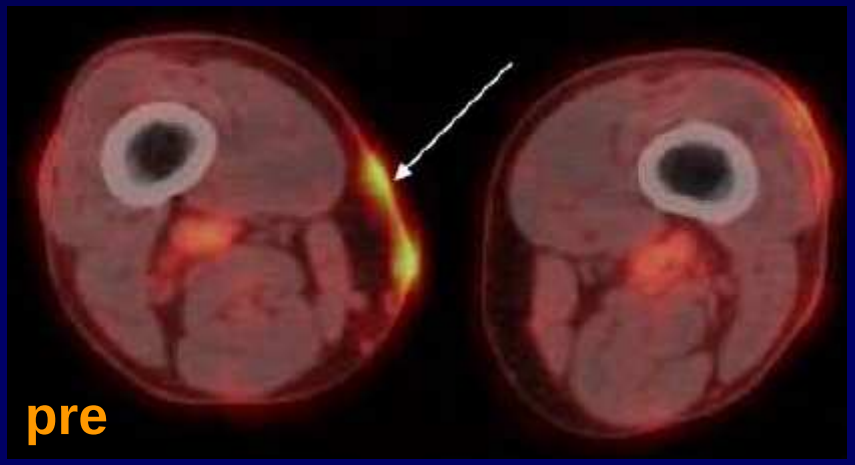
cutaneous lesions

Kako et al. Ann Oncol 2007;18:1685-90

Cutaneous Lesions - Response

- PET possibly helpful in objective response assessment and quantification





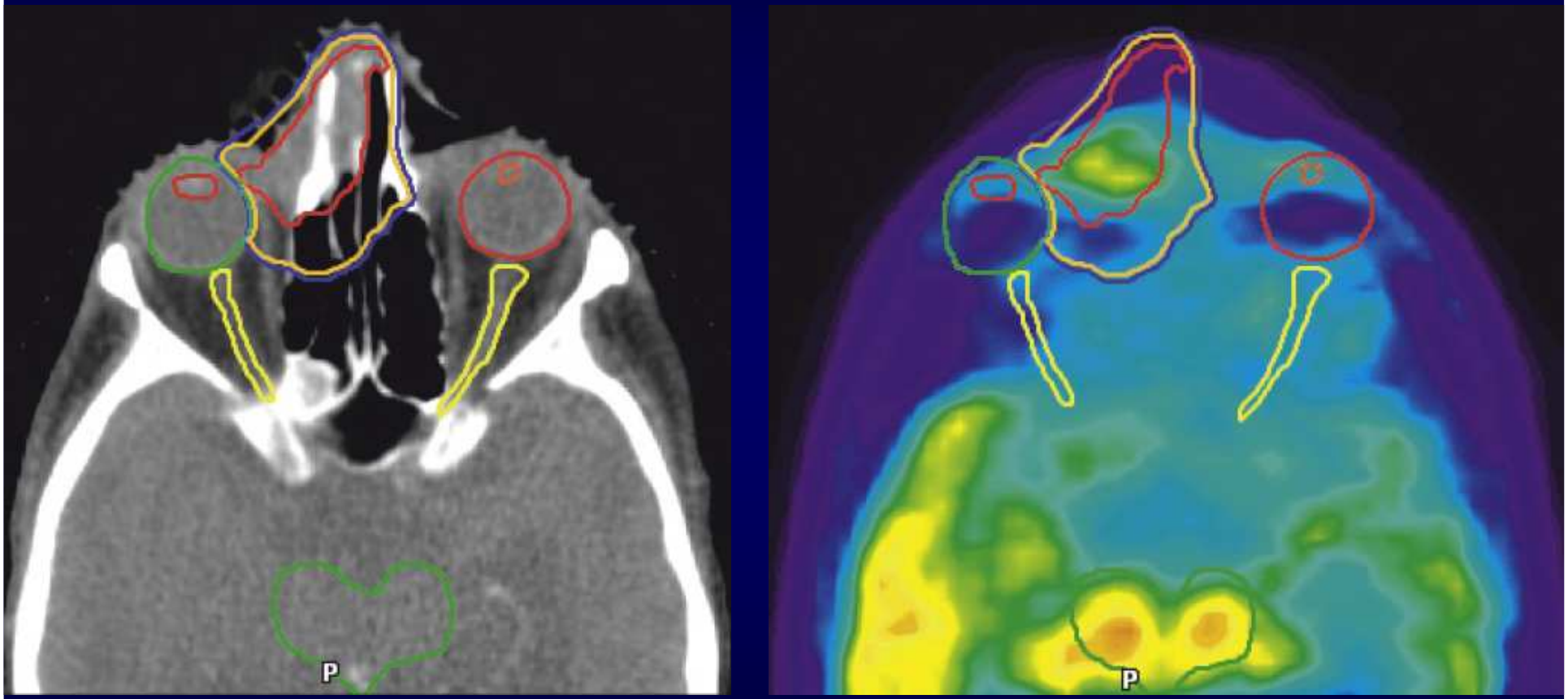
Kuo et al. Mol Im Biol 2008;10:306-14

FDG PET in Enteropathy-type TCL

- Frequently associated with celiac disease
- CT: bowel wall thickening and LAN – nonspecific signs occurring with either entity
- PET: high uptake in ETCL, but lower or no uptake in celiac disease
  - SUV_{max} 6.5 – 8.5 versus 2.2 – 4.6*
- PET more sensitivity and specific than CT
- PET/CT may guide endoscopic biopsies

*Hoffmann, Gut 2003; Hadithi, J Nucl Med 2006

Utility of PET for RT Planning



49 M, recurrent extranodal NK/T-cell lymphoma, nasal type

McDonald, Burrel et al. Radit Oncol 2011;6:182

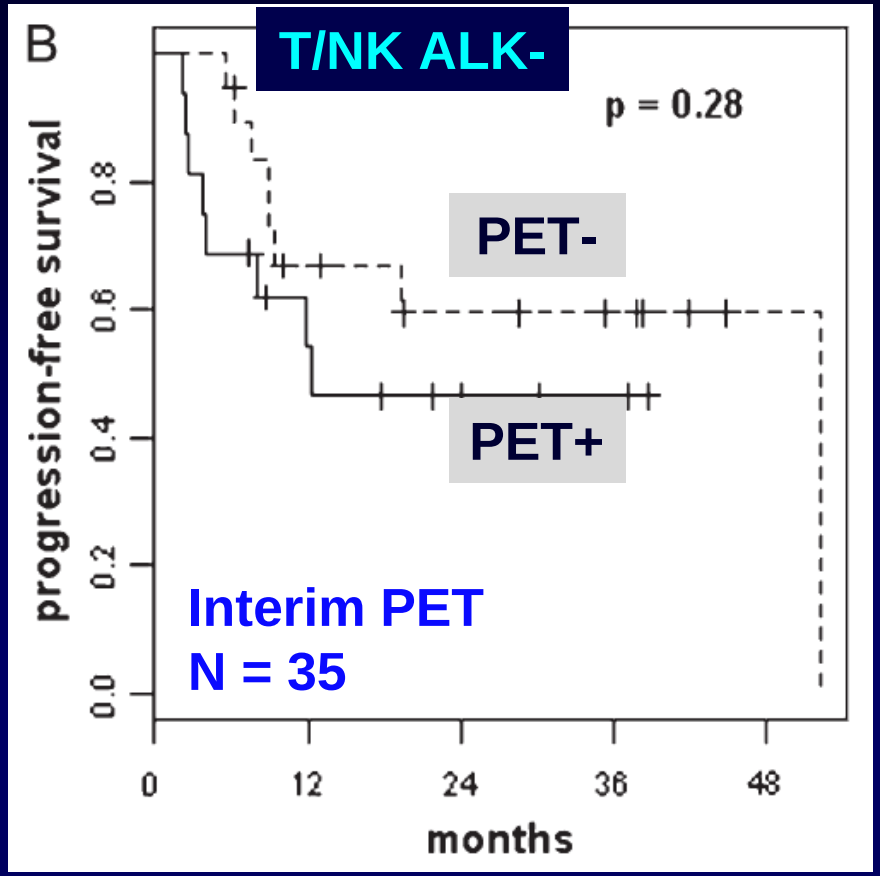
Response Assessment and Prognosis

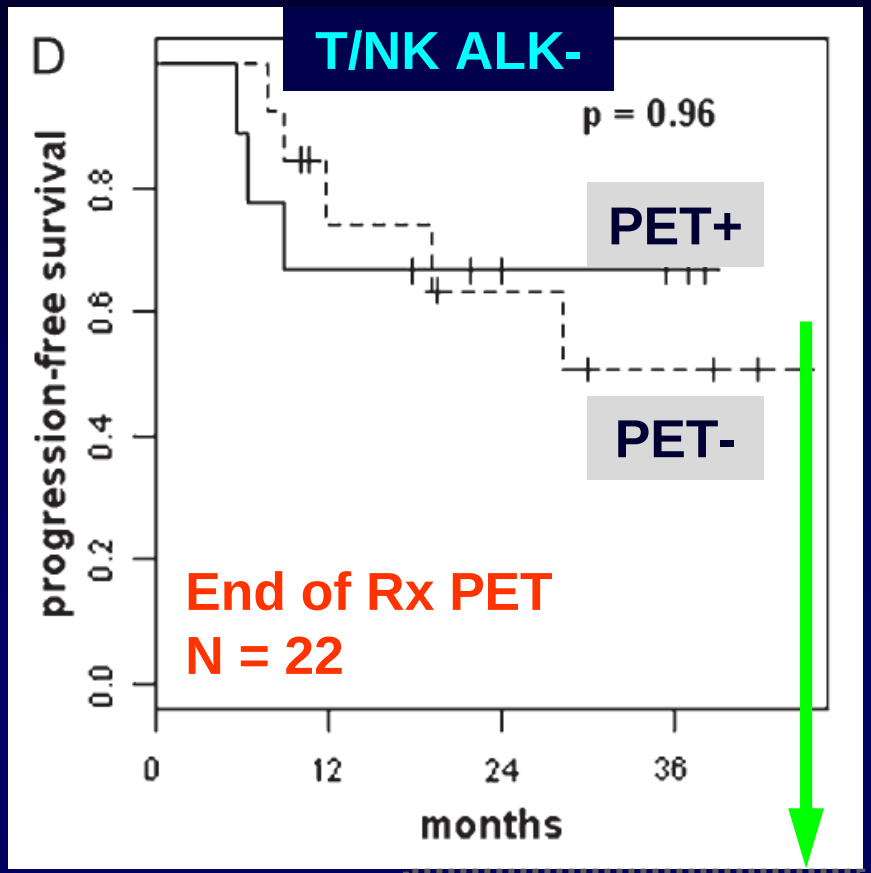
Role of FDG PET in NK/T-cell Lymphoma

GOELAMS Study

- 54 patients before (n=40), during (n=44) and after therapy (n=31); various drug regimens
- 2 groups: ALK+ ALCL *versus* ALK- ALCL plus NK/T-cell
- FDG PET:
  - IHP criteria for end of treatment
  - Interim: 3 point scale: mild – moderate – high uptake (“pure visual”)
- Findings
  - Abnormal uptake in all cases
  - 25/44 interim studies were FDG+
  - Better NPV in ALK+ than in ALK- cases (interim 100% vs 58%)
  - ALK-: neg. interim or end of Rx scan ≠ better PFS or OS

Cahu et al. Ann Oncol 2011;22:705-11





Many FP and FN

	PET+	PET-	*p-value*	PET+	PET-	*p-value*
4yr PFS	46%	59%	0.28	67%	61%	0.73
4 yr OS	42%	69%	0.24	75%	62%	0.71

Cahu et al. Ann Oncol 2011;22:705-11

GOELAMS Study

- Good initial data
- Basis for discussion and design of future trials
- Small sample size
- Selection bias?
- Baseline scan only available for ~75% of pts
- 3 point visual score for interim scan
- Why are PPV and NPV for the end of treatment scan so low?

Much room for improvement

Need to gather more data and design prospective studies with well-defined PET protocol and agreed/reproducible interpretation criteria

Staging and Prognostic Value
MSKCC Study

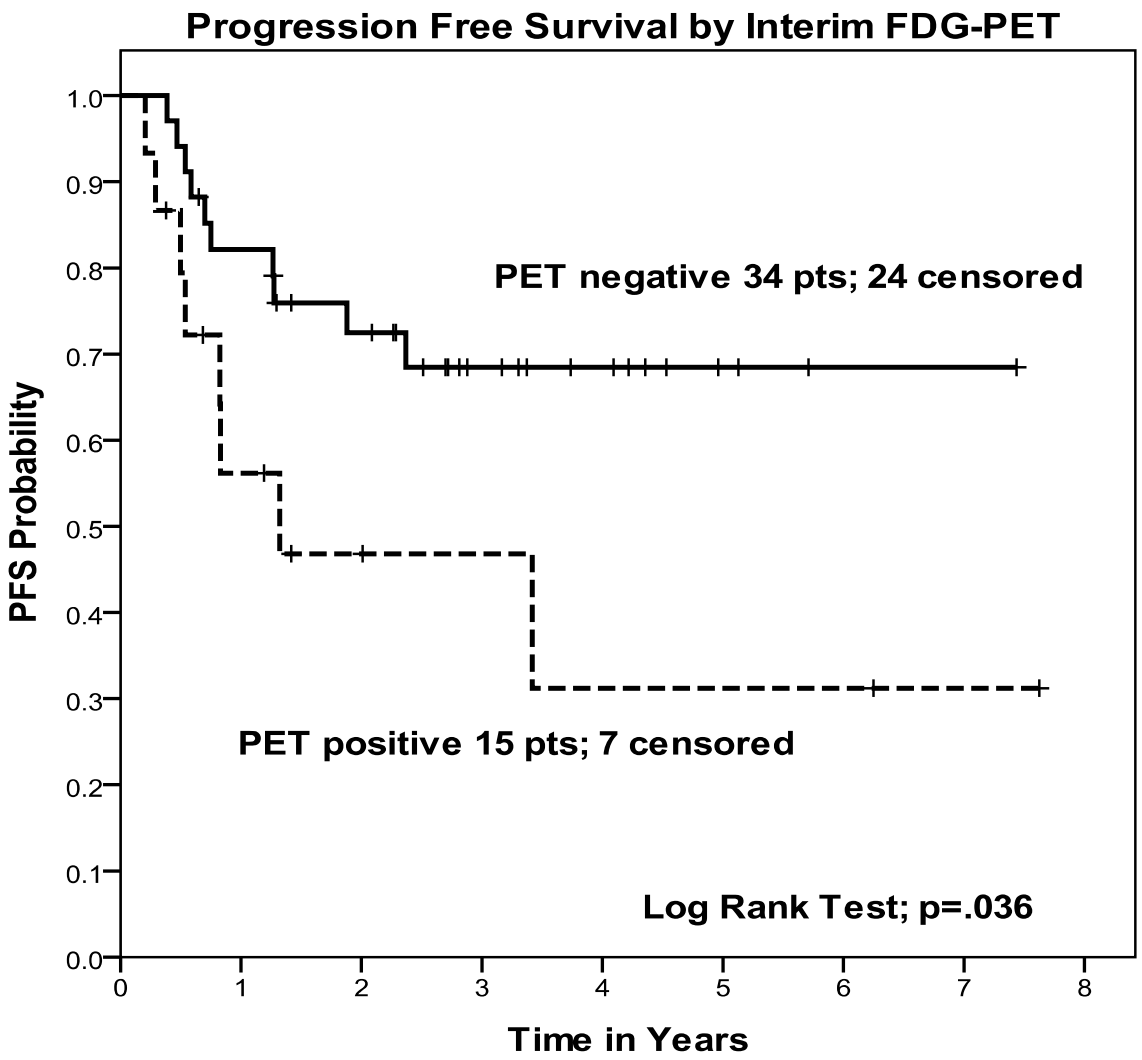
- 94 pts with peripheral T-cell lymphoma
- PET for staging, interim (n=50), end of treatment
- **Interim scan:**
  - after median of 4 cycles
  - cut-off liver: 15 FDG+, 34 FDG-, one equivocal
  - FDG- patients had better PFS (independent of further treatment)
  - no difference in OS (incurable disease)

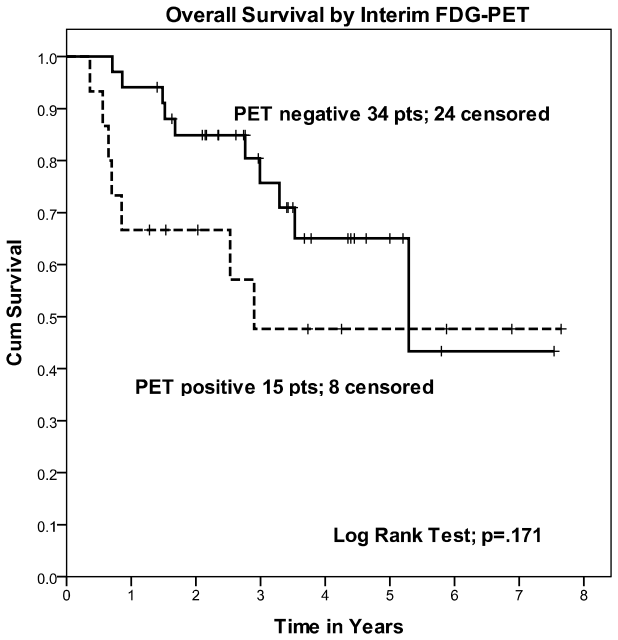
Casulo, Horwitz et al. MSKCC 2012

Characteristic	No.	%
Staging Cohort	94	
Histology		
PTCL, NOS	35	37.2
AITL	17	18
ALCL, ALK- or unknown	12	12.7
ALCL, ALK+	11	11.7
NK/T cell lymphoma	10	10.6
ATLL	6	6.3
EATL	3	3.2
Disease State		
Initial Diagnosis	77	82
Relapsed Disease	17	18
Interim restaging cohort	50	
Histology		
PTCL-NOS	19	38
ALCL, ALK+	9	18
NK/T cell lymphoma	8	16
AITL	6	12
ALCL, ALK- or unknown	5	10
EATL	2	4
HTLV-1 associated lymphoma	1	1.42
Treatment		
Initial Chemotherapy	No.	%
CHOP	19	38
CHOP-ICE	24	48
*Other	7	14
Consolidative Treatment		
Autologous Stem cell transplant	22	44
Allogeneic Stem cell transplant	7	14

Prognostic Value of Interim PET in PTCL

MSKCC 2012

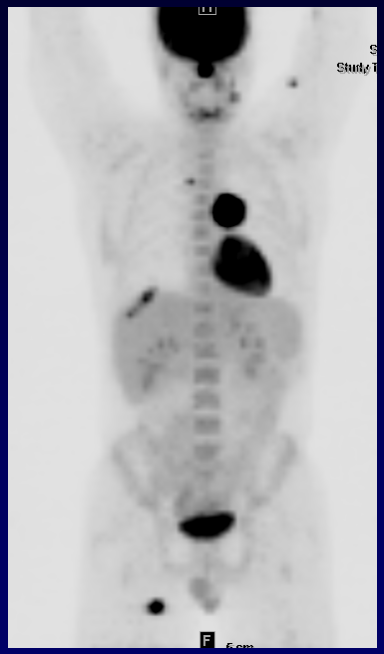




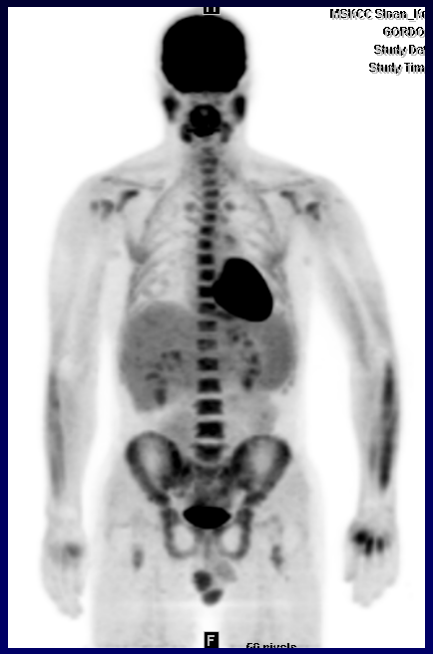
Casulo, Horwitz et al. MSKCC 2012

Interim PET Negative

- Pt 1, GG
- NK/T-cell lymphoma
- Negative interim and end of Rx scans
- Disease free 3 yrs later



Sep 2009



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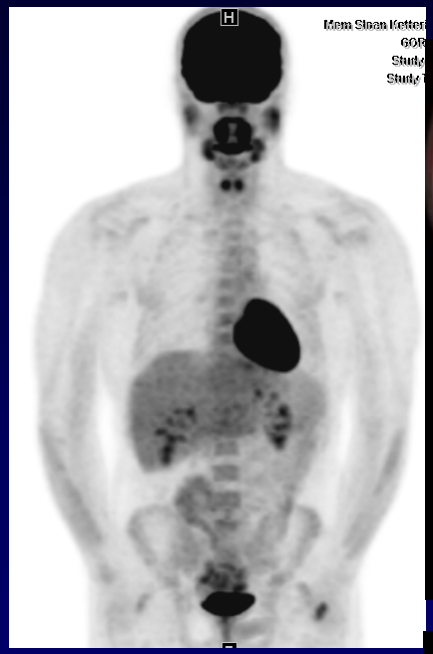

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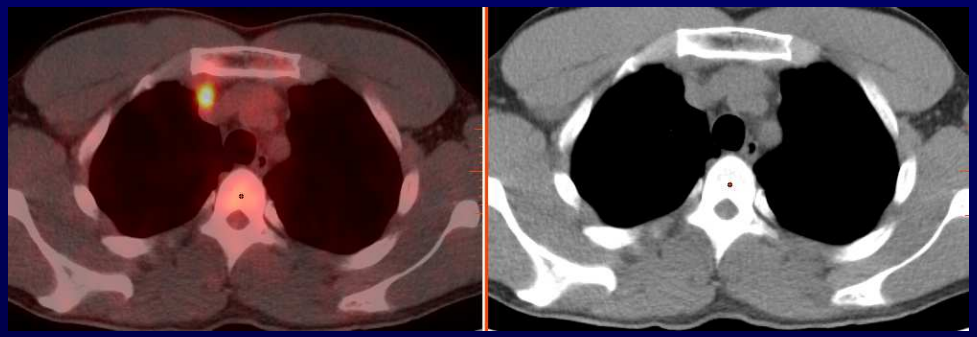
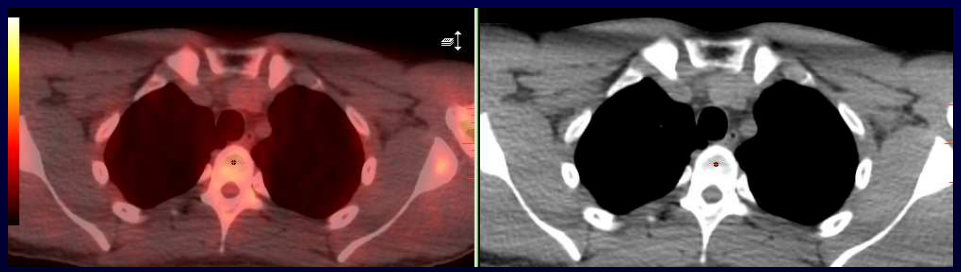
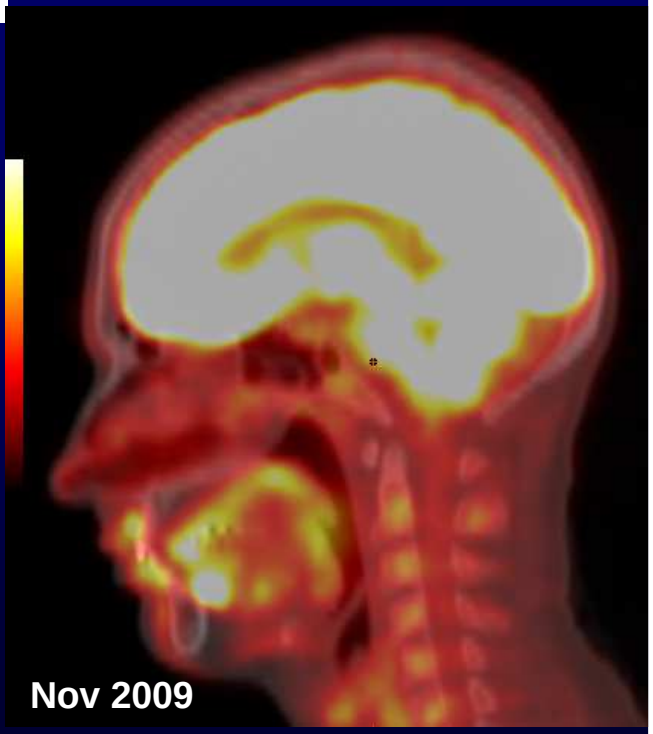
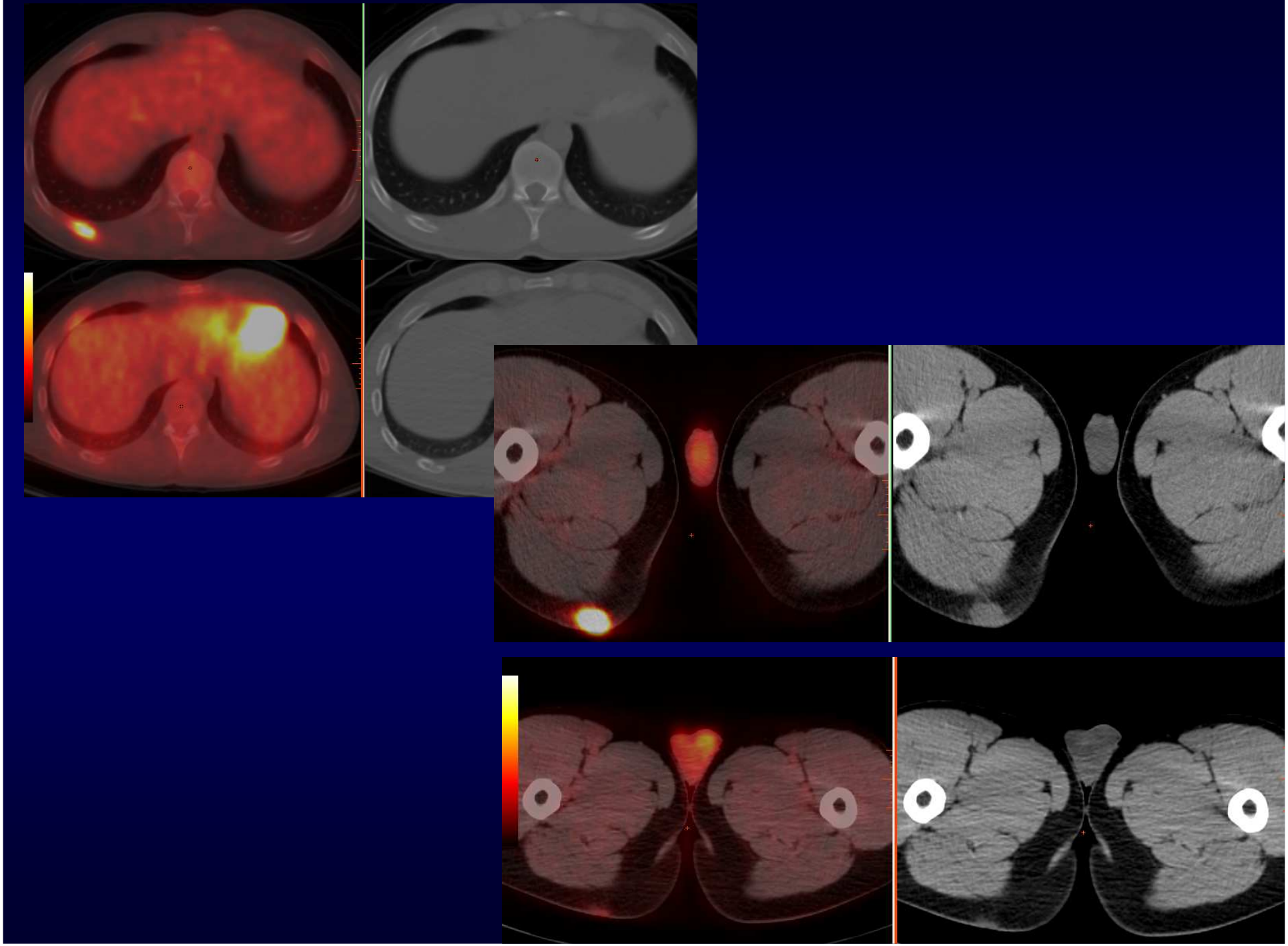


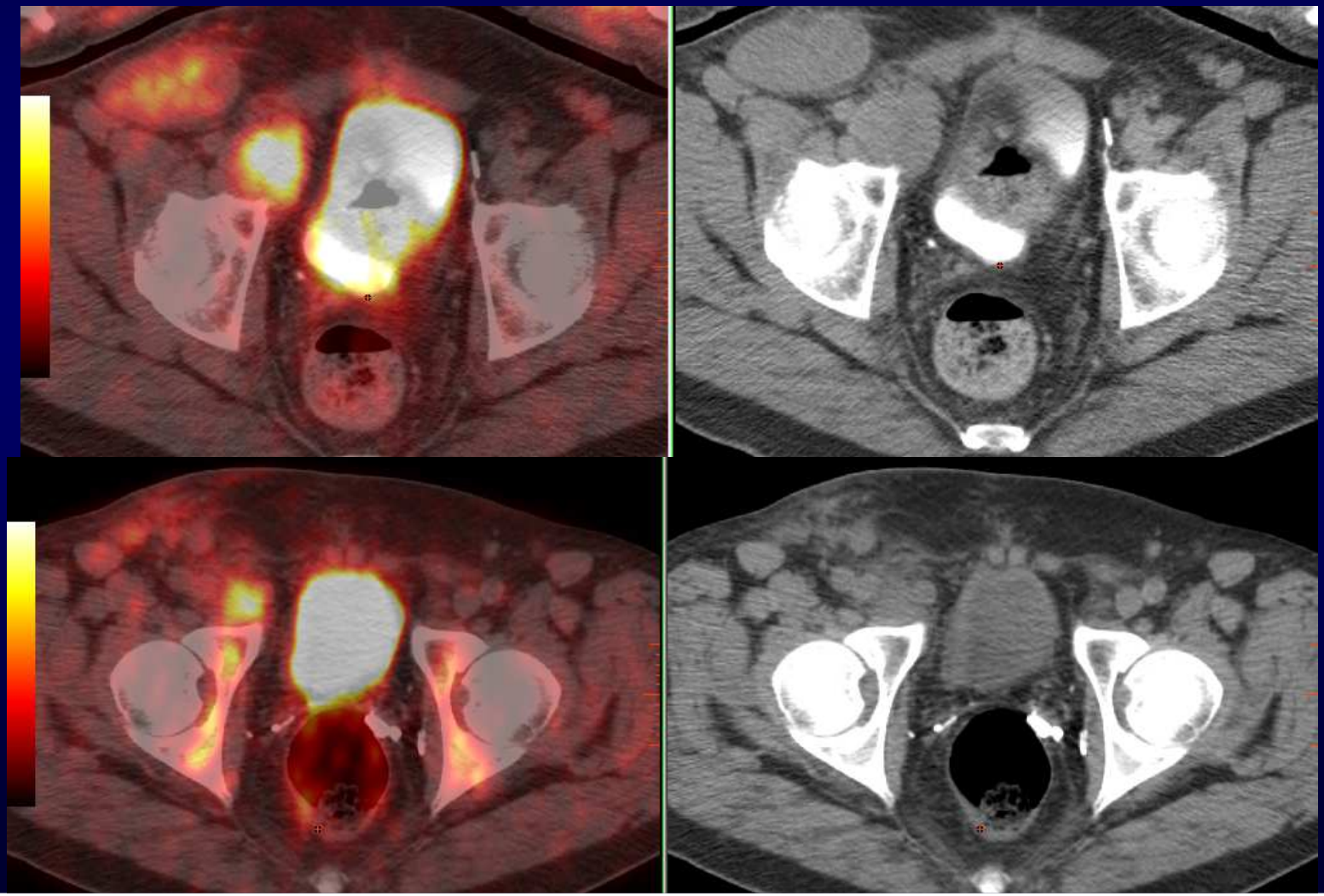






Interim PET Positive

- **PTCL**
- Interim positive; DoD 1.5 yrs later



FDG PET in PTCL
Discussion Points

- Criteria for FDG uptake?
  - End of treatment (Deauville?)
  - Interim (Deauville?)
- Appropriate time point for interim scans?
- How to deal with variety of histologies and treatment regimens?
- Need prospective studies in which FDG PET/CT is an integral part of protocols

Follow-Up Recommendations
(open for discussion)

- If initially PET was positive → follow with PET
- Always use PET for follow-up in conditions that are not well assessed by CT *(nasal, bowel, subcut)*
- T cell: > ½ of patients relapse; therefore, the probability for a FP in follow-up is much smaller than, for instance, in early stage HL
- Appropriate time points for imaging in f/u?
- Primary nodal disease → follow with CT if initial post Rx PET is negative

Some opportunities for integrating FDG PET in clinical trials…

courtesy Steve Horwitz, MSKCC

Utility ^{18}Fluoro-deoxyglucose Positron Emission Tomography for Prognosis and Response Assessments in a Phase 2 Study of Romidepsin in Patients with Relapsed or Refractory Peripheral T-Cell Lymphoma

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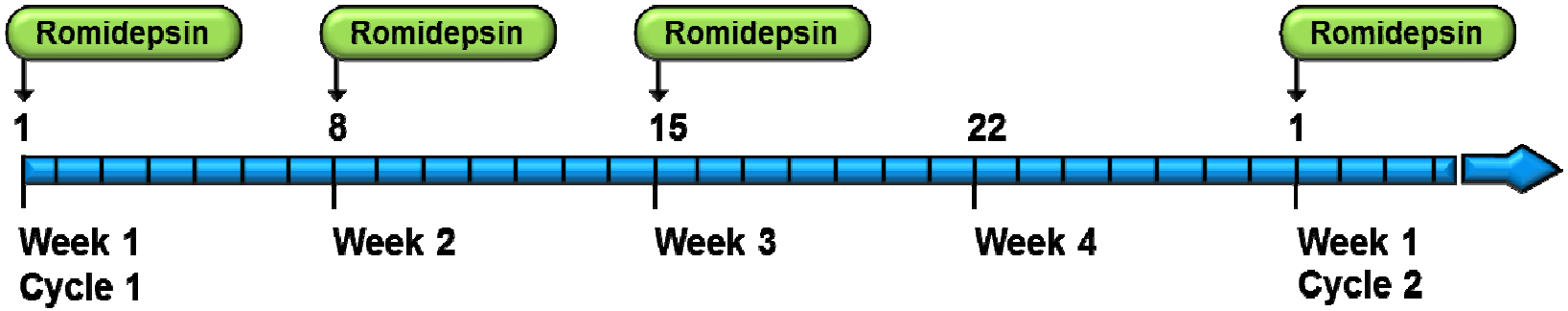
Introduction

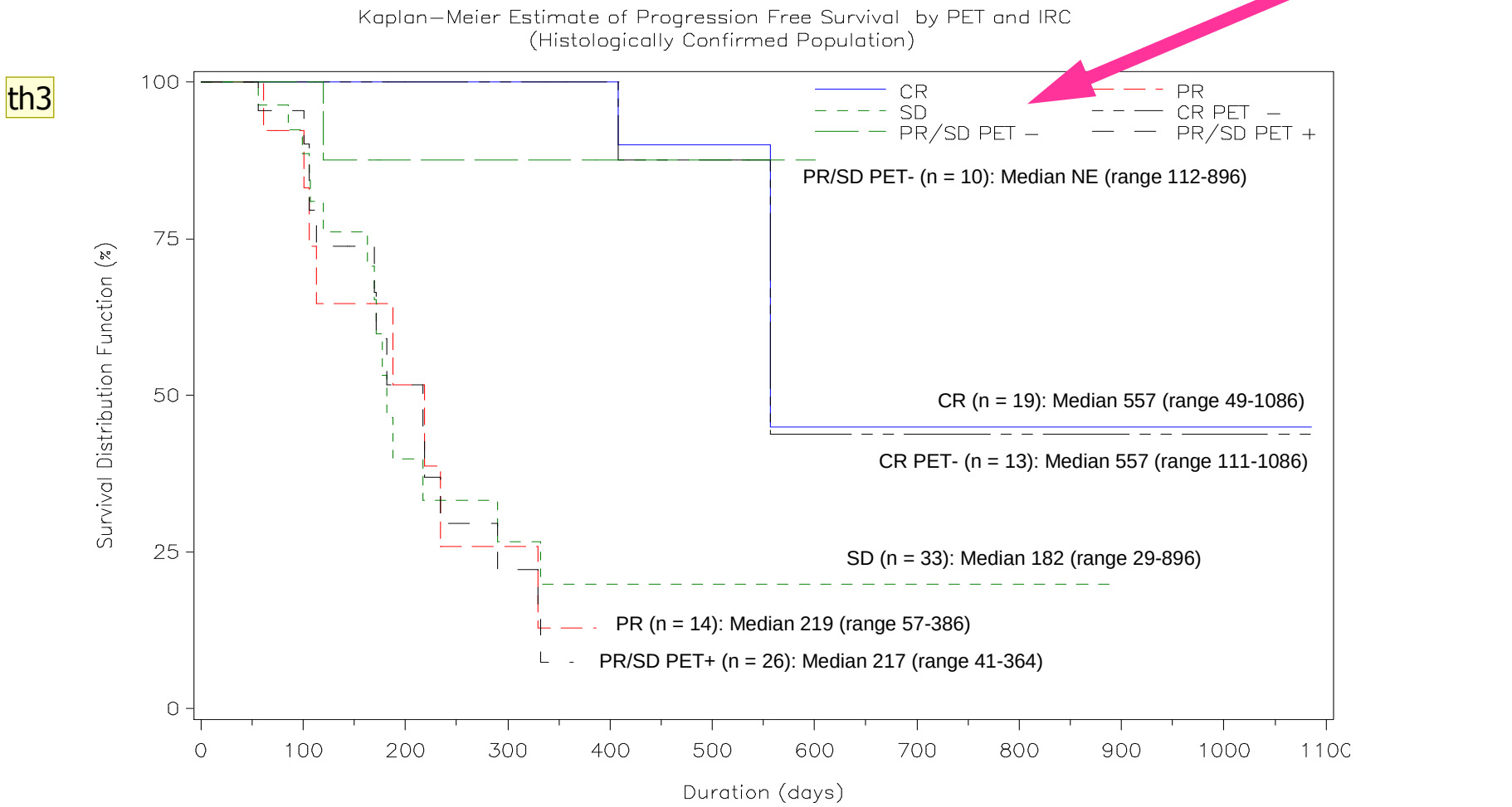
- **Romidepsin** is a novel bicyclic **histone deacetylase inhibitor**
  - FDA approvals:
    - 2009: Patients with cutaneous T-cell lymphoma who received at least one prior systemic therapy
    - 2011: Patients with peripheral T-cell lymphoma (PTCL) who received at least one prior therapy
  - Two phase 2, single-arm, open-label trials in patient with relapsed/refractory PTCL have been completed with overall response rates of 38% (17/45, NCI1312)[1] and 25% (33/130, GPI-06-0002)[2]
- PTCL is a rare heterogeneous group of lymphomas resulting from clonal proliferation of mature post-thymic lymphocytes[3]
  - Aggressive clinical behavior
  - Poor long-term survival
  - No standard of care
- International Workshop Response Criteria (IWC) for non-Hodgkin's lymphomas (NHL)[3] utilizes CT/MRI scans for assessment of disease

Study Schema



- Romidepsin 14 mg/m^2 (4 hour intravenous injection) on days 1, 8, and 15 of a 28-day cycle x 6 cycles
- Responding patients could continue to receive treatment beyond 6 cycles at the discretion of the patient and investigator
- Response was assessed every 2 cycles with follow-up every 2-3 cycles

Figure 4. Progression-Free Survival (PFS)



- Patients who achieved CR/CRu had prolonged PFS compared to other response groups
  - Overall, patients who achieved PR or SD had similar, shorter PFS
  - However, the subset of patients with PR or SD who were PET-negative also had prolonged PFS similar to CR/CRu

Romidepsin study. Horwitz et al 2011

Diapositive 42

th3

SH: what does a curve of SD/PR conventional but PET- look like? that is to day what does a curve with conventional CR, PR, SD and then curves of CR/PET CR, PR-SD/PET CR, SD-PR/PET +, CR/PET+
maybe the interpretation should be CR-good, if not CR PET-good, PET +bad so pet doesnt trump convnetional but adds in non CR pts.

RESPONSE: The two PFS curves either by response or by PET status have been swapped out for this one curve based on your suggestions. It will be clarified when redrawn. It does in fact appear that - as you said - CR is good (and addition of PET- doesn't make 'better'), but that patients who were PR or SD by IRC AND PET- also did well - and there were 10 of these patients.
thuang; 28/07/2011

The Future Directions in the Treatment of T-cell lymphomas: Are We Improving Survival?

- Results of initial therapy-is anything better than CHOP?
- Relapsed disease-best approach?
- **New Therapies in Peripheral T-cell lymphoma**
- Areas where improvement is more clear
- Other ways me might improve sooner rather than later

Studies of Relapsed/Refractory PTCL

Treatment	N	ORR	PFS months	DR	Comments
Pralatrexate	109	29%	3.5	10.1	FDA approved
Romidepsin	130	25%	4	17	FDA approved
Gemcitabine	39	51%			CTCL + PTCL
Bendamustine	60	50%		3.5	Preliminary
Lenalidomide	23	30%	3		Allowed newly diagnosed

O'Conner OA, et al. *J Clin Oncol*. 2011;29:1182-1189

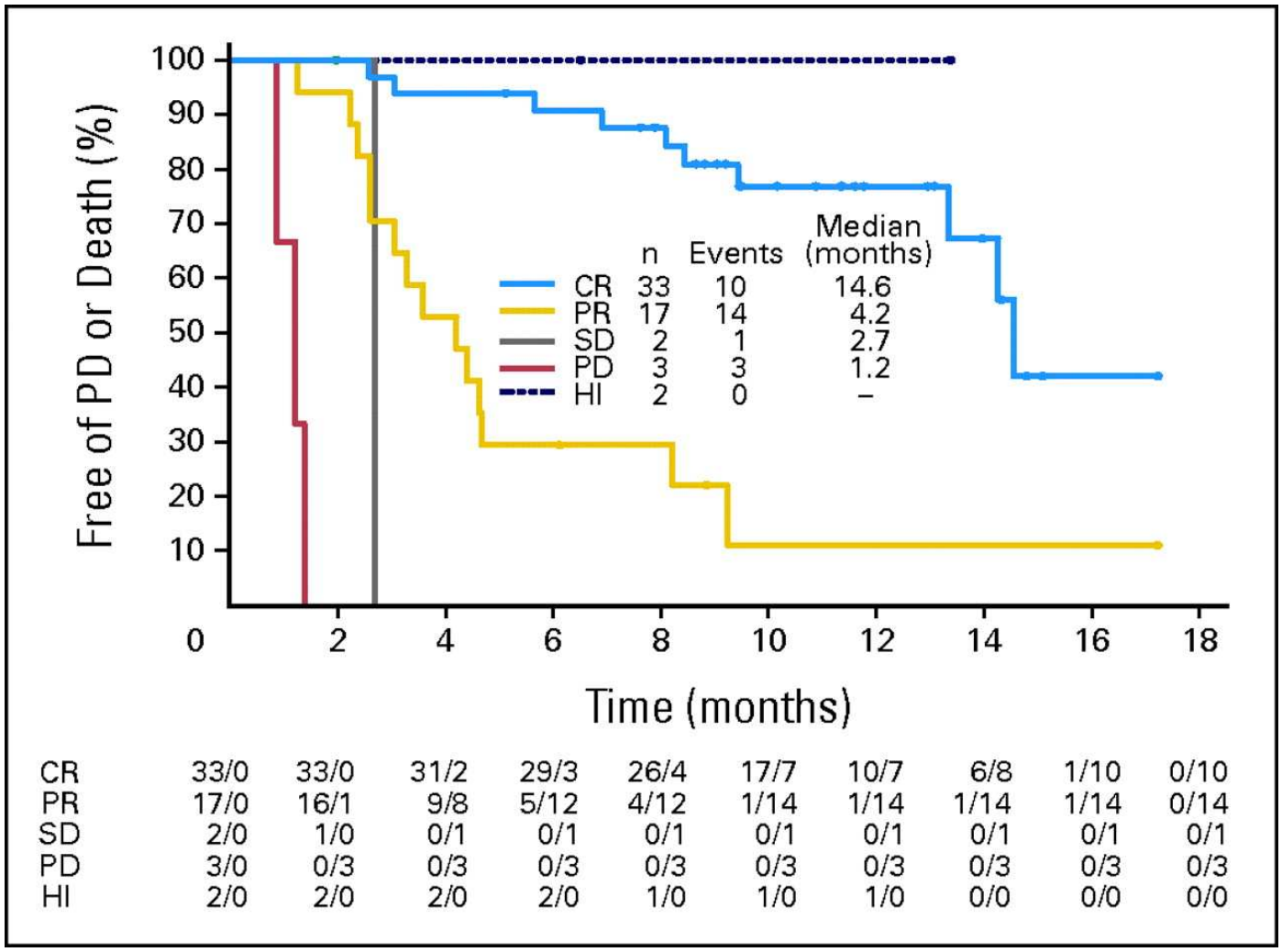
Coiffier B et al. . *J Clin Oncol*. 2012; Epub

Zinzani P L et al. Ann Oncol 2010;21:860-863

Damaj G, et al. 11th ICML; Lugano 2011. A126.

Dueck et al., Cancer. 2010 116(19):4541-8

Brentuximab Vedotin in Relapsed ALCL: PFS



Pro B et al. JCO 2012;30:2190-2196

Experimental Data
FLT PET for Early Response Assessment in ALK+ ALCL

- Experiments with 2 ALK+ ALCL cell lines
- HSP-90 inhibitor *(NVP-AUY922)* and mTOR-inhibitor *(everolimus)*
- In vitro and xeno-transplant studies (µPET FDG and FLT)
- SUDHL:
  - Sensitive to both drugs
  - Clear ↓ in FLT uptake at day 5 (~ ↓ki-67 and ↑ caspase-3)
  - No change in FDG at early time points
- Karpas299
  - Resistant to NVP-AUY922 but sensititive to everolimus
  - Clear ↓ in FLT-uptake only w/ everolimus

Li, Graf, Herrmann, Dechow et al. Cancer Res epub ahead Oct 2012

SUMMARY I

- **Definite role for FDG PET/CT in initial staging when CT alone does not show the disease properly** *(nasal type, enteropathy type, extranodal sites [e.g. spleen], subcutan. panniculitis type)* **and/or sites are outside standard CT FOV**

- **Baseline scan should always be done if the intention is to use PET for response assessment and follow-up**

- **Although there is no proof that baseline scan changes stage or management in a large fraction of patients, the EoD should always be determined appropriately → role for combined PET/CT with iv contrast at staging**

SUMMARY II

- FDG-positive dz. should be followed by PET
- Negative PET at the end of treatment is possibly not as reliable (prognostic) as in HL and DLBCL
- Role of interim scans remains to be determined
- Is there a role for PET-response adapted therapy in aggressive PTCL?

Empire State Building. 3 October 2008

ESB Photo Competition: 1st place: Andrea Akpotowho