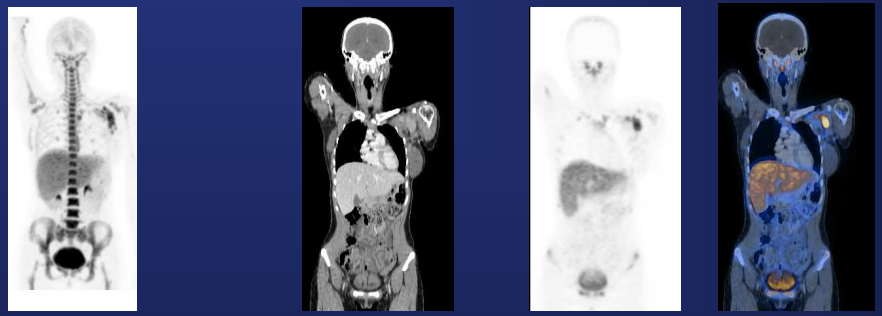
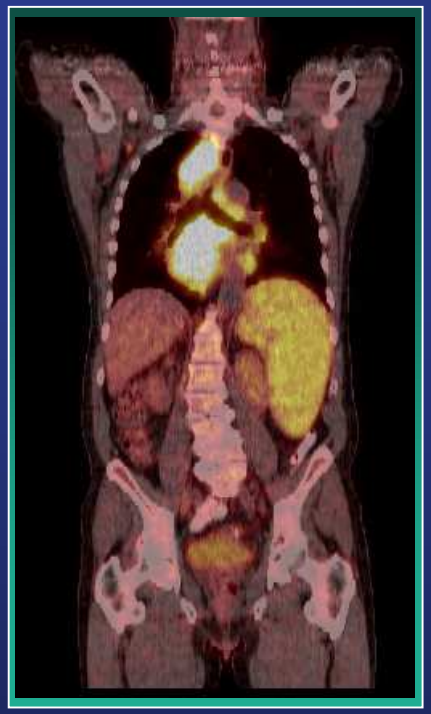
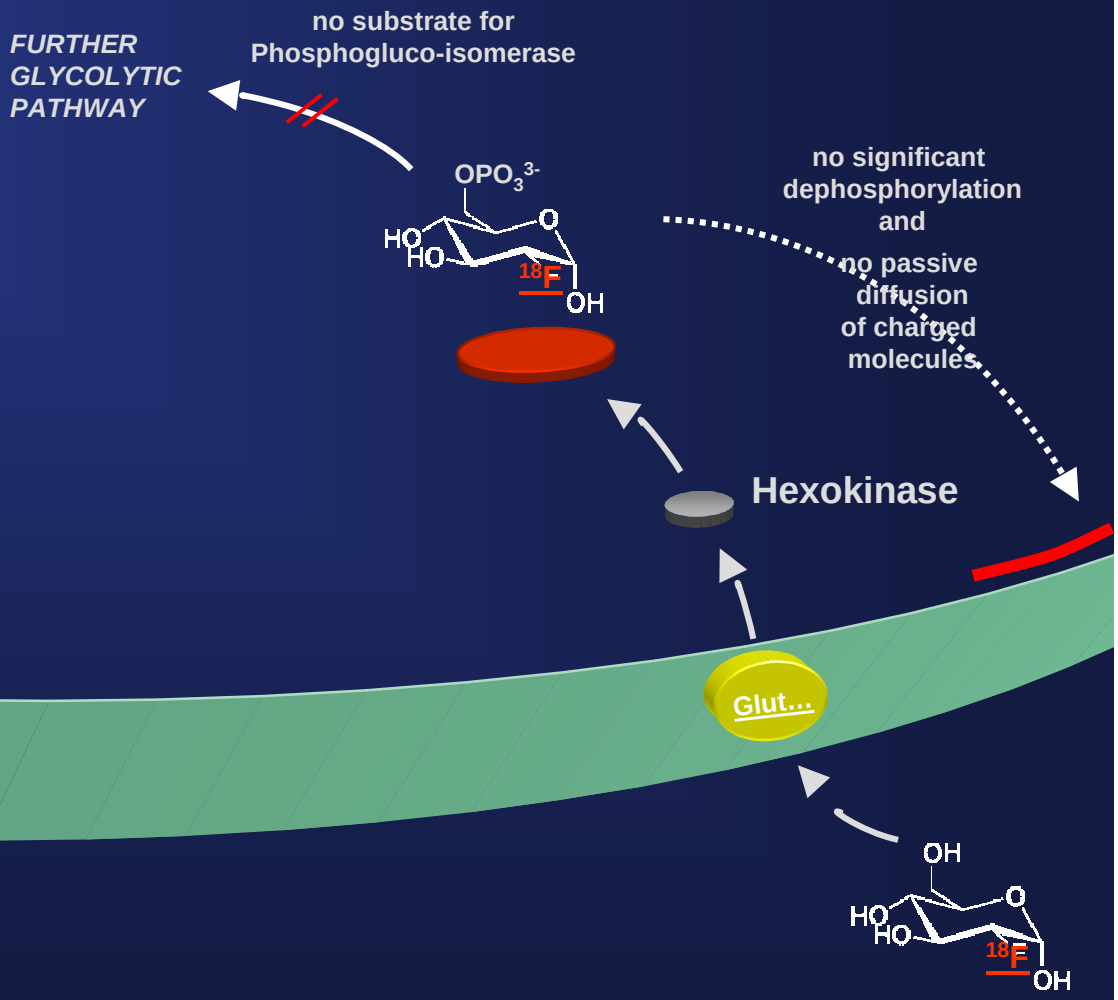
18F-Thymidine in Lymphoma: Imaging Proliferation



Andreas K. Buck
Technische Universität München

Molecular imaging of glucose utilization



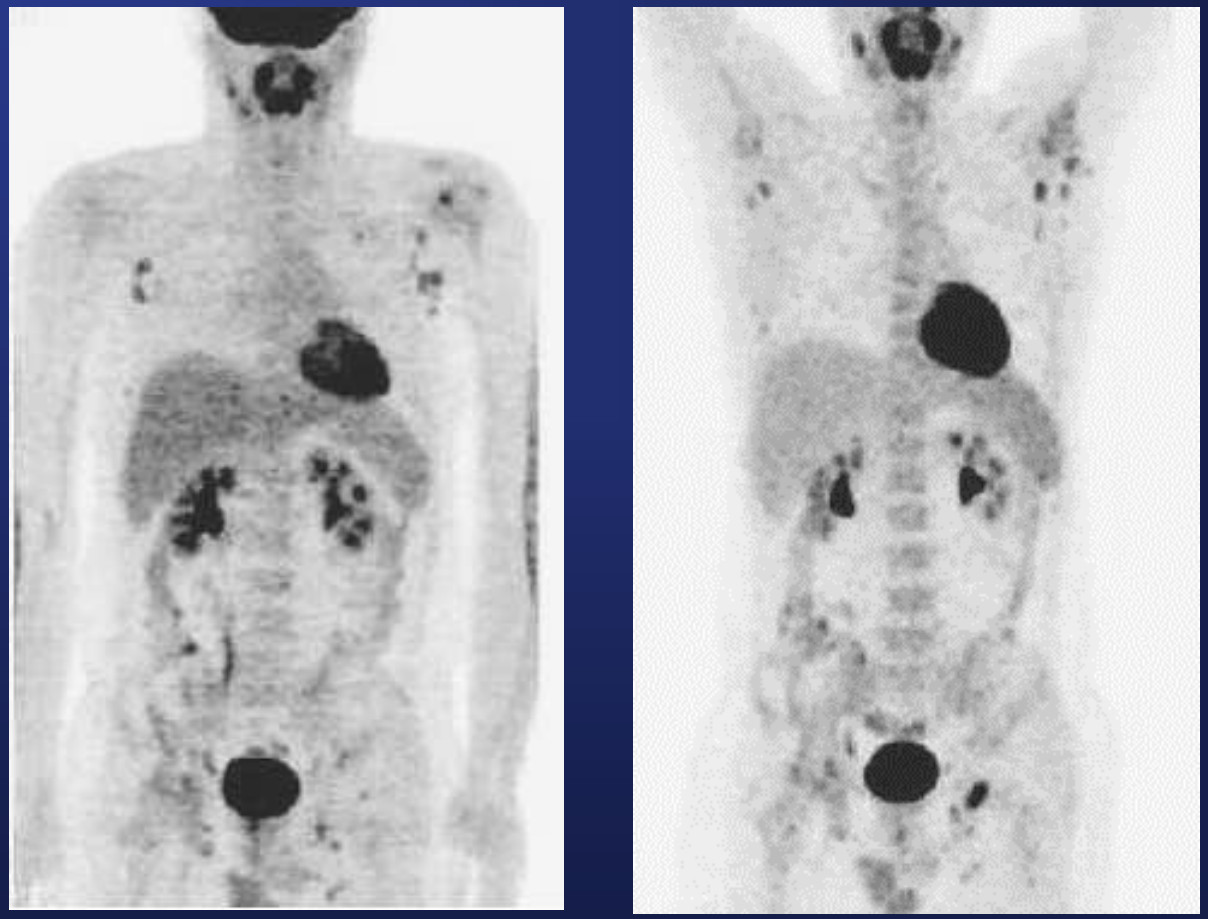


Potential advantages of imaging proliferation

- FDG-PET (PET/CT): high diagnostic accuracy for (re-)staging and therapeutic monitoring in Hodgkin`s disease and aggressive NHL
- Reduced specificity, tumor grading: 45% in ´grey zone` (NHL)

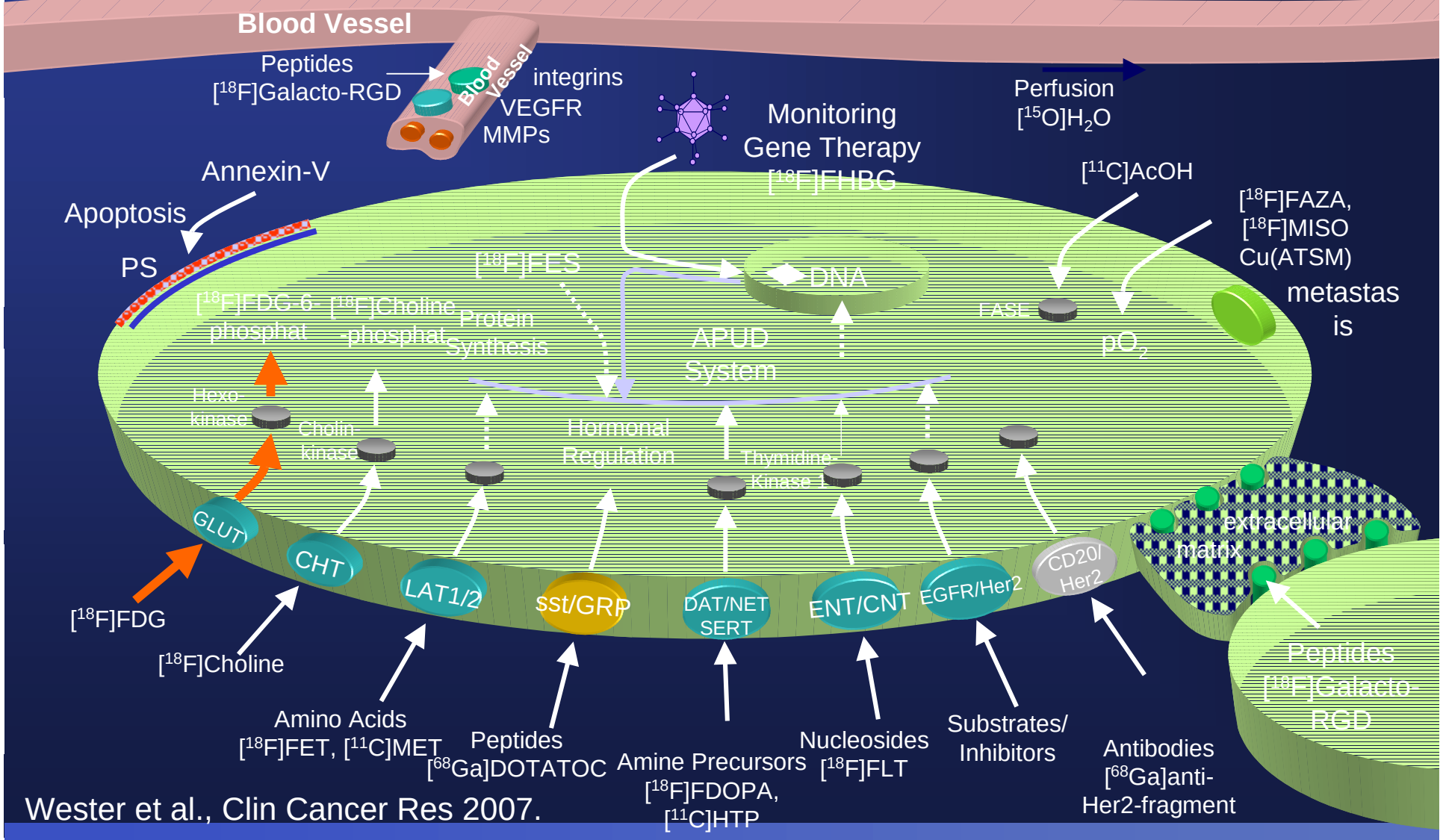
  (Schoder et al. JCO 2005)
- Hypothesis: alteration of DNA synthesis reflects cell injury better than glucose utilization

Unspecific FDG-uptake 1 year after remission of aggressive NHL



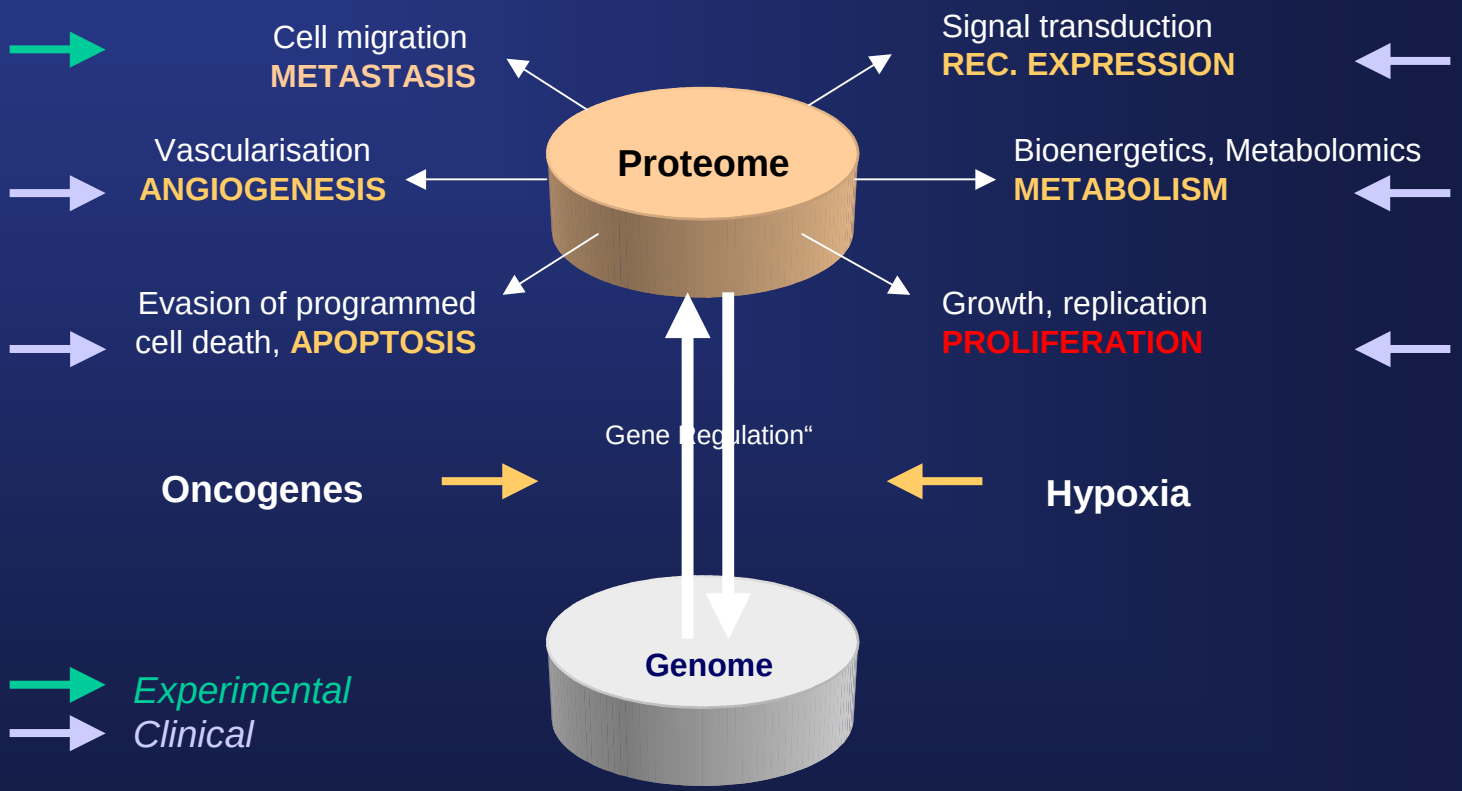
Histology: Lymphadenopathy (courtesy of P. Castellucci, Bologna)

Molecular Probes for PET in Oncology



Wester et al., Clin Cancer Res 2007.

Imaging of Target Systems Cancer



Hanahan and Weinberg (modified) Cell Press, 2000

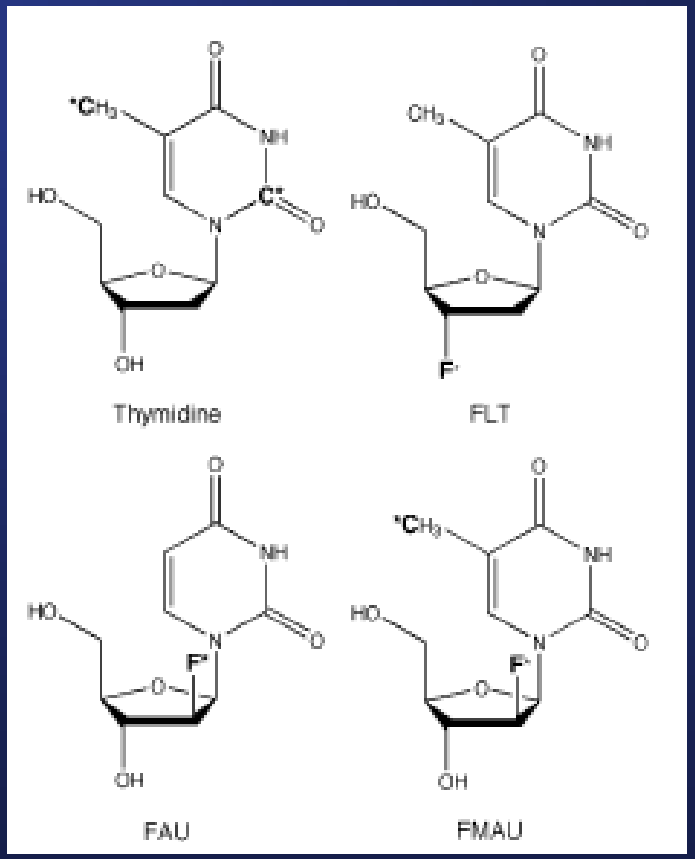
Potential advantages of imaging proliferation

- Differentiation viable tumor / inflammatory, benign lesions
- Detection of lymphoma in organs with high physiologic FDG-uptake (brain)
- Tumor grading / transformation to more aggressive histology
- Drug development

Assessment of proliferative activity *in-vitro*

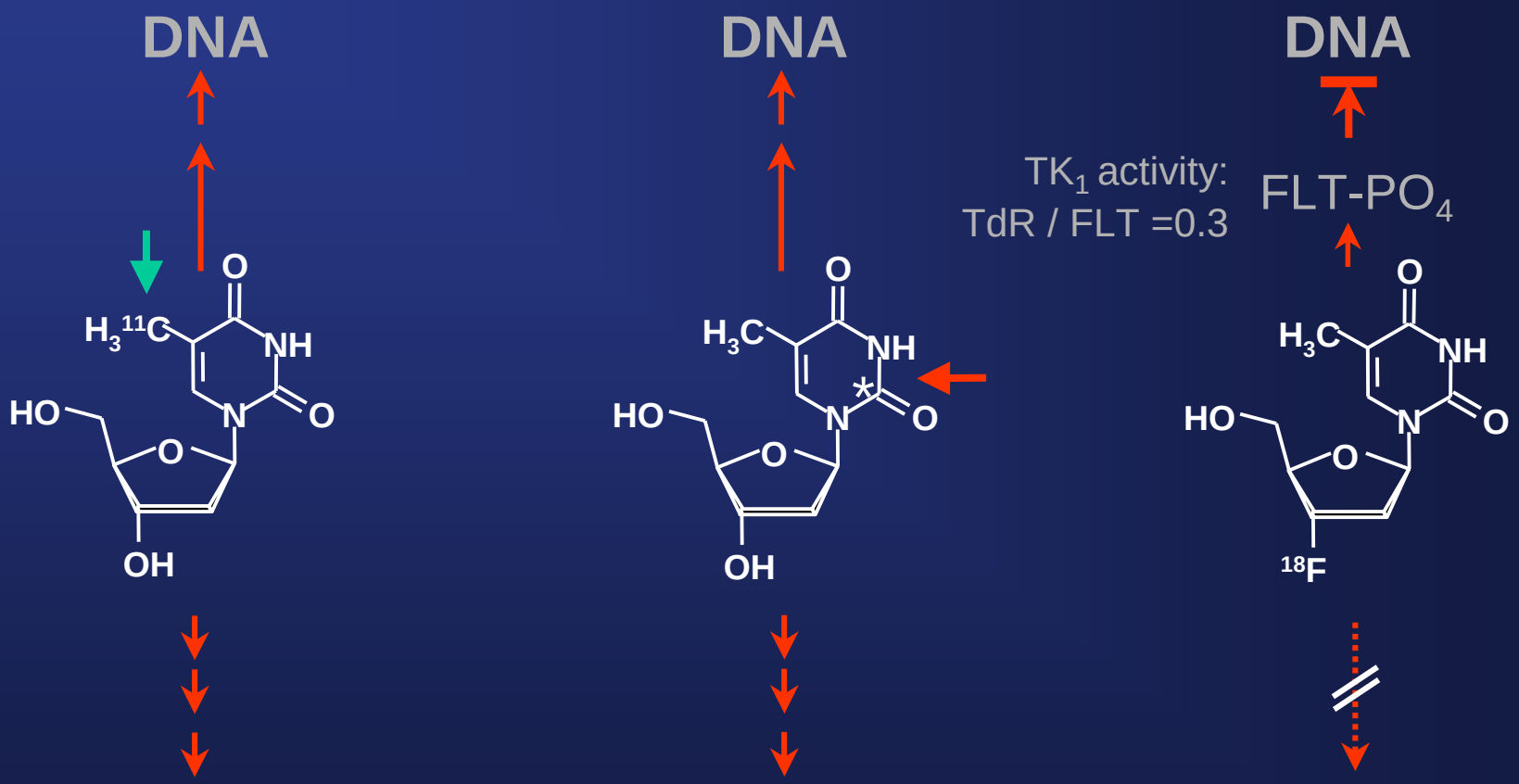
- standard: thymidine analogs
- thymidine not used for RNA synthesis (other than adenine, cytidine and guanine)
- thymidine is taken up by proliferating cells and utilized for synthesis of DNA
  - [^{3}H]Thymidin / TLI
  - *BUdR*
  - *Monoclonal antibodies specific for Ki-67 (MIB-1 mAb, expression during G1-, S- or G2-phase)*
  - *PCNA*

Assessment of proliferation with radiolabeled thymidine analogs

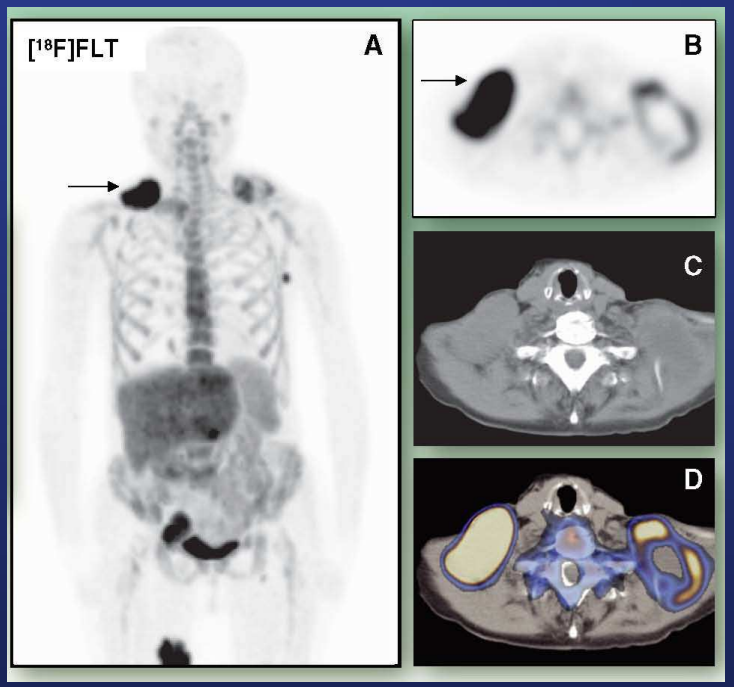


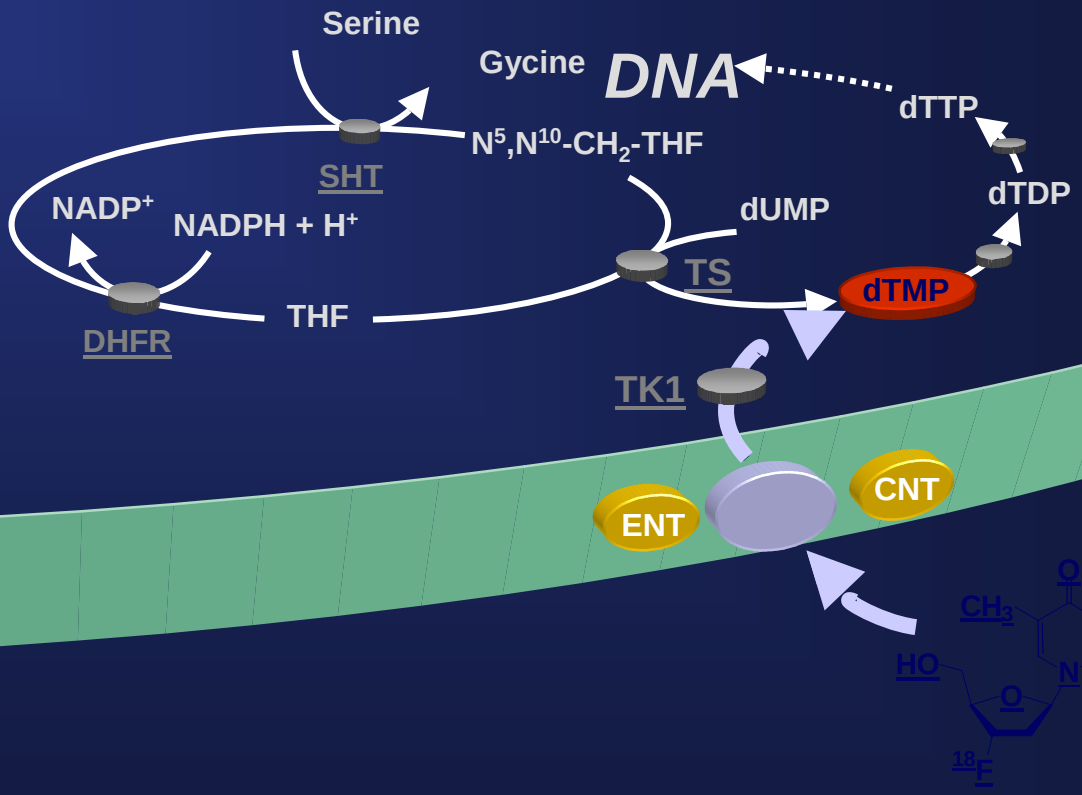
A.F. Shields, Mol Imaging Biol 2006

Metabolization of [^{11}C]Thymidine and [^{18}F]FLT

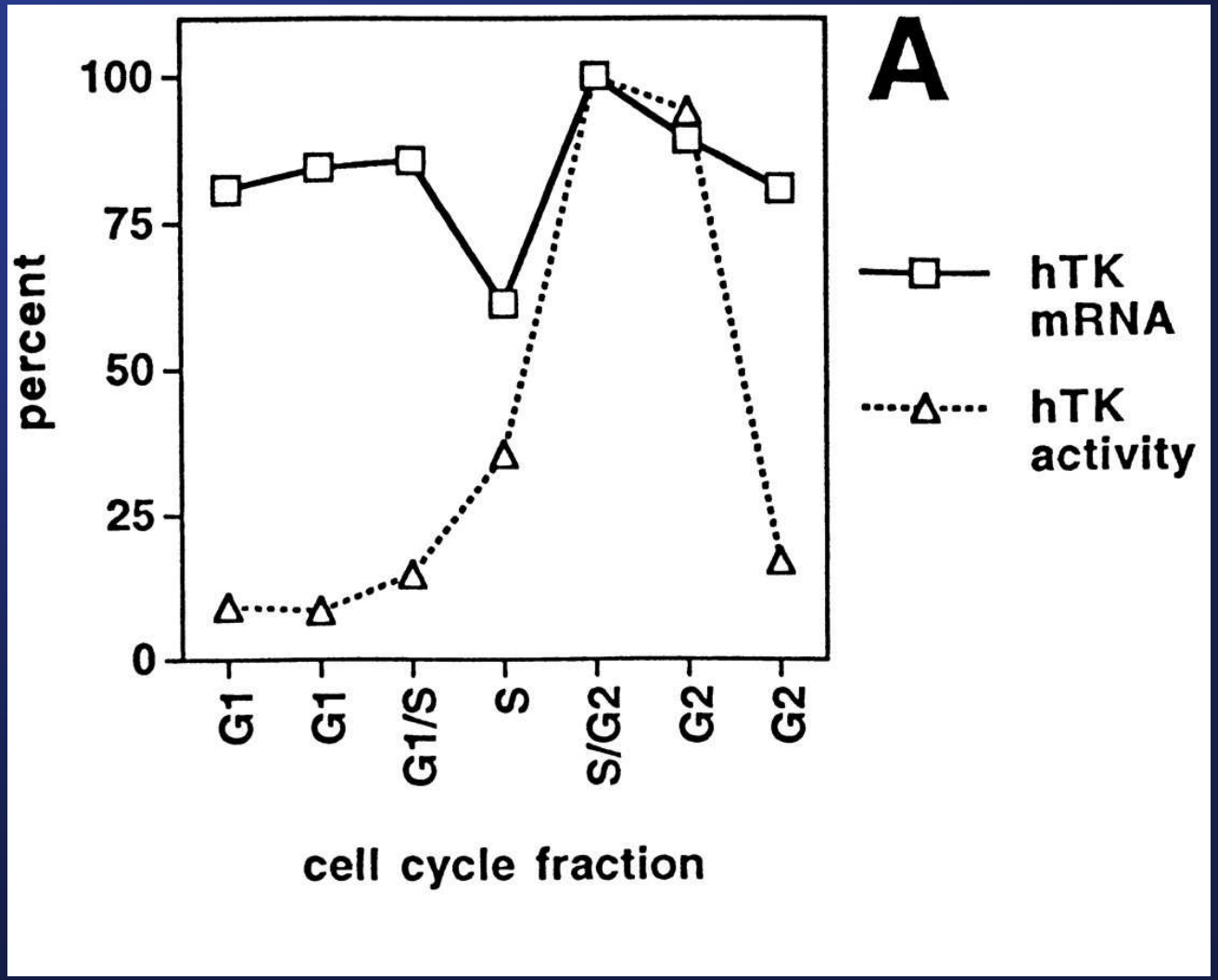


Imaging Cell Proliferation



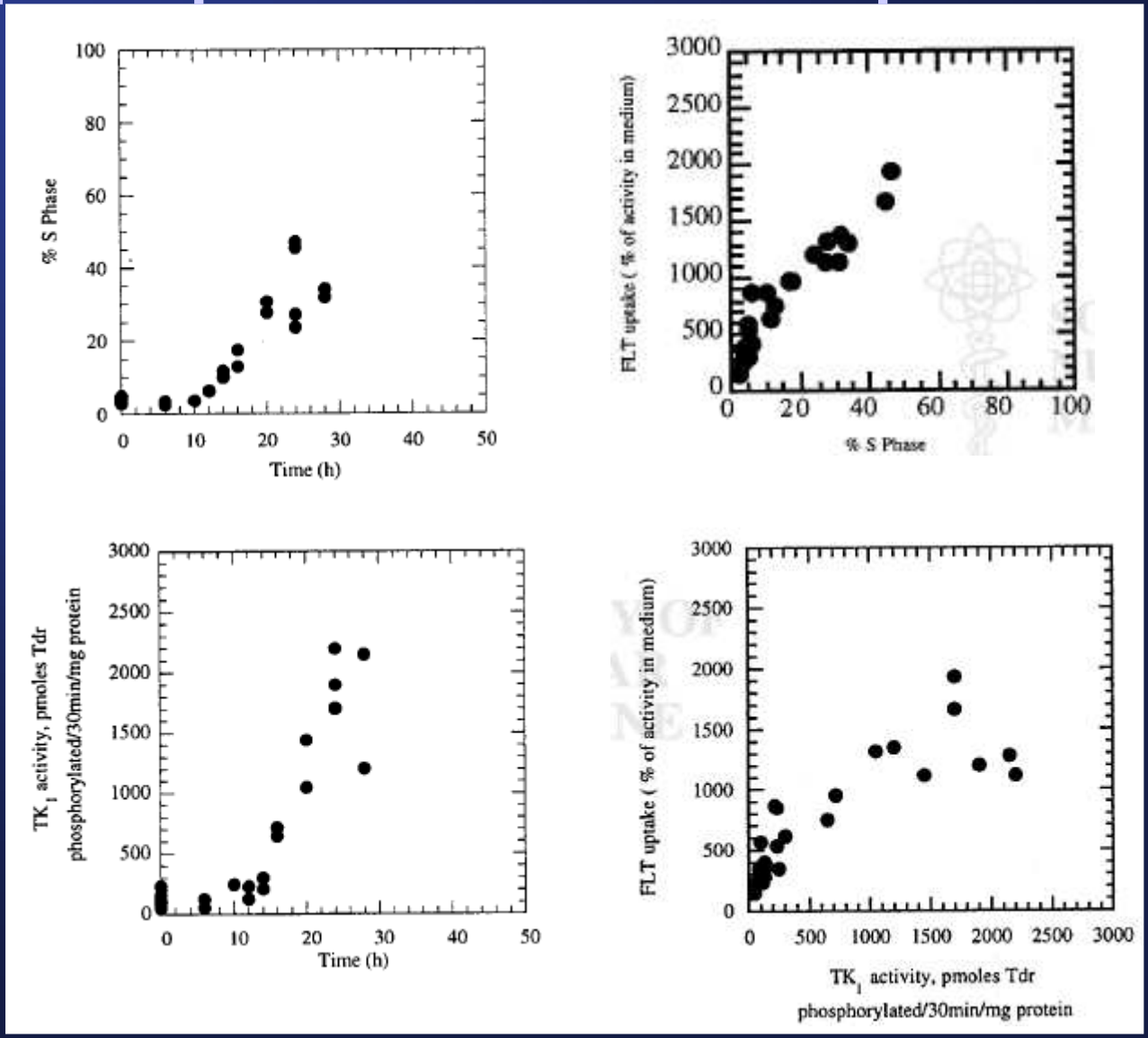


TK1-activity during cell cycle



Pezkoller lecture, Cancer Res 2003.

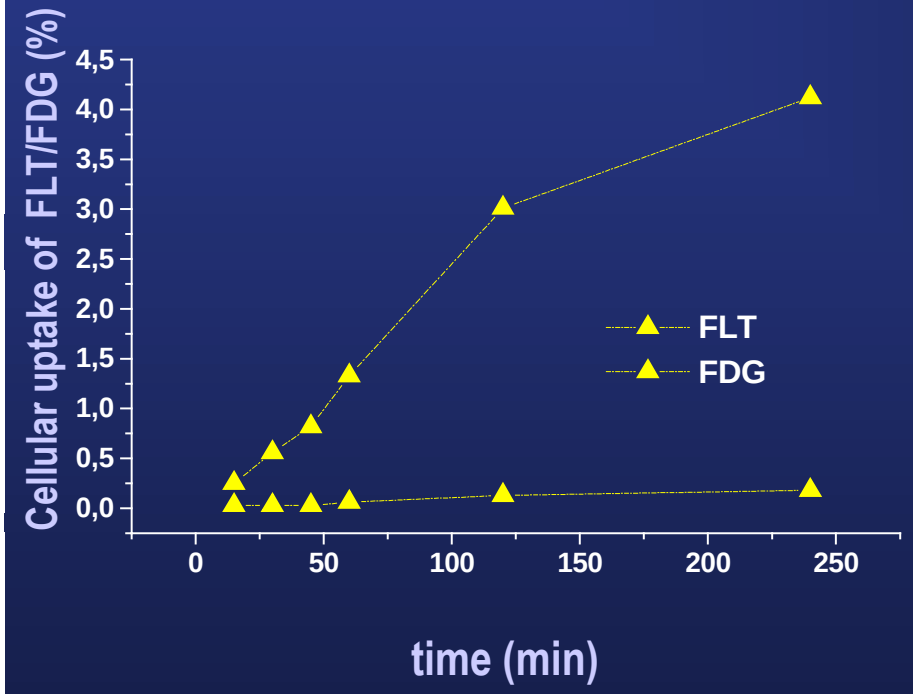
[^{18}F]FLT uptake correlates to S-phase fraction



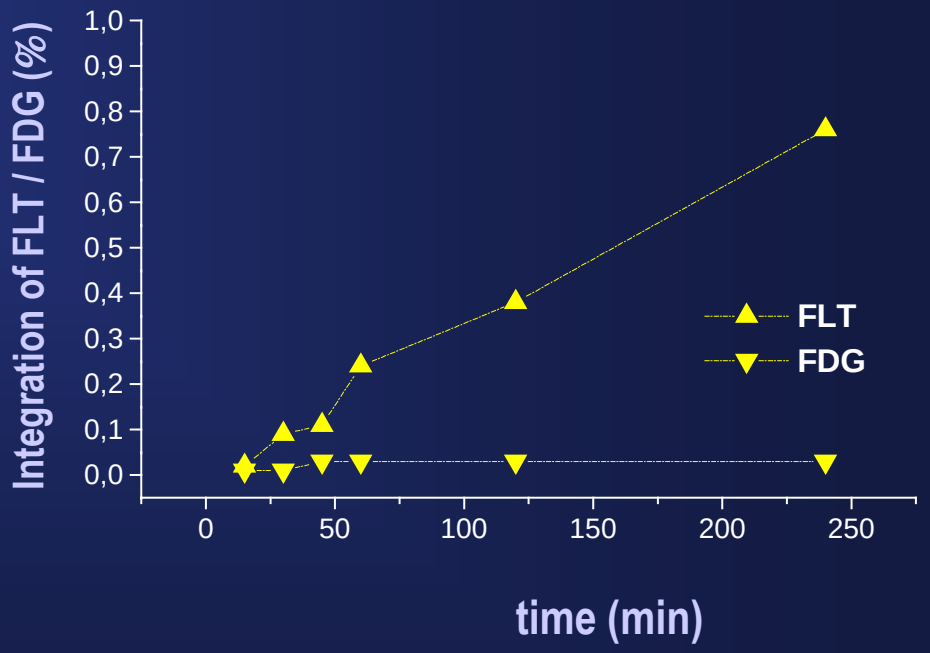
Rasey et al., J Nucl Med 2002.

[^{18}F]FLT in BxPc-3 pancreatic carcinoma cell line

cellular uptake



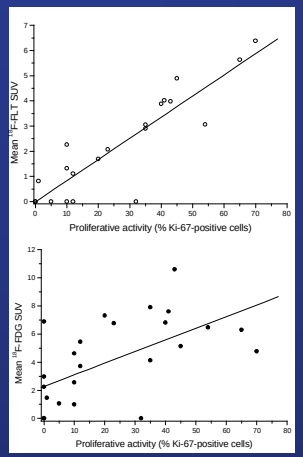
Incorporation into DNA

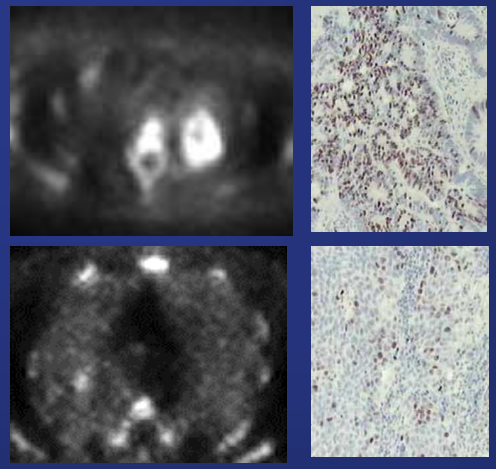


Seitz et al., Eur J Nucl Med 2001.

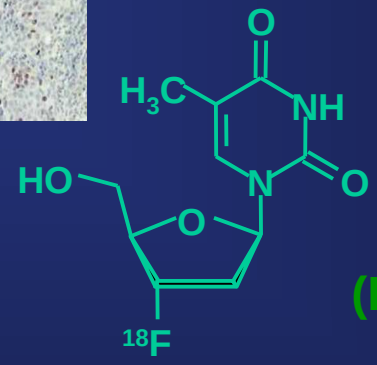
Non-invasive imaging of proliferation in solid cancers

Lung cancer (NSCLC)

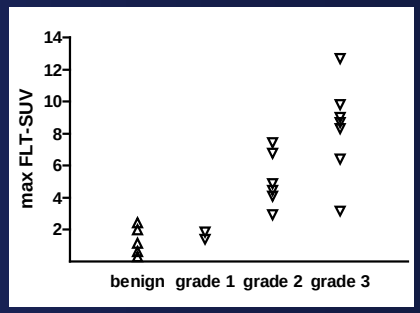




Buck et al., Cancer Res 2002.
Buck et al., J Nucl Med 2003.

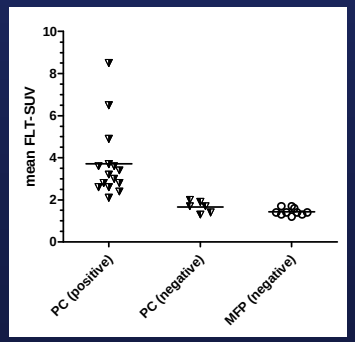


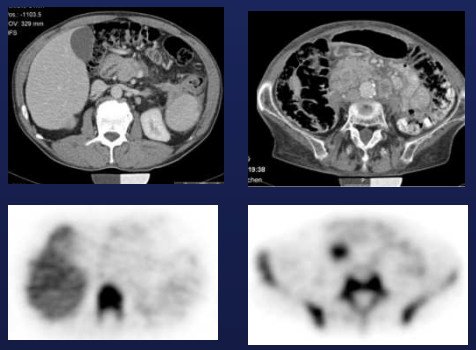
Bone / Soft tissue sarcoma



Buck et al., Clin Cancer Res 2008.

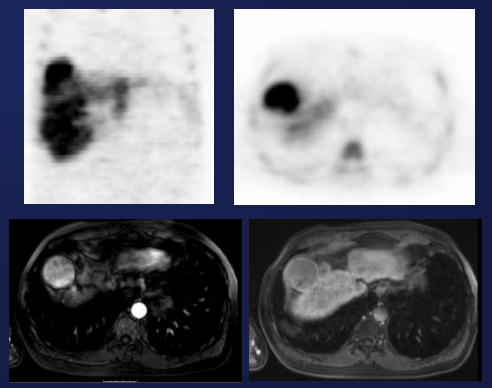
Pancreatic cancer / Mass forming pancreatitis





Herrmann, Buck, J Nucl Med. 2008.

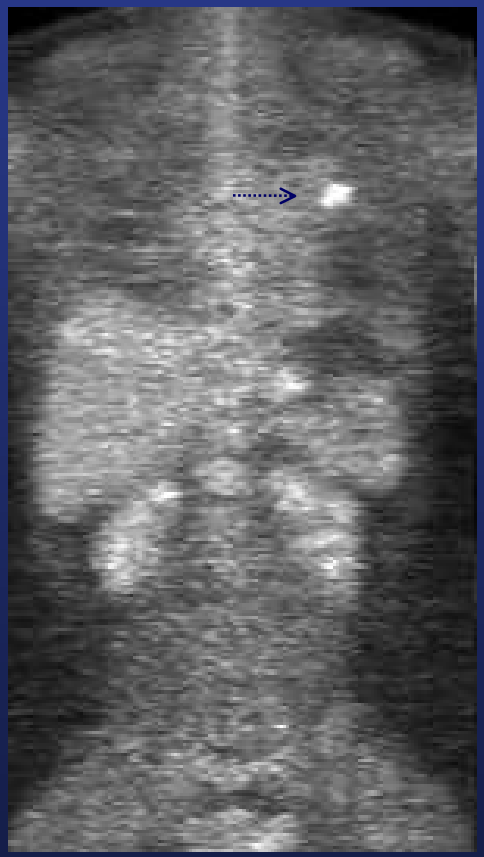
GI tract cancers (HCC, CCC, gastric cancer)



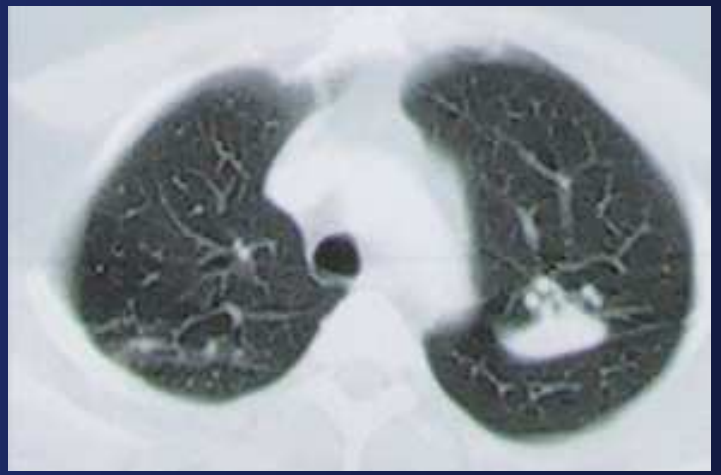
Herrmann, Buck, J Nucl Med. 2008.
Herrmann, Buck, J Nucl Med. 2009.

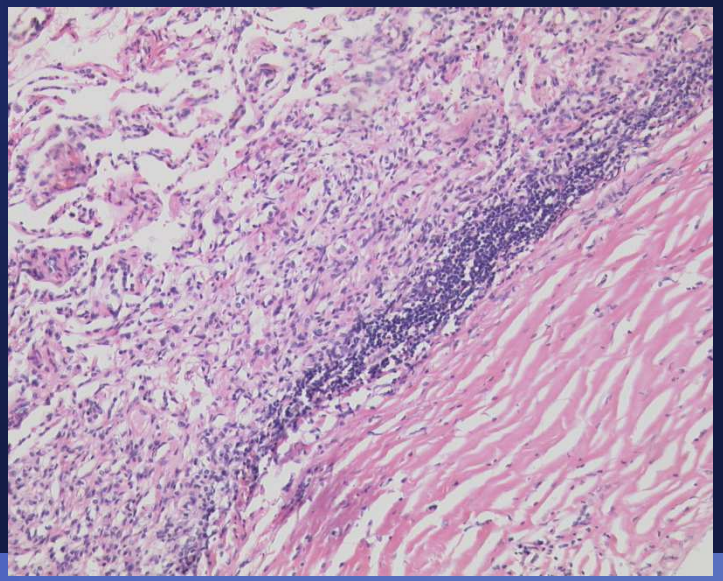
Specific uptake in malignant tumors

FDG-PET



FLT-PET





Buck et al., Eur J Nucl Med Mol Imaging 2005.

Specific uptake in malignant lung lesions

FLT-PET / histology	+	-	
+	19	2	21
-	0	15	15
	19	17	36

Sensitivity:	90%
Specifity:	100%
PPV:	100%
NPV:	88%
Accuracy:	94%

FDG-PET / histology	+	-	
+	18	1	19
-	4	11	15
	22	12	34

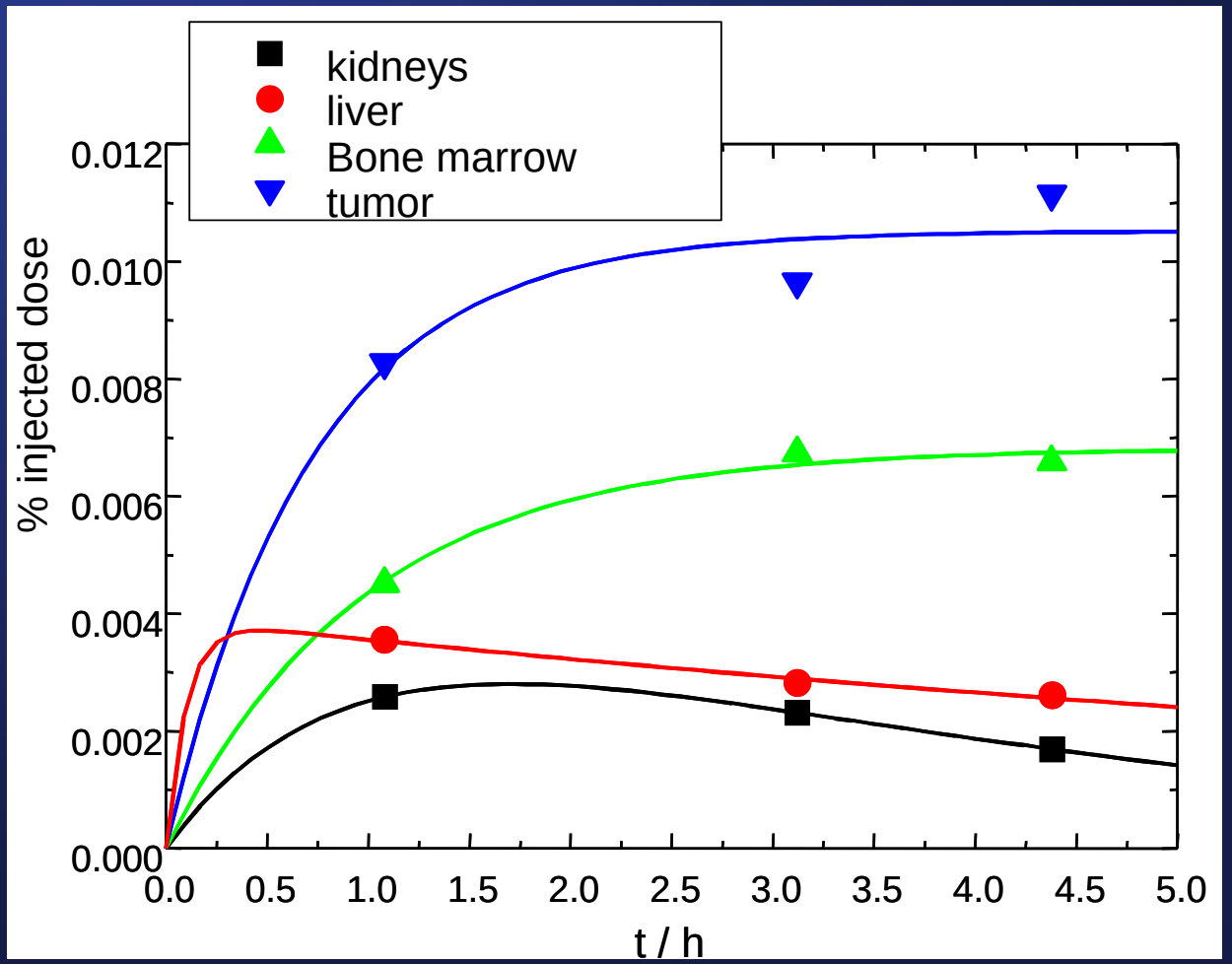
Sensitivity:	94%
Specificity:	73%
PPV:	82%
NPV:	92%
Accuracy:	85%

Specific uptake in malignant tumors
(Laryngotracheitis)

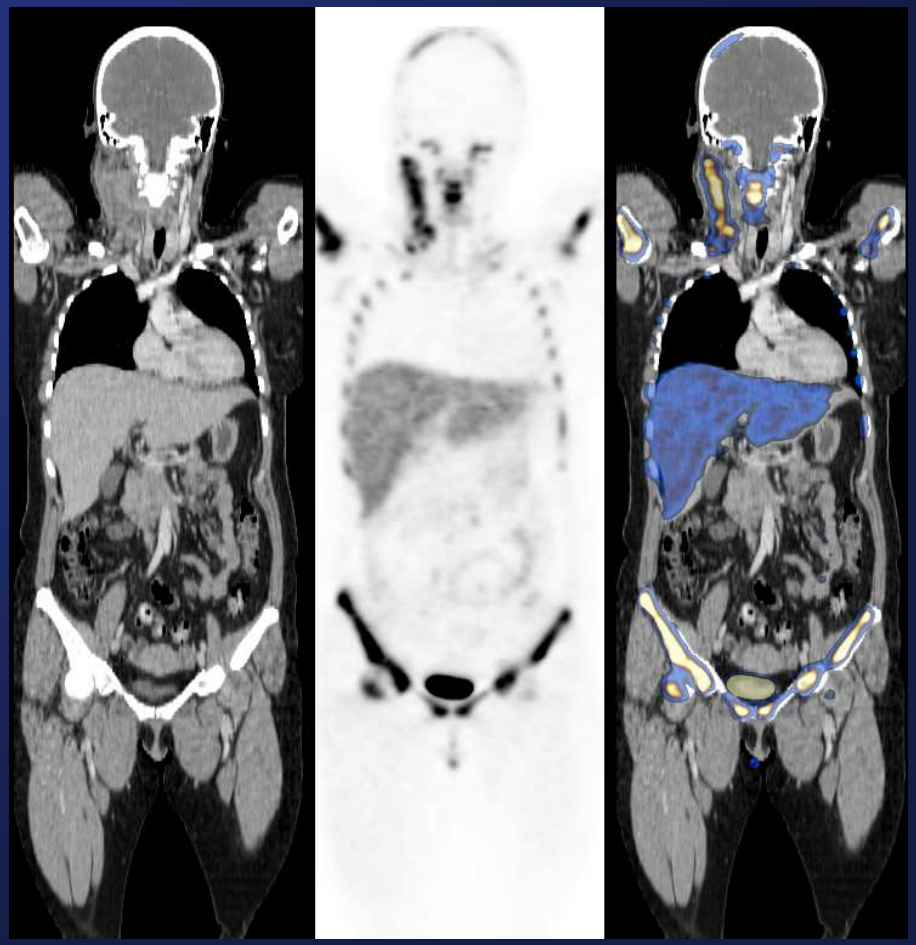
FDG-PET

FLT-PET

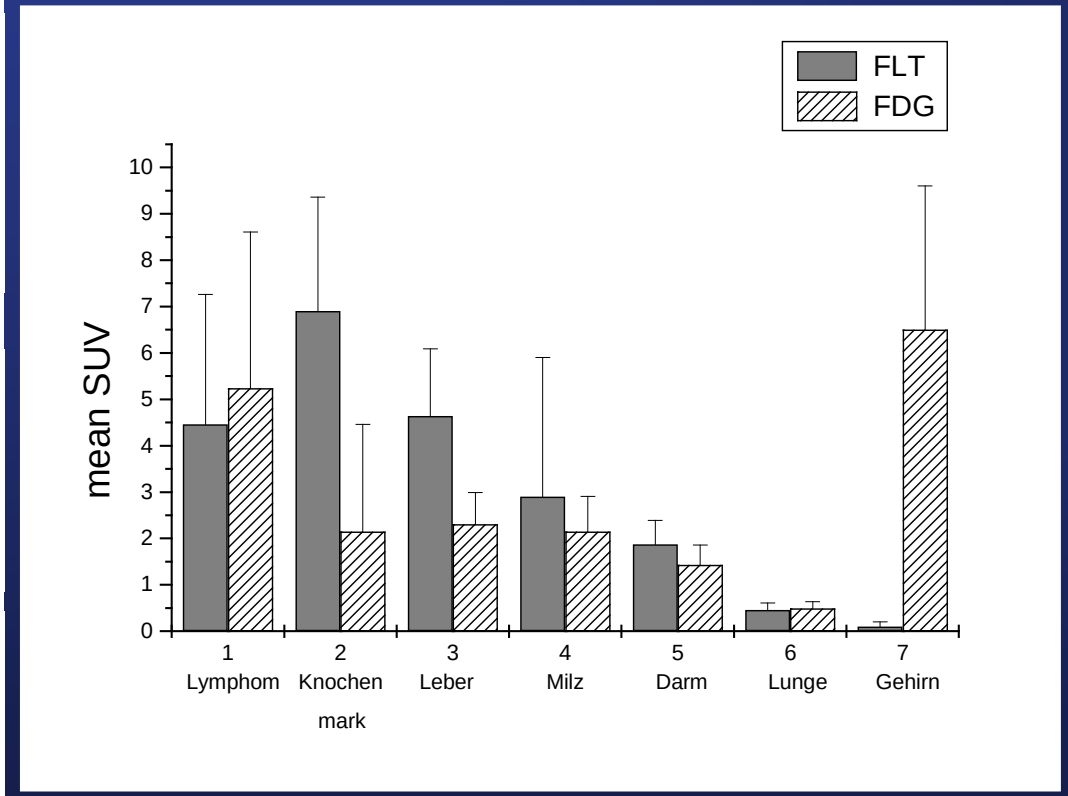
Biodistribution of [^{18}F]FLT in follicular lymphoma



[^{18}F]FLT in NHL (DLBCL)



Biodistribution of FLT and FDG 1h after i.v.-injection (370 MBq)



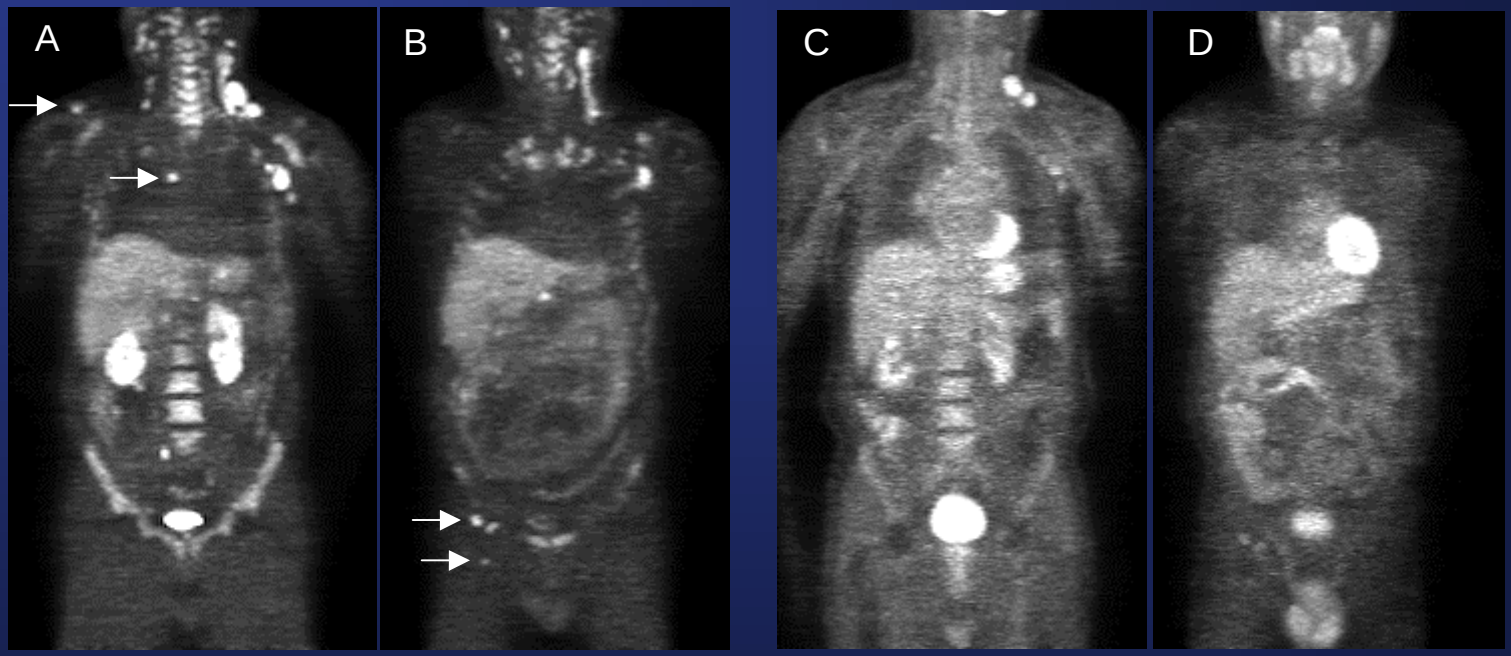
	FLT	FDG
Lymphom	4,5 +/- 2,7	5,0 +/- 3,3
Knoch.-mark	6,9 +/- 2,4	2,2 +/- 0,7
Leber	4,6 +/- 1,4	2,3 +/- 0.6
Milz	2,9 +/- 3,0	2,1 +/- 0,7
Darm	1,8 +/- 0,5	1,4 +/- 0,4
Lunge	0,46 +/- 0,1	0,5 +/- 0,1
Gehirn	0,21 +/- 0,1	6,5 +/- 3,1

Buck et al. Cancer Res 2006.

[^{18}F]FLT for (re-)staging malignant lymphomas

Large cell diffuse B-NHL (stage IV)

FLT-PET FDG-PET

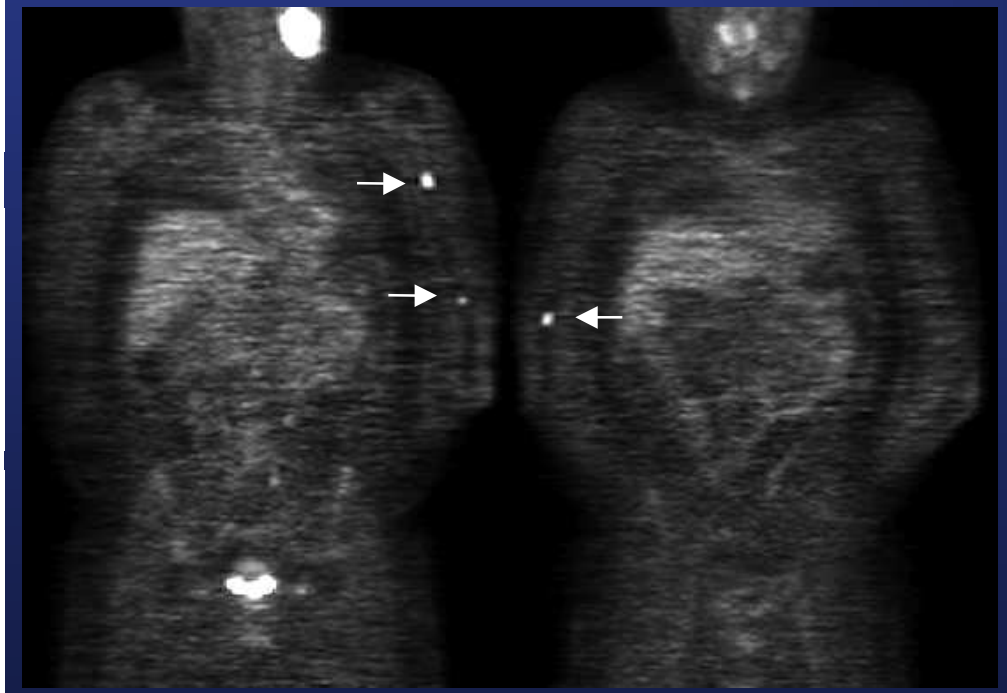


- no change of Ann Arbor classification
- bone lesions not detected in 2 pts.
- additional lesions detected in 4 pts.

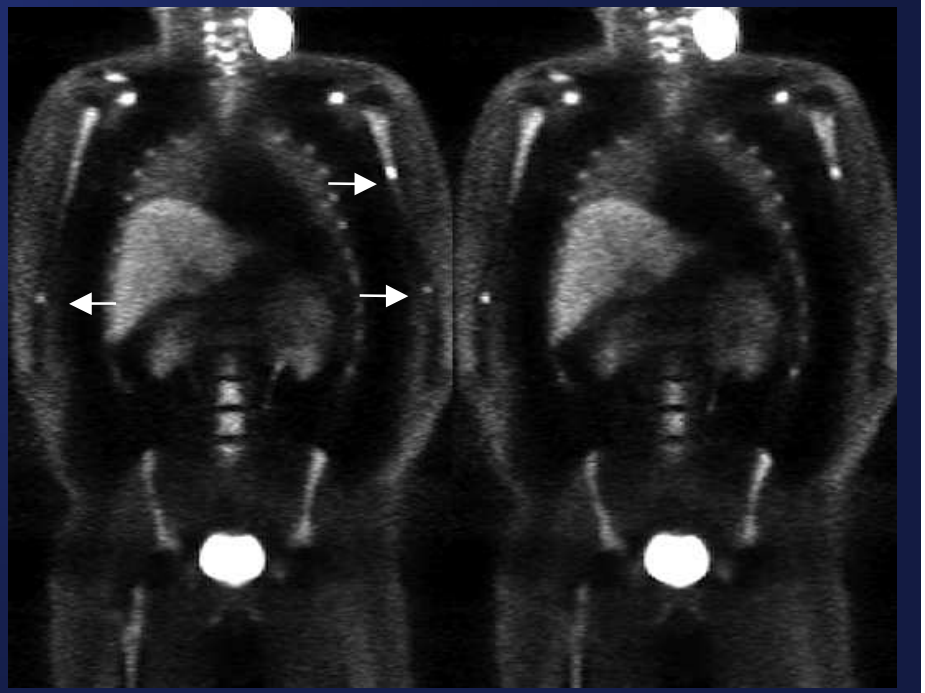
Buck et al. Cancer Res 2006.
Wagner, Seitz, Buck et al. Cancer Res 2003.

Detection osseous lesions
(large cell centroblastic B-NHL)

FDG-PET



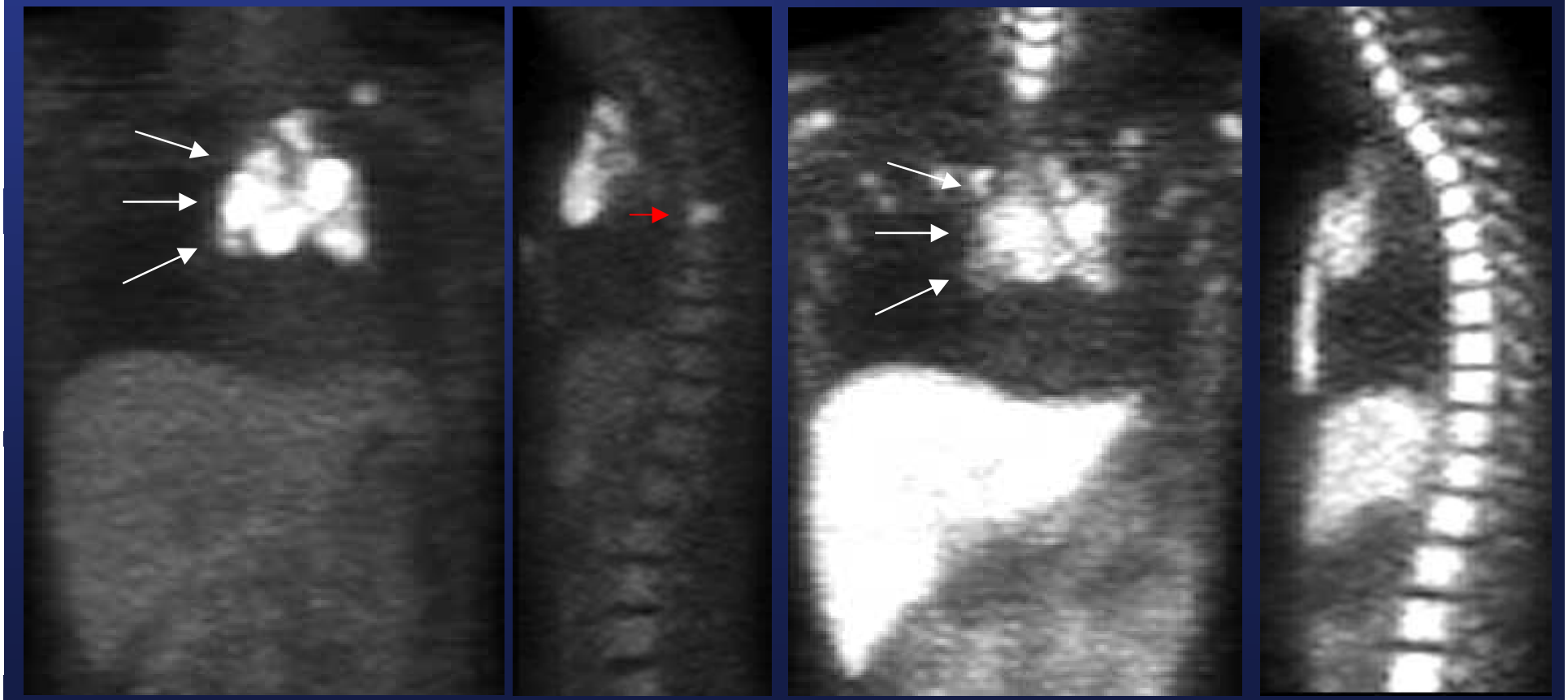
FLT-PET



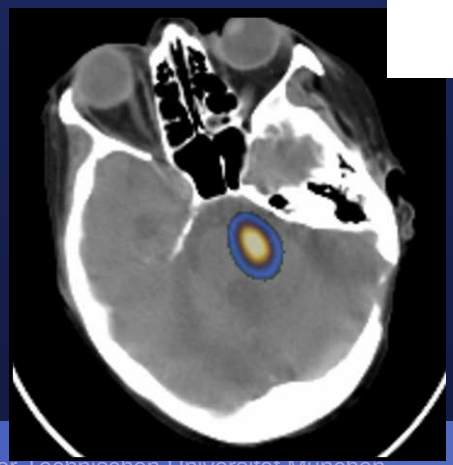
Detection of bone manifestation in Hodgkin`s disease

FDG-PET

FLT-PET

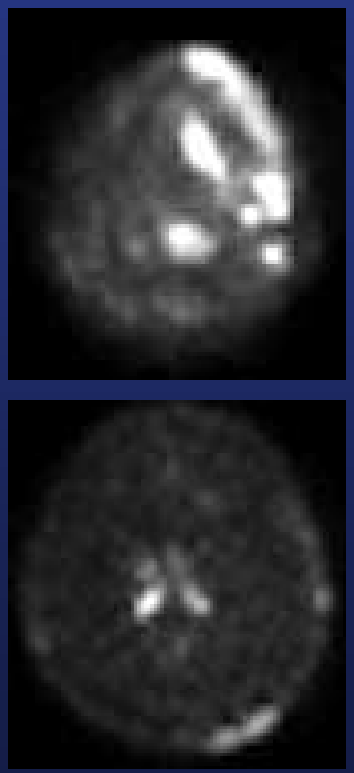


Detection of cerebral lymphoma (large cell centroblastic B-NHL)

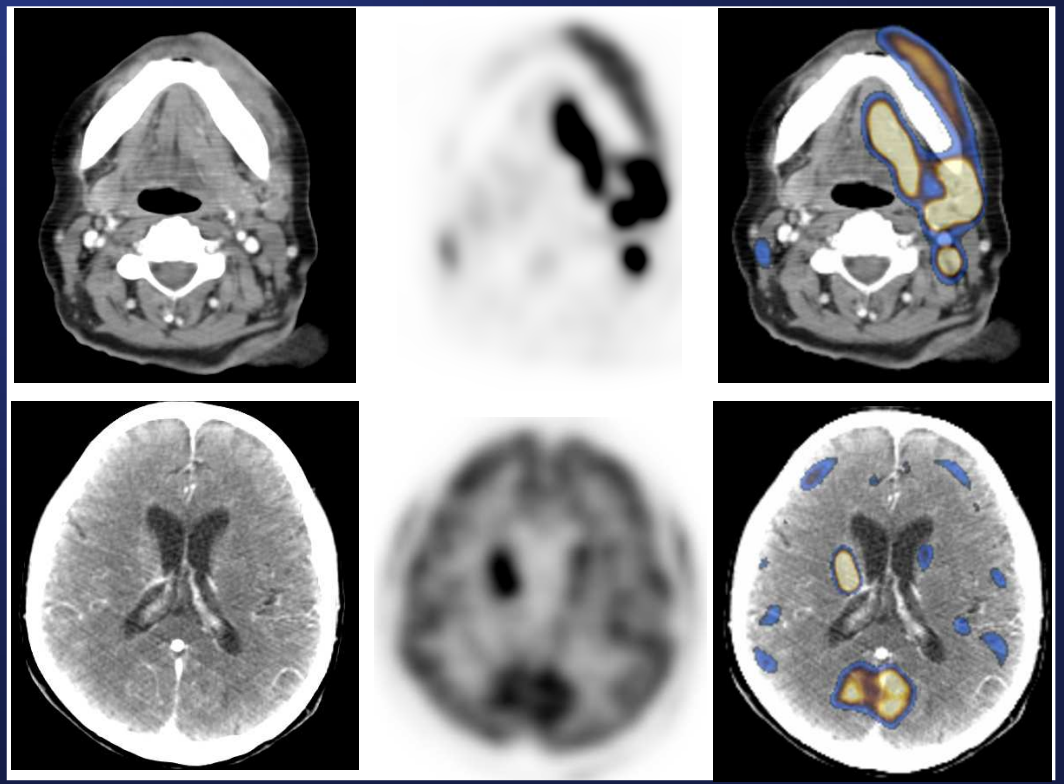


Detection of brain lesions
(large cell centroblastic B-NHL)

FLT-PET



FDG-PET/CT

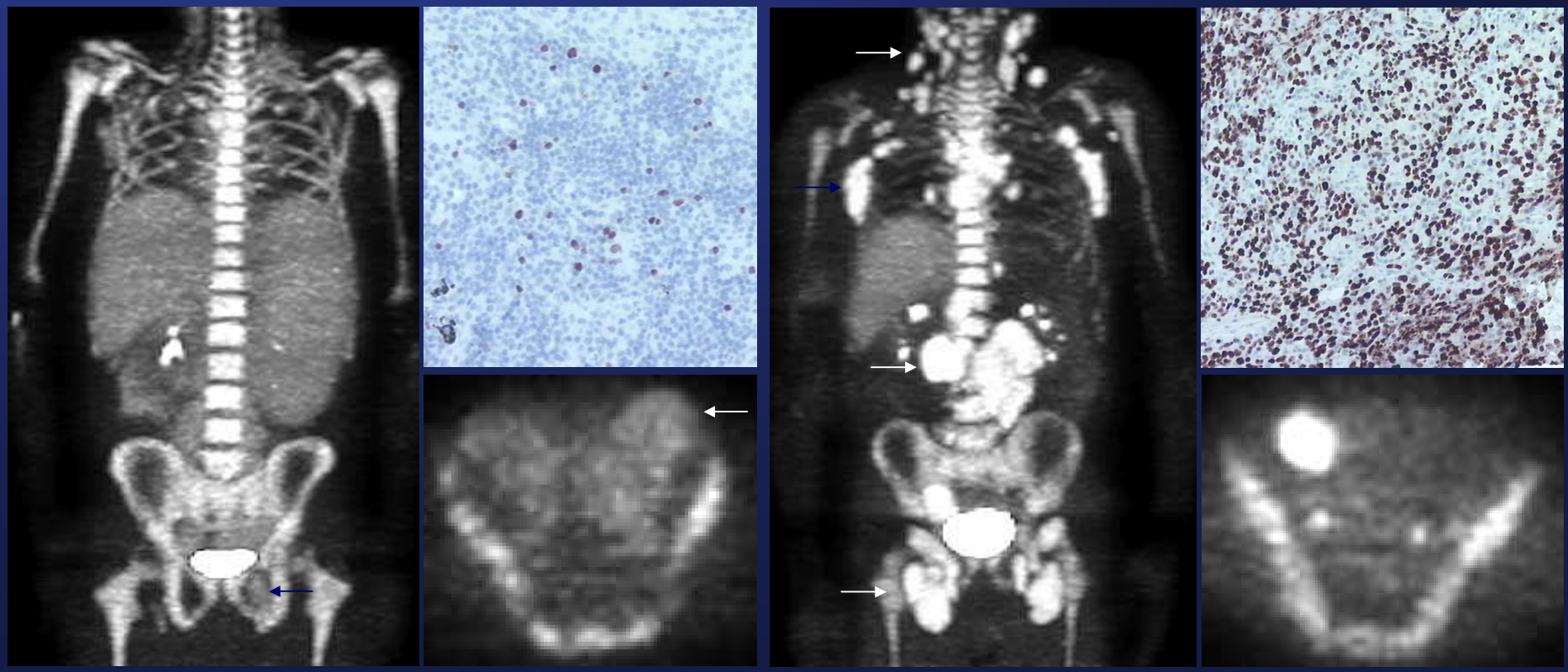


4wk

Grading of lymphoma with FLT-PET

Follicular lymphoma grade I

Large cell anaplastic lymphoma

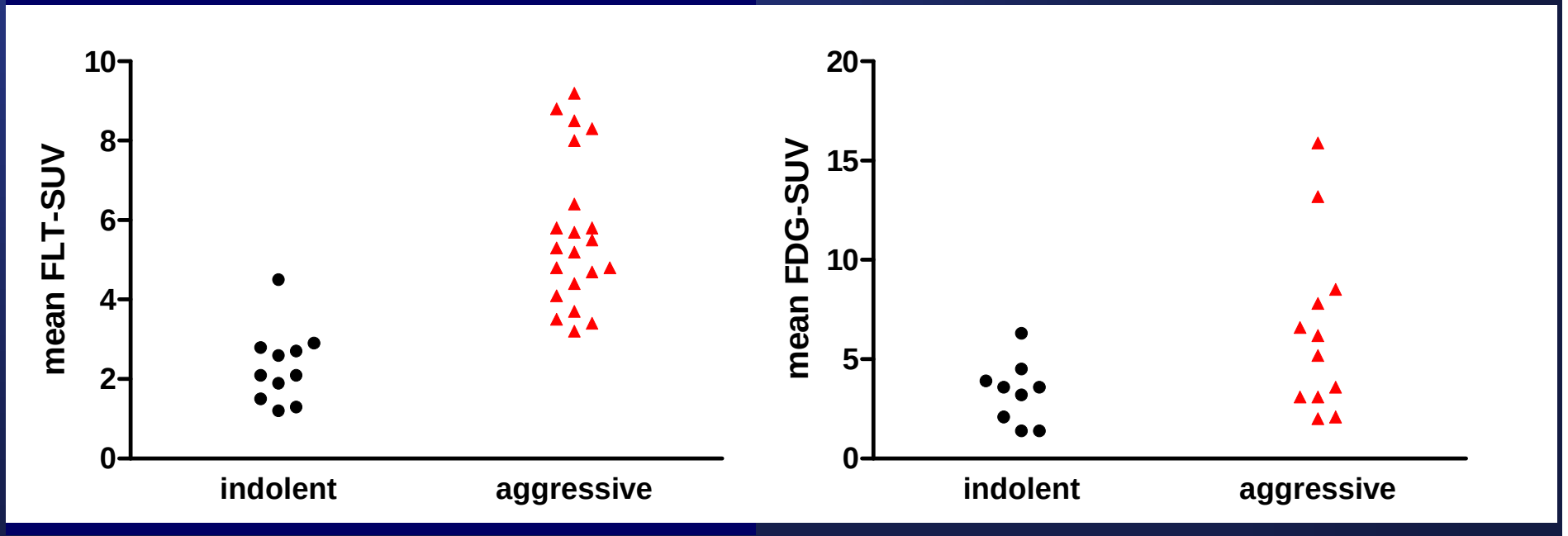


[Buck et al. Cancer Res 2006]

Grading of lymphoma with FLT-PET

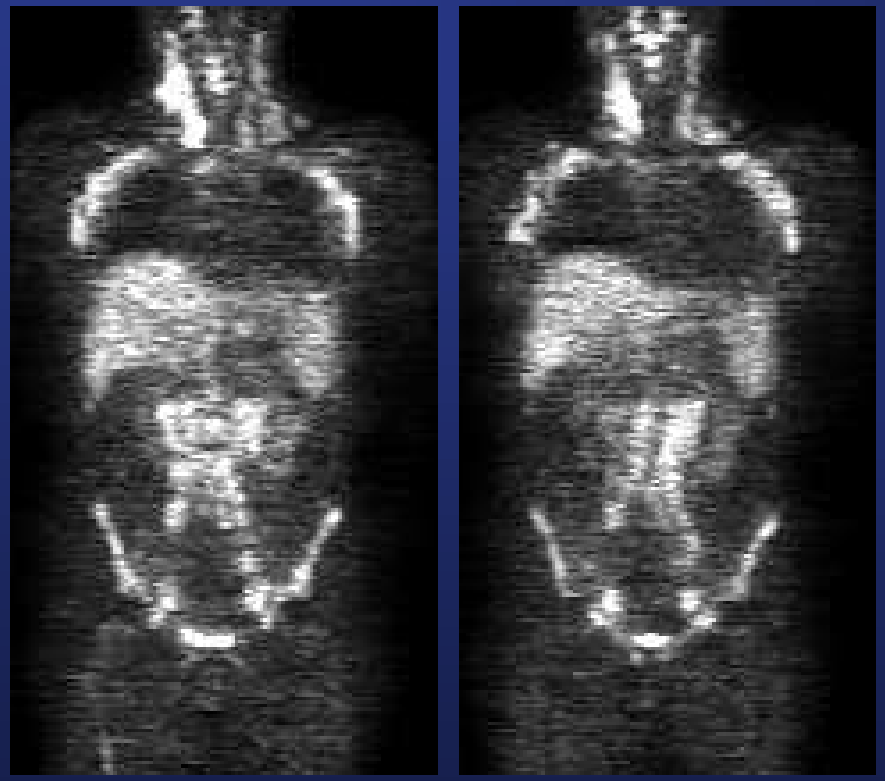
FLT

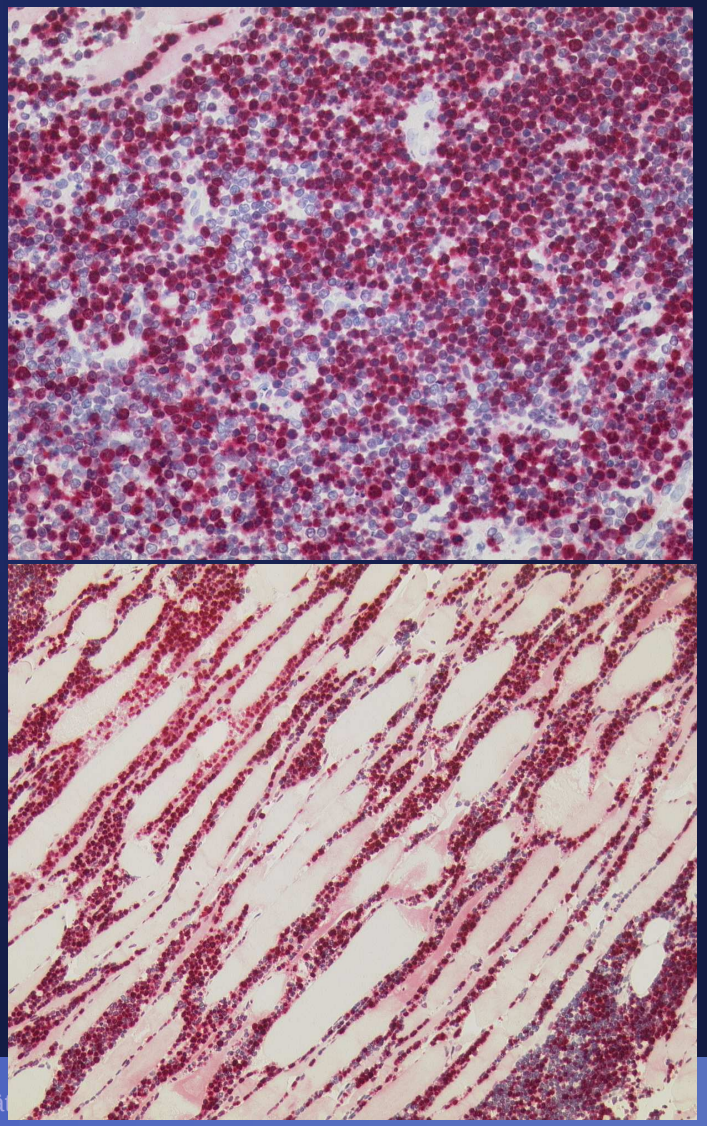
FDG



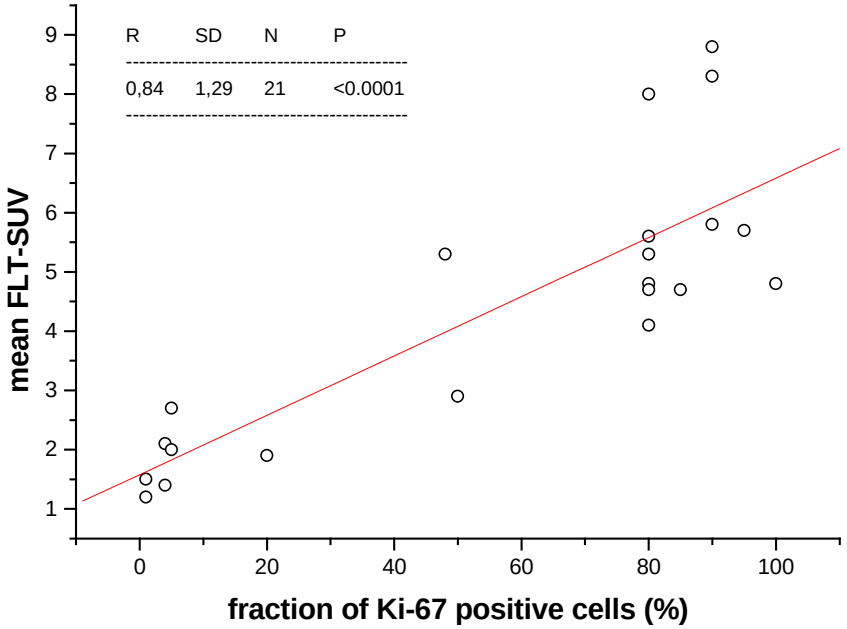
Buck et al. Cancer Res 2006.

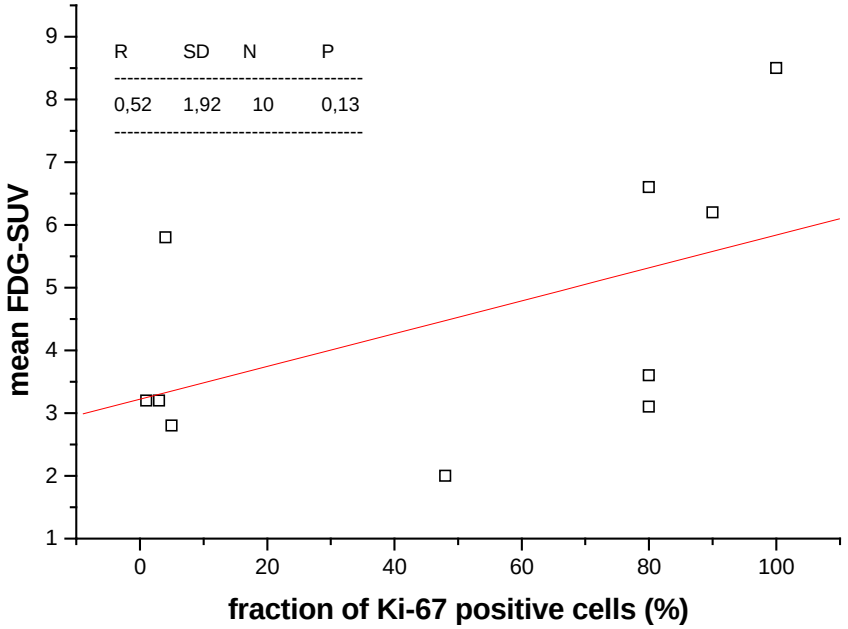
Pt. 19: follicular NHL grade I, recurrence: grade 3





Correlation of FLT- SUV with proliferative activity (Ki-67 index)

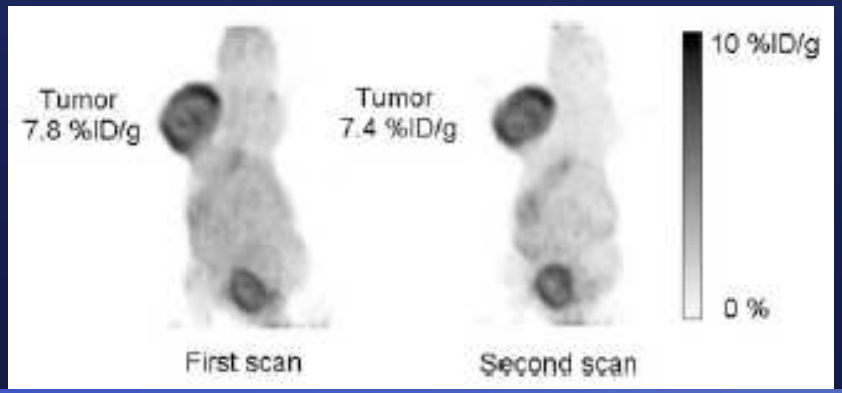




Buck et al. Cancer Res 2006.

Response assessment with [^{18}F]FLT

- „Inhibition of tumor proliferation may represent an early marker for response to therapy leading to earlier treatment decisions“
- Scans must be reproducible so that serial scans reflect therapy effects
- Reproducibility shown for [^{18}F]FLT microPET and human studies
- moderately low variability -14% (FDG in human studies: 6-10%)



Tseng et al., J Nucl Med 2005.

[^{18}F]FLT for assessment of therapy response

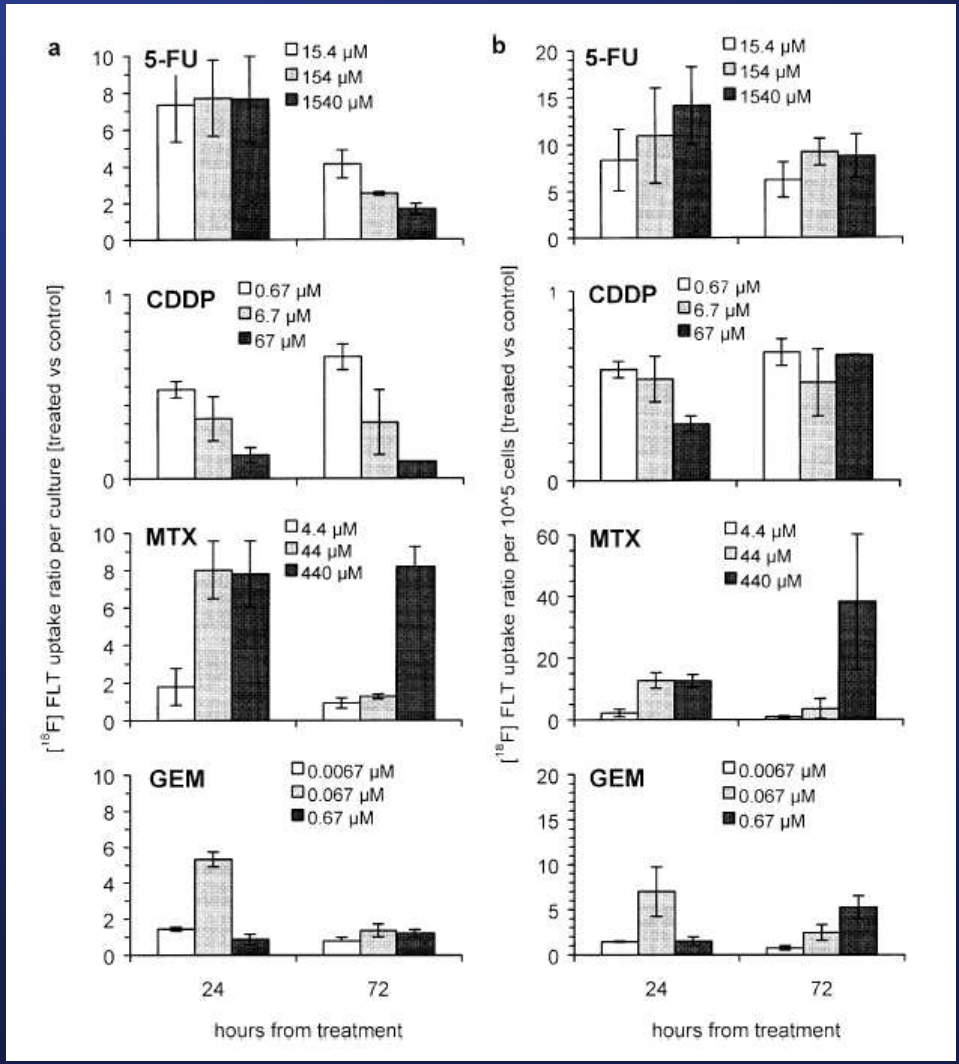
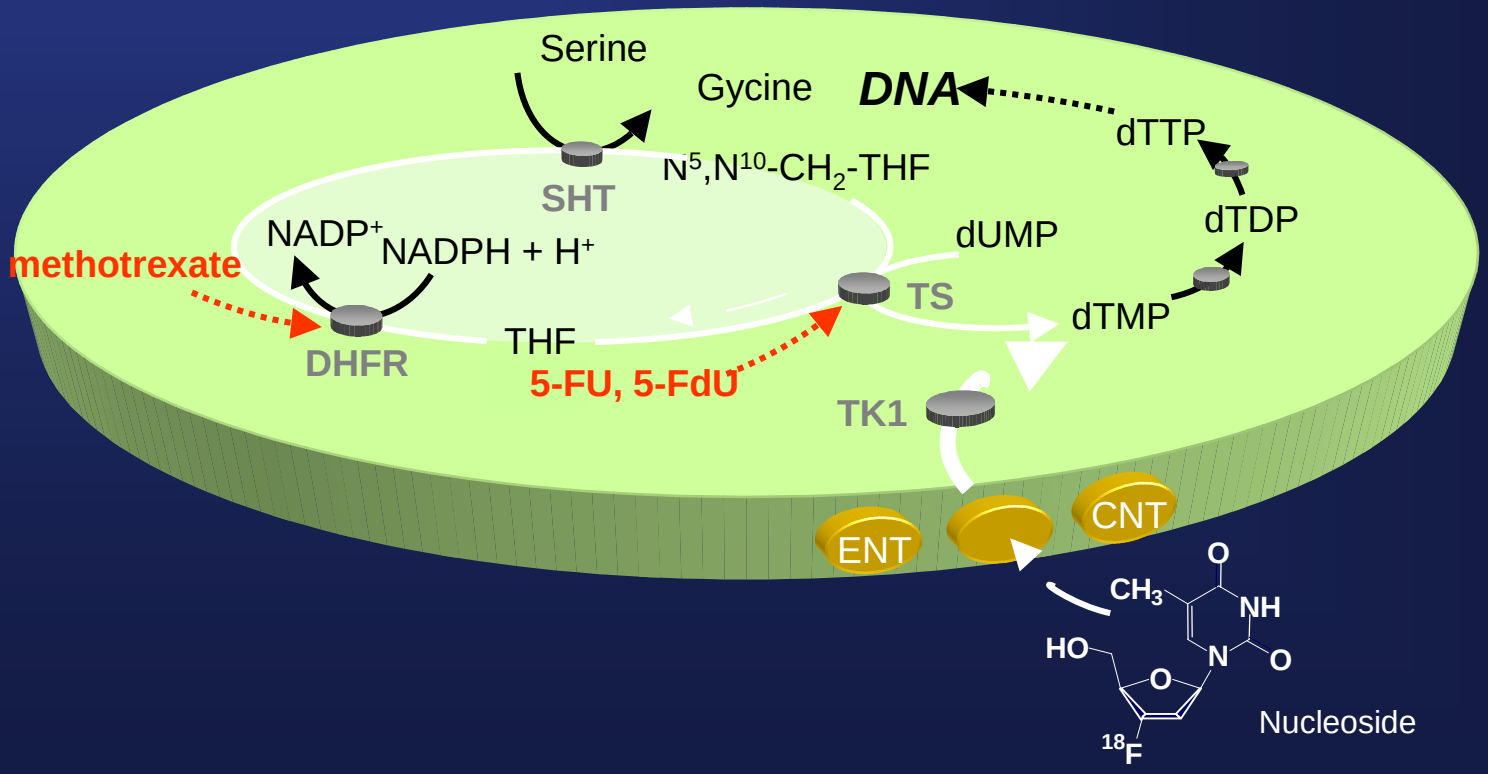


Fig. 2. Cellular uptake of [^{18}F]FLT per culture (**a**) or normalised for 10^5 cells (**b**) at different doses of 5-FU, MTX, CDDP or GEM. The drug concentrations in the culture media are given in µ*M*. FLT accumulation was measured after 24 or 72 h recovery from treatment. The data are expressed as mean values normalised for the control from repeated experiments, with error bars representing SD

Dittmann et al., EJNMMI 2002.

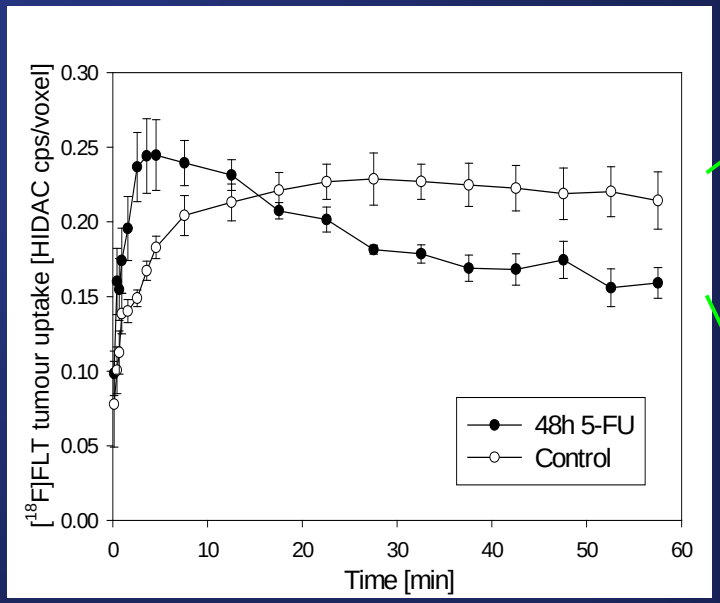
de novo synthesis of thymidylate and salvage pathway

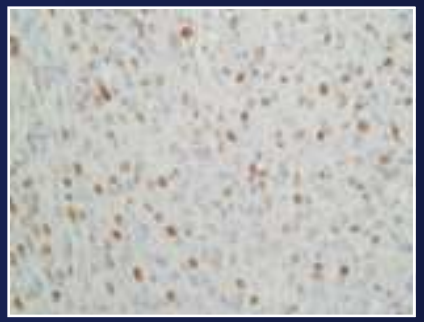
Chemotherapeutic drugs inhibit thymidylate synthase (TS) or dihydrofolatreductase (THFR) und can therefore upregulate the salvage pathway (increase of [^{18}F]FLT-uptake)



SHT: serine hydroxymethyl transferase
TK1: thymidine kinase
ENT: equilibrative nucleoside transporter
DHFR: dihydrofolate reductase
dUMP: deoxyuridine monophosphate
CNT: concentrative nucleoside transp.
TS: thymidylate synthase
dTMP: deoxythymidine monophosphate (thymidylate)

[^{18}F]FLT- PET in RIF-1 sarcoma mouse model





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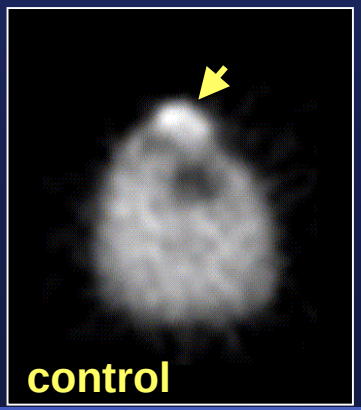
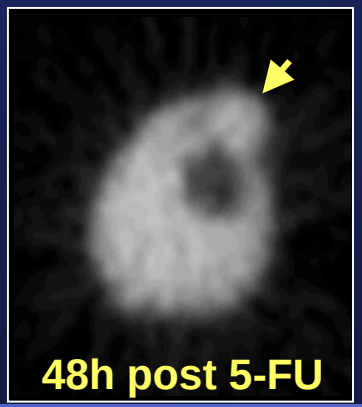
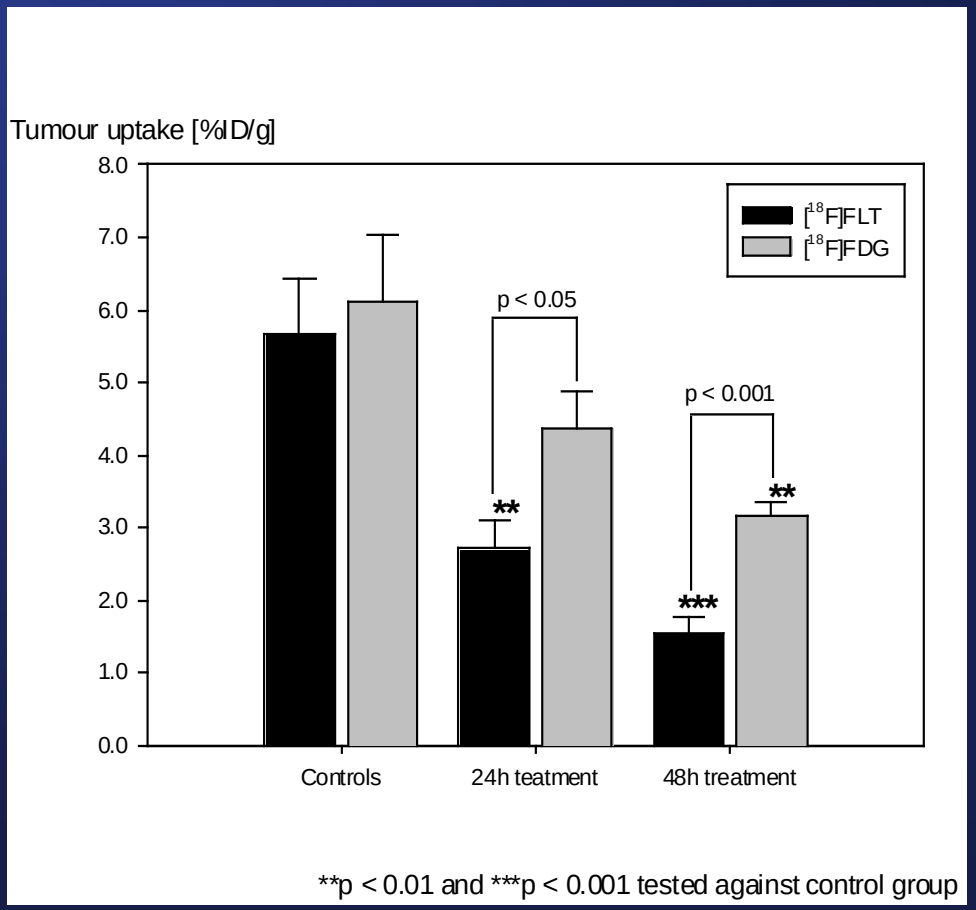




Barthel et al, Cancer Res., 2005.

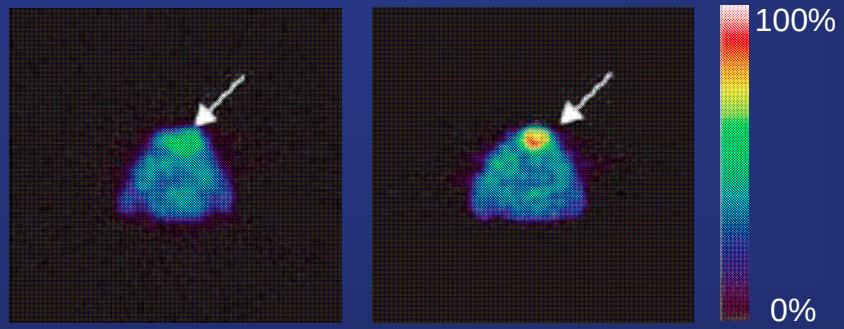
[18F]FLT- and [18F]FDG-PET in RIF-1 sarcoma mouse model



[18F]FLT- and [18F]FDG-uptake in RIF-1 tumors after treatment with 5-FU (165 mg/kg; i.p.)

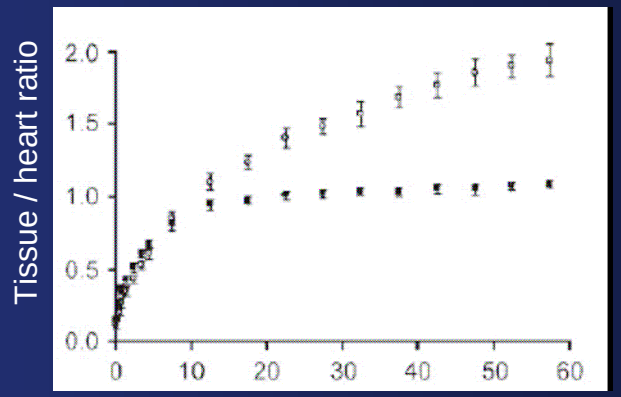
Uptake of [^{18}F]FLT after inhibition of *de novo* synthesis of TMP (thymidylate)

[^{18}F]FLT-PET 60 min after treatment



control (PBS) 5-FU (165 mg/kg i.p.)

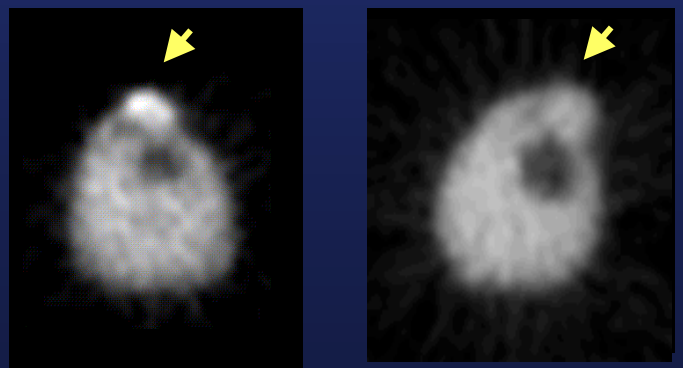
[Perumal et al, Cancer Res 2006]



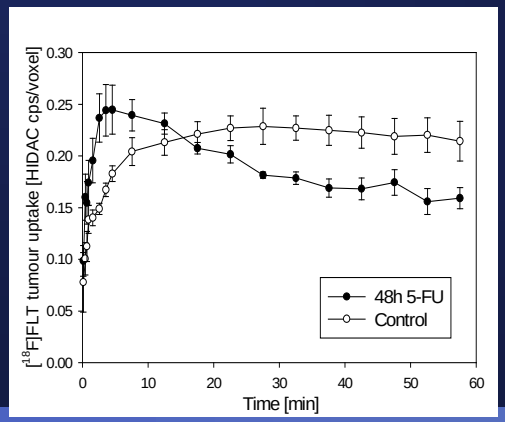
5-FU (165 mg/kg i.p.)

control (PBS)

[^{18}F]FLT-PET 48 h after treatment

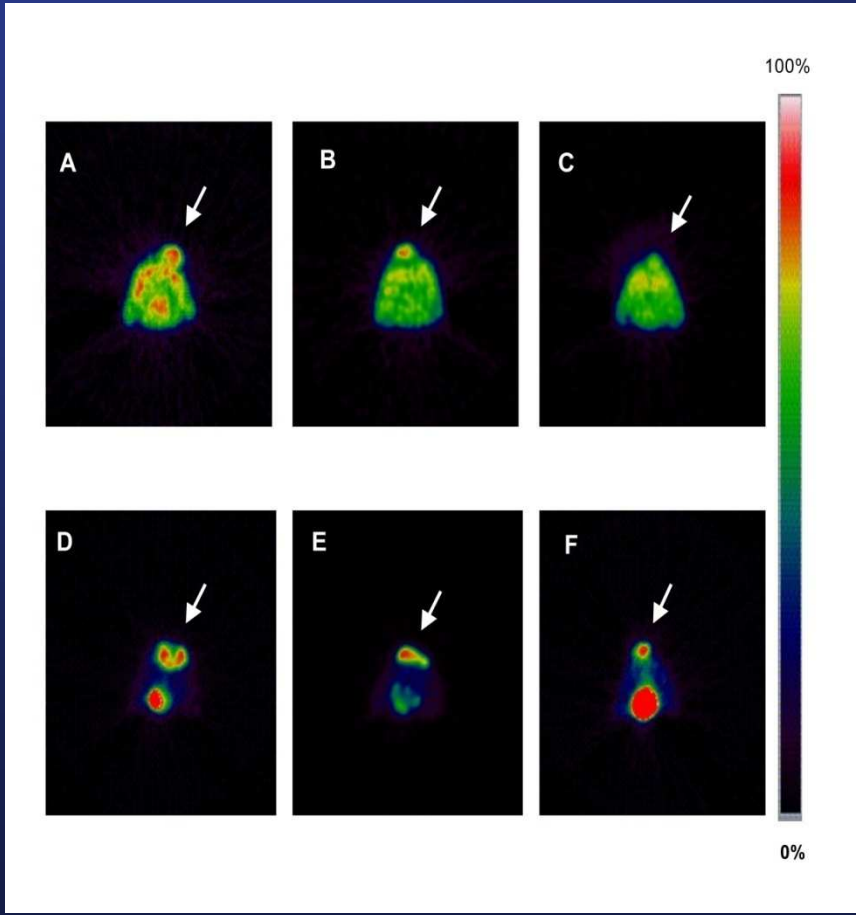


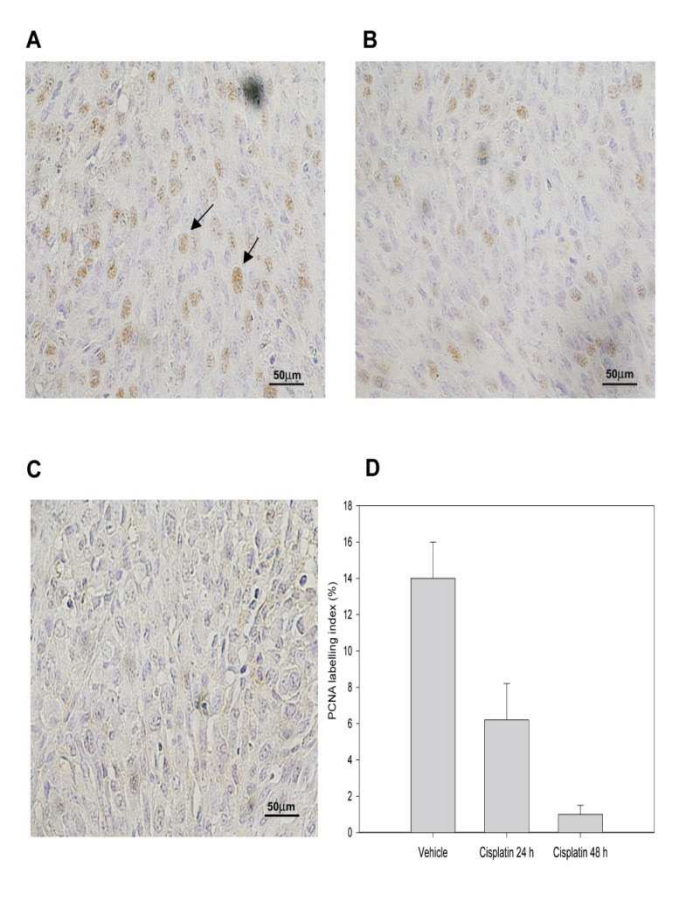
control (PBS) 5-FU (165 mg/kg i.p.)



Barthel et al, Cancer Res. 2005.

Significant reduction of FLT-uptake in RIF-1 tumors 24 h after chemotherapy with cisplatin

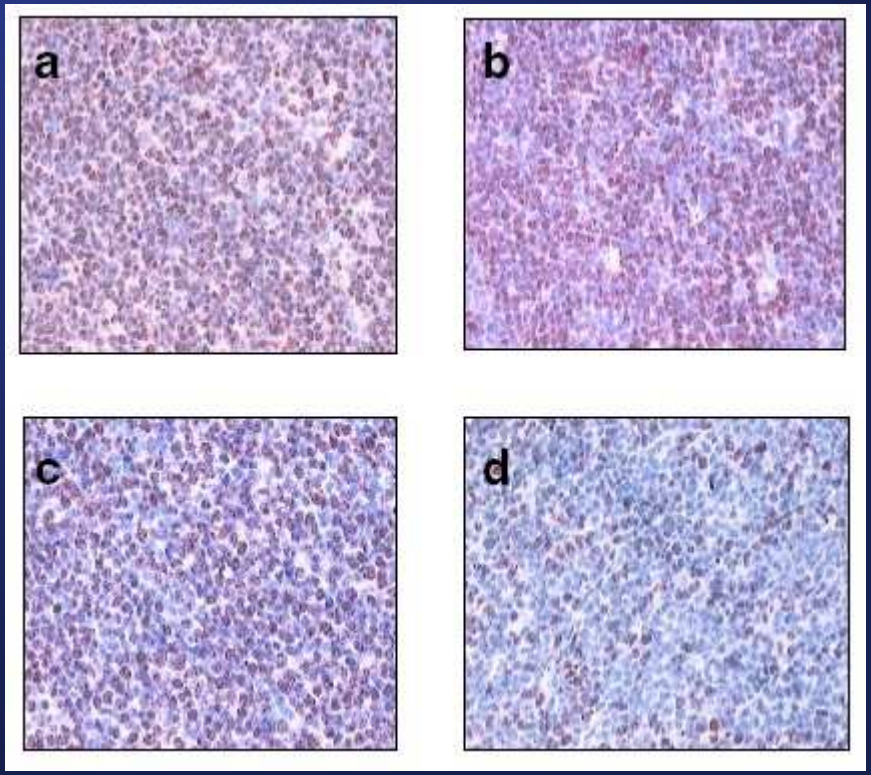




[Leyton et al., Cancer Res 2005]

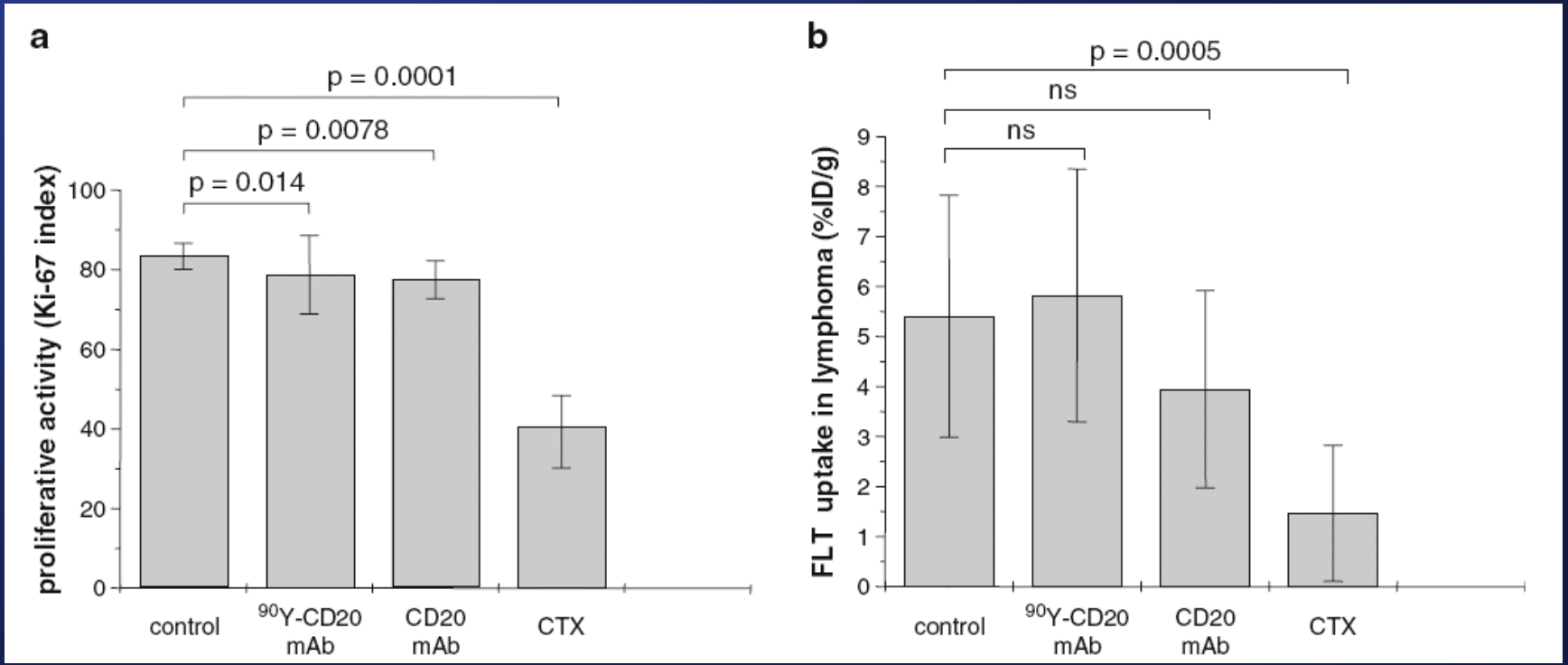
Proliferation fraction 48 h after therapy

control immunotherapy



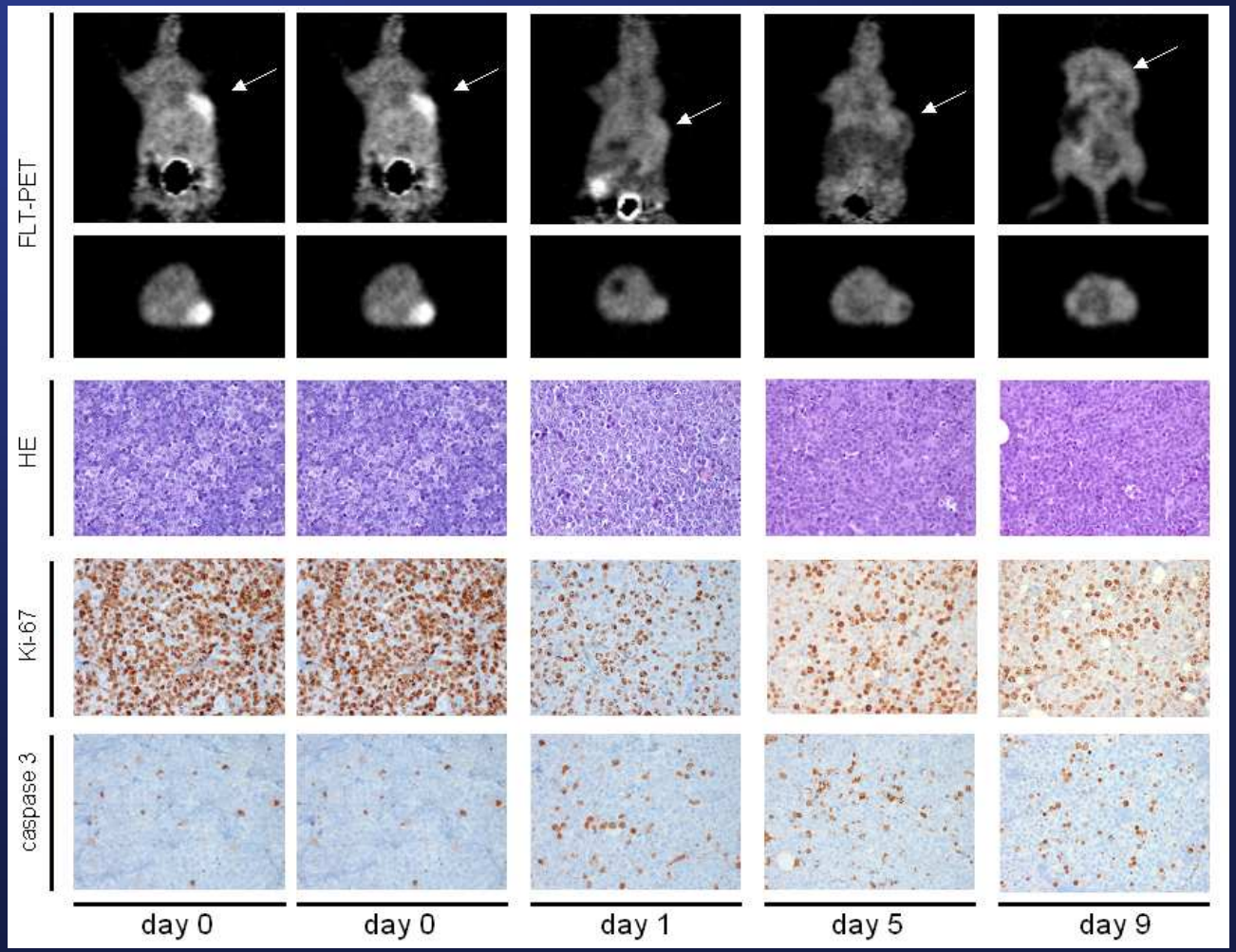
radioimmunotherapy chemotherapy

Proliferative activity and FLT-uptake 48 h after treatment



Buck et al ; Eur J Nucl Med Mol Imaging 2007.

Early reduction in FLT-uptake correlates to decreased proliferation and induction of apoptosis



Graf, Herrmann, Buck; Mol Imaging Biol 2008.

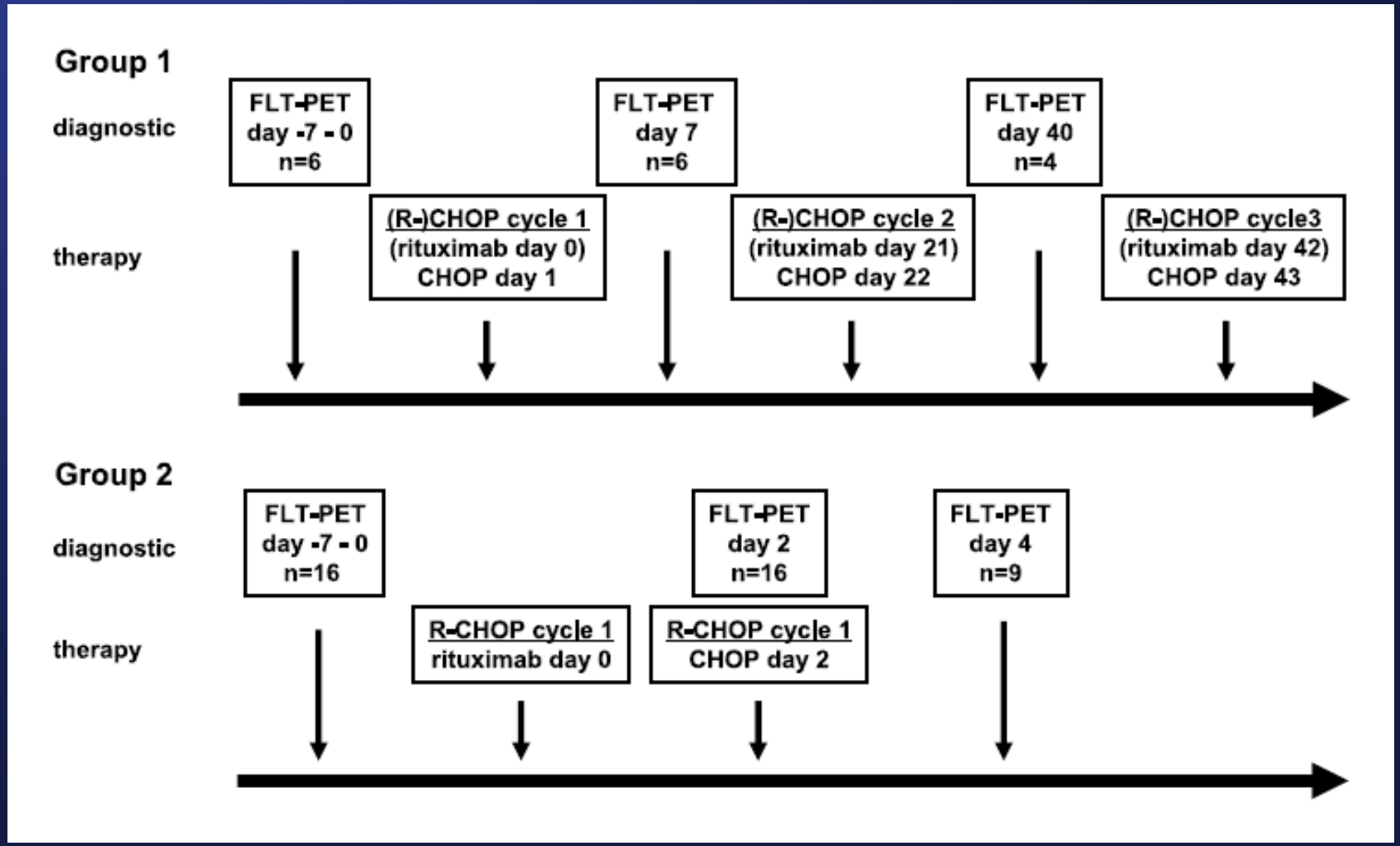
Anticipated alterations of metabolism of radionucleosides after various treatments

Drug	Target	Effect on tumor size	Anticipated effect on TK1	Anticipated imaging response
Cisplatin	DNA formation	↓	↓	↓
Cyclophosphamide	DNA formation	↓	↓	↓
Doxorubicin	DNA formation	↓	↓	↓
Gemcitabine	DNA formation	↓	↓	↓
Actinomycin D	DNA polymerase	↓	↓	↓
Irinotecan	Topoisomerase	↓	↓	↓
Vincristine	Microtubules	↓	↓	↓
NVP-LAQ824	TK synthesis	NC	↓	↓
PKI-166	Epidermal growth factor receptor tyrosine kinase	NC	↓	↓
Bevacizumab	Vascular endothelial growth factor	NC	↓	↓
Rituximab	B lymphocytes	↓	NC	↓
5-Fluorouracil, capecitabine	TS blockers	↓	↑	↑, then ↓
Methotrexate	Folic acid synthesis	↓	↑	↑, then ↓

↓ = decreased; NC = no change; ↑ = increased.

Bading & Shields, JNM 2008.

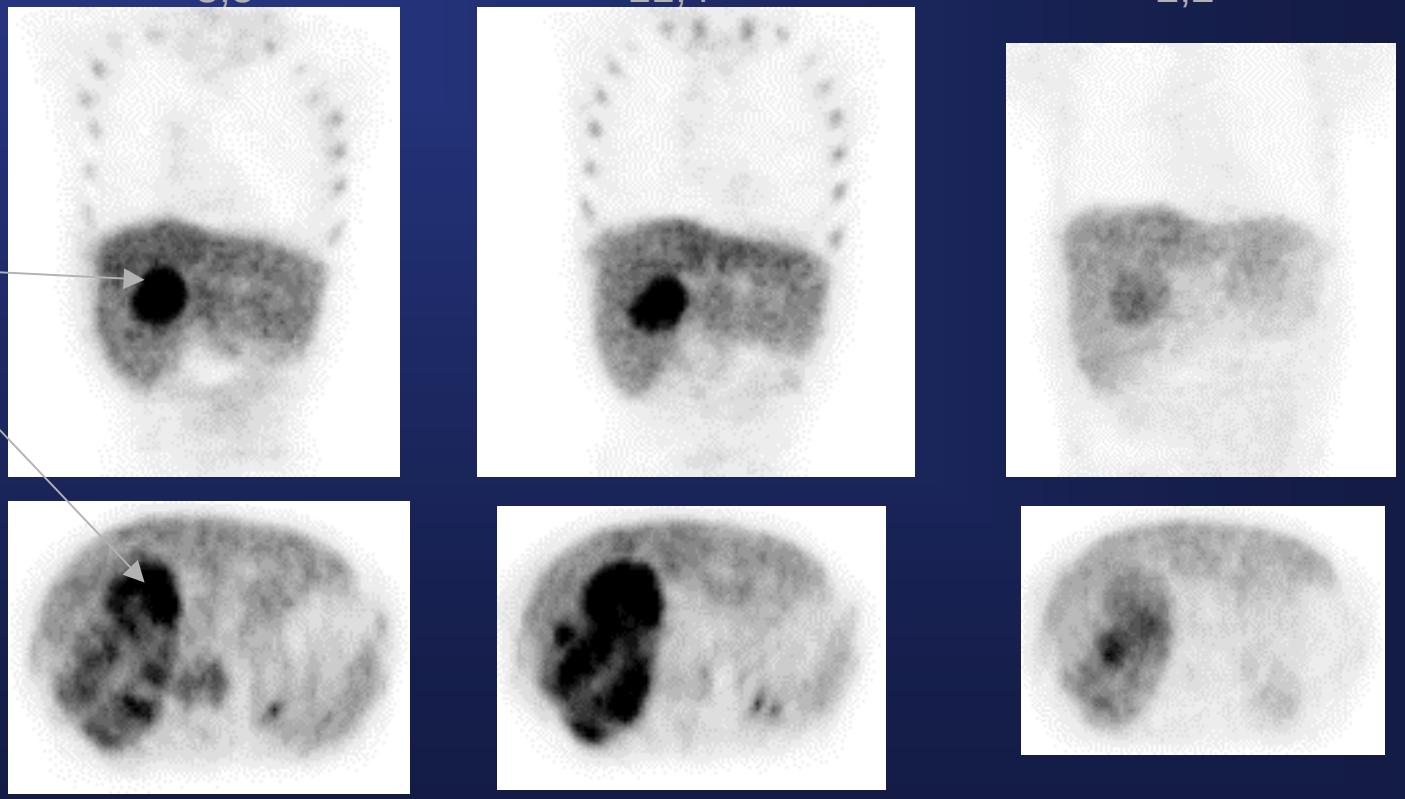
Early prediction of response in aggressive B-NHL



Early prediction of response in aggressive B-NHL

Time course	before tx	after rituximab	after CHOP
	day -1	day 2	day 5
SUV mean:	8,5	11,4	2,2

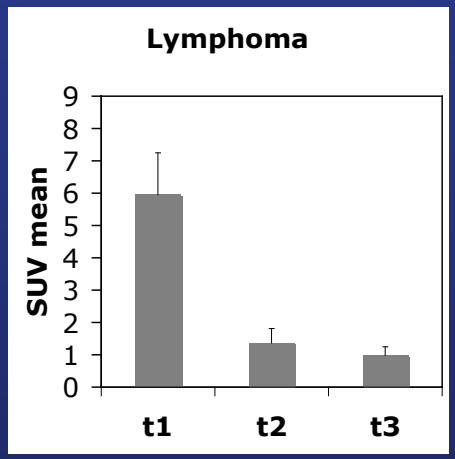
tumor

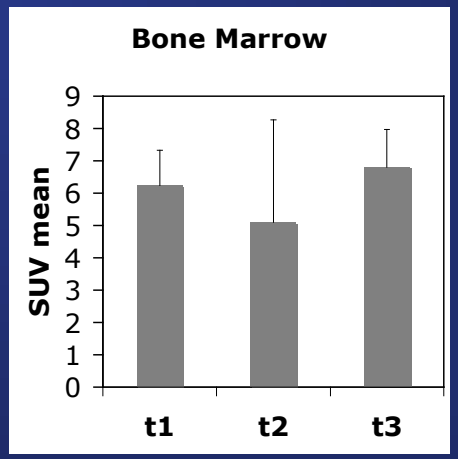


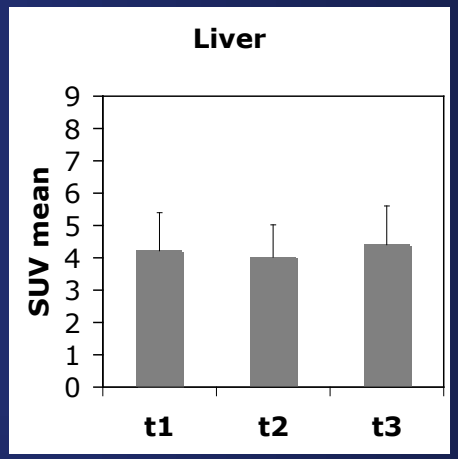
Herrmann, Dechow, Buck, Clin Cancer Res 2007.

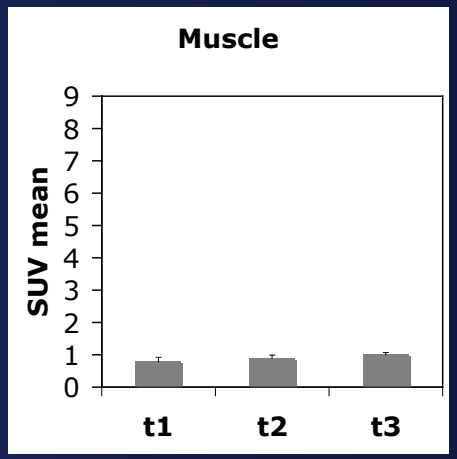
Early prediction of response in aggressive B-NHL

Group 1

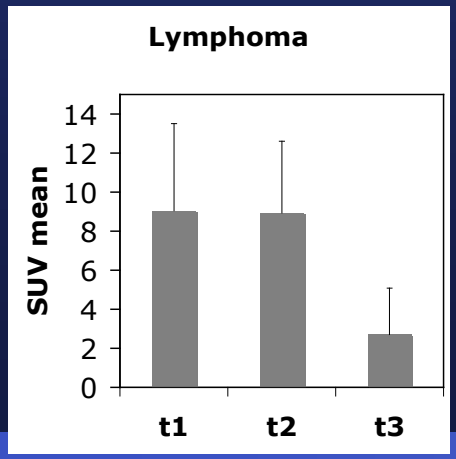


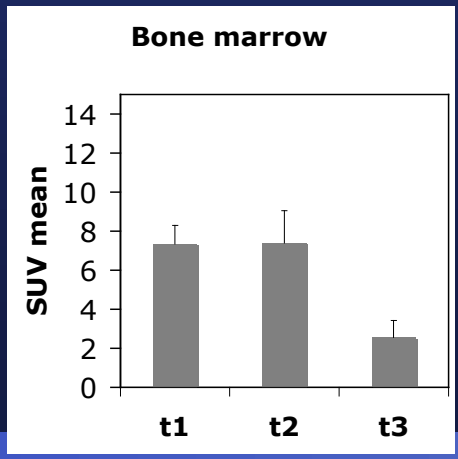


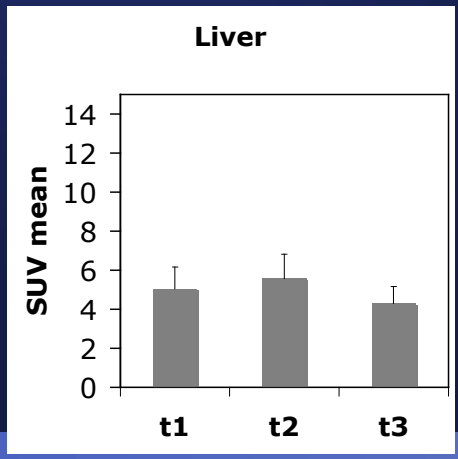


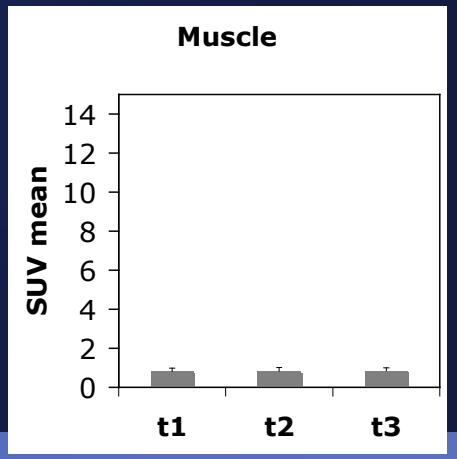


Group 2

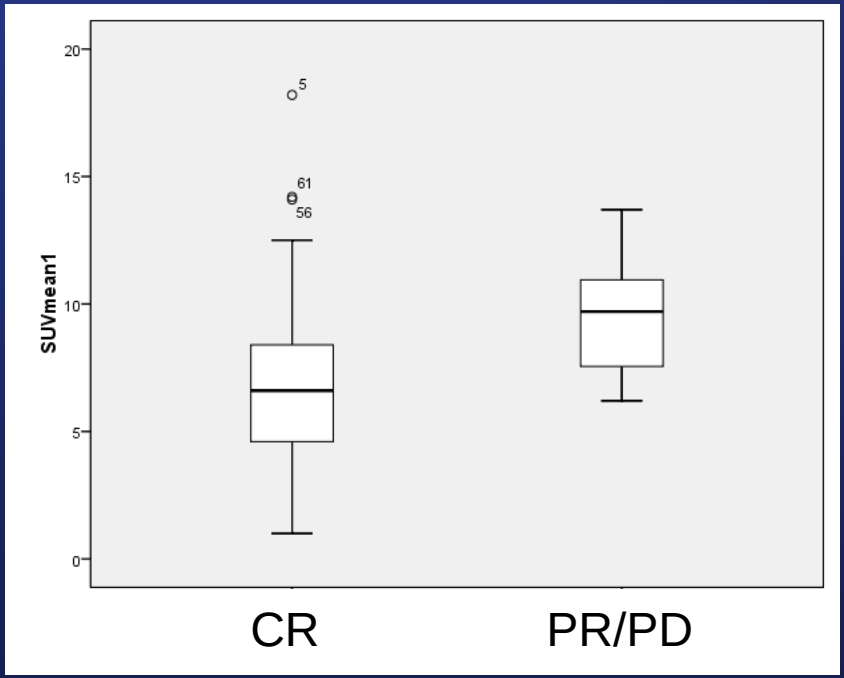








Initial FLT-uptake in 70 patients with DLBCL: CR vs. PR/PD



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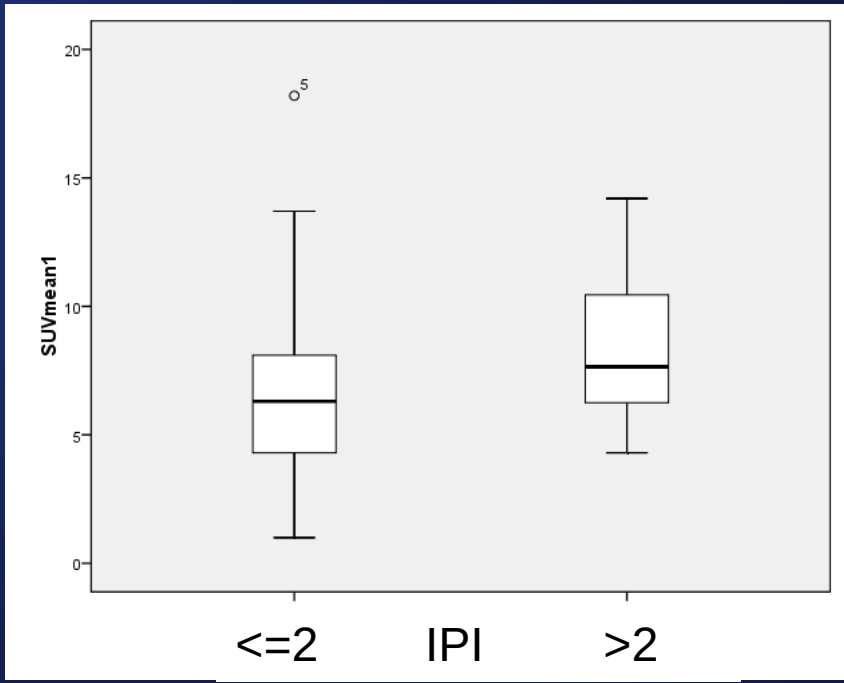

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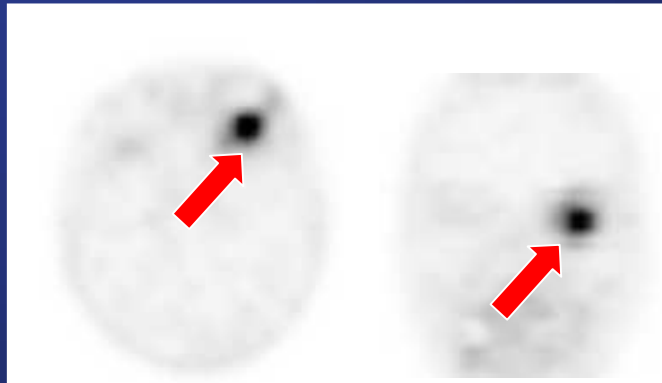
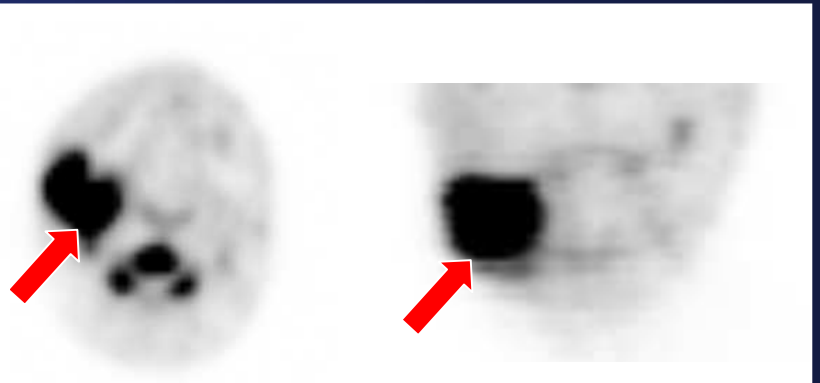
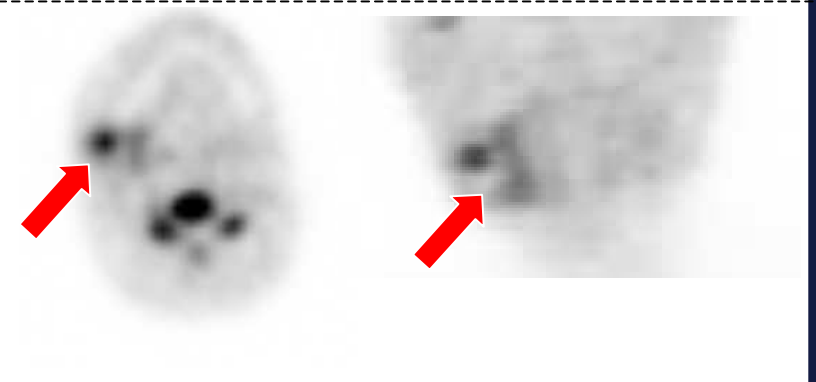
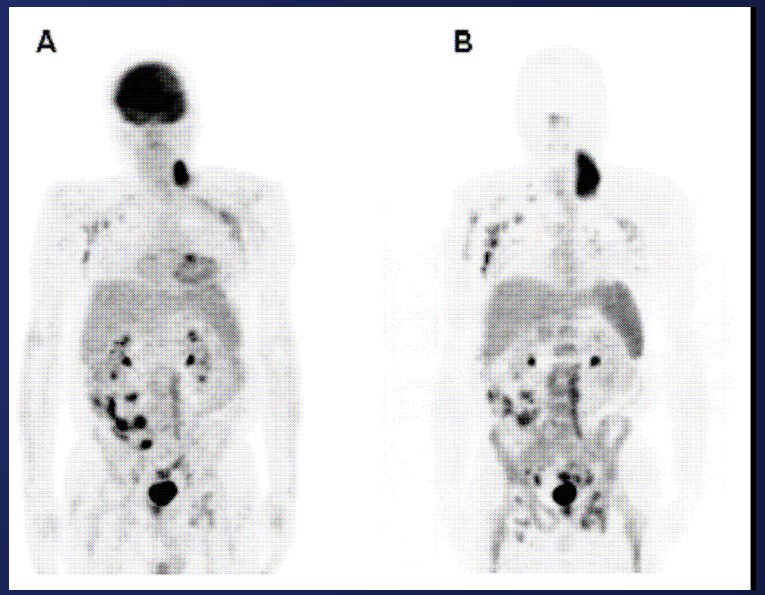
Prediction of response in DLBCL (70 pts.)

	Complete response at FLT-PET	Partial response at FLT-PET
Initial scan		
Interim scan (d+7 after R-CHOP)		

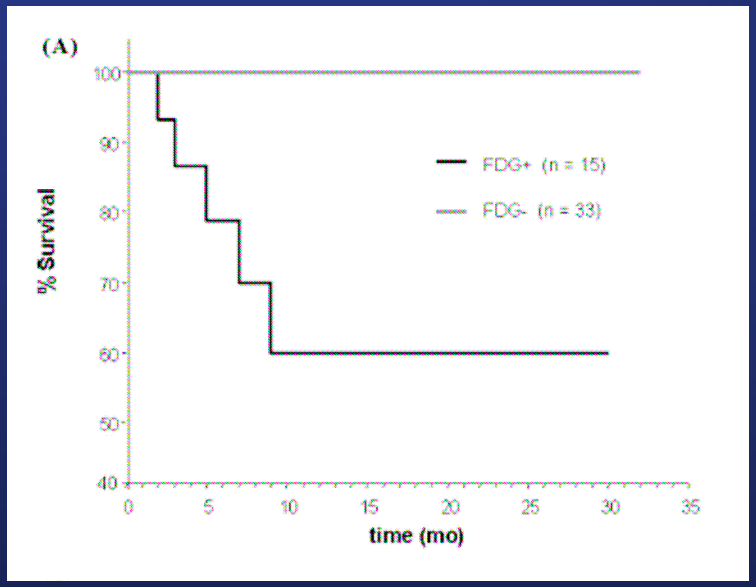
Imaging residual lymphomas with FLT- and FDG-PET

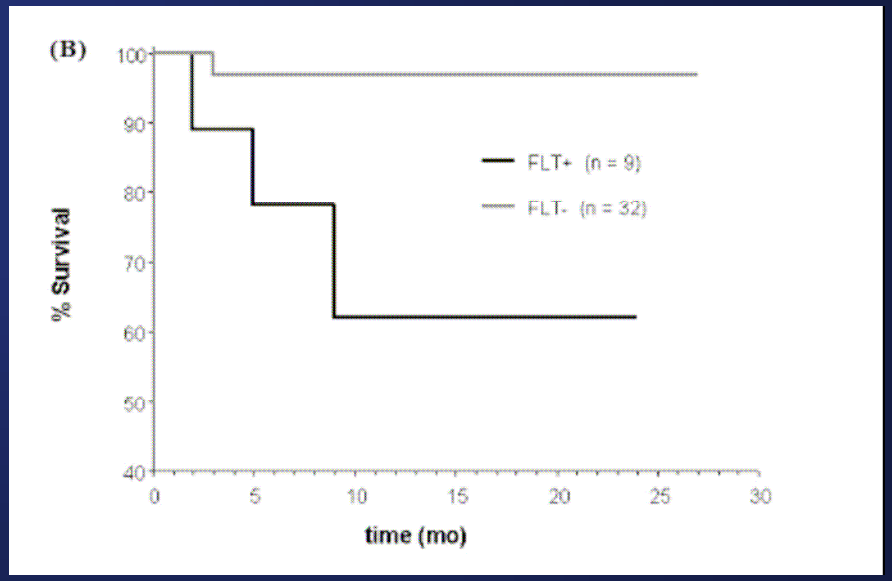
- 48 pts. with NHL (33) or HD (15)
- Both FLT- and FDG-PET after completion of RCTx
- Correlation of pos./neg. scans to survival



Kasper et al, Leukemia Lymphoma 2007.

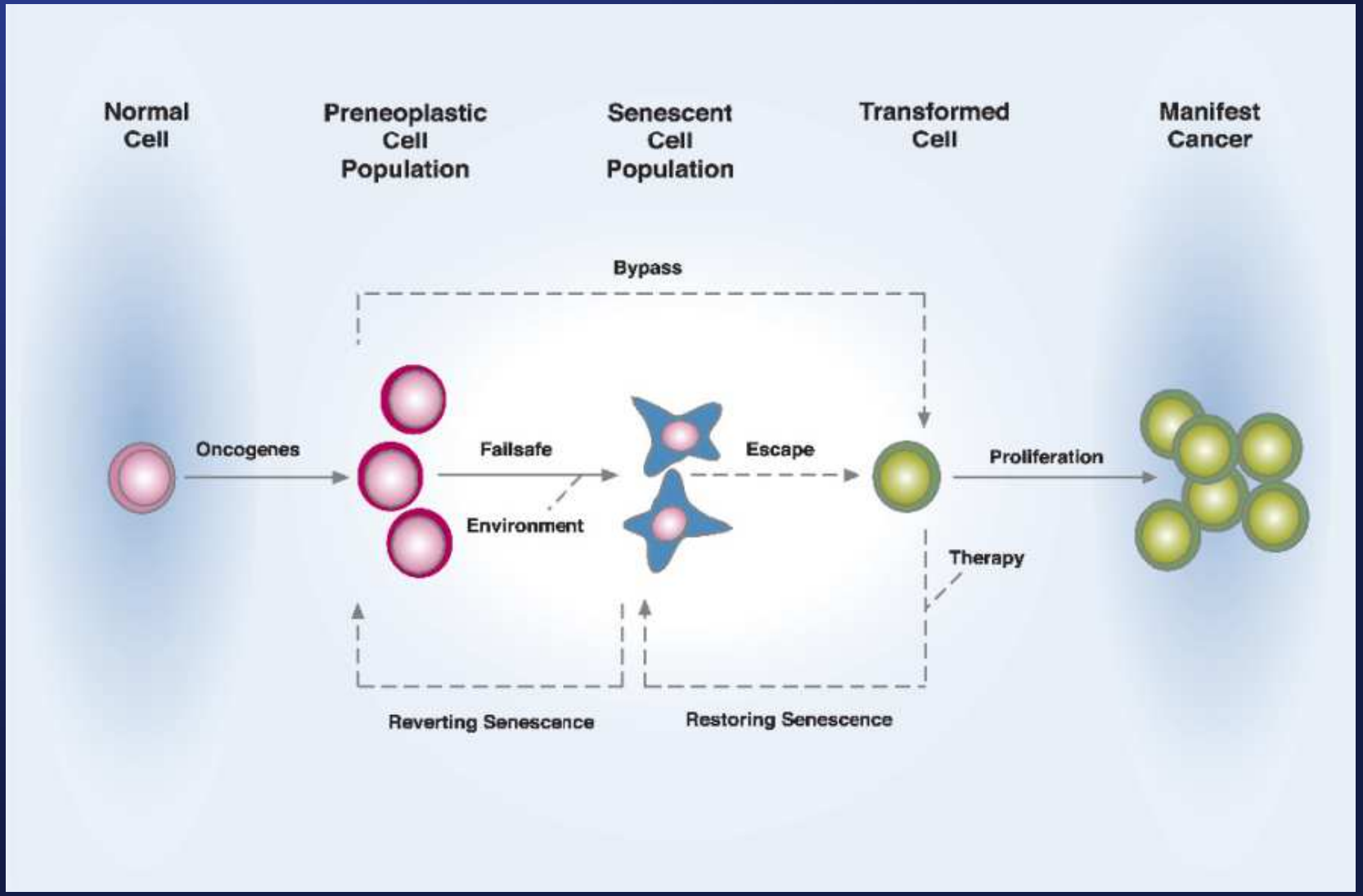
Imaging residual lymphomas with FLT- and FDG-PET





Kasper et al, Leukemia Lymphoma 2007.

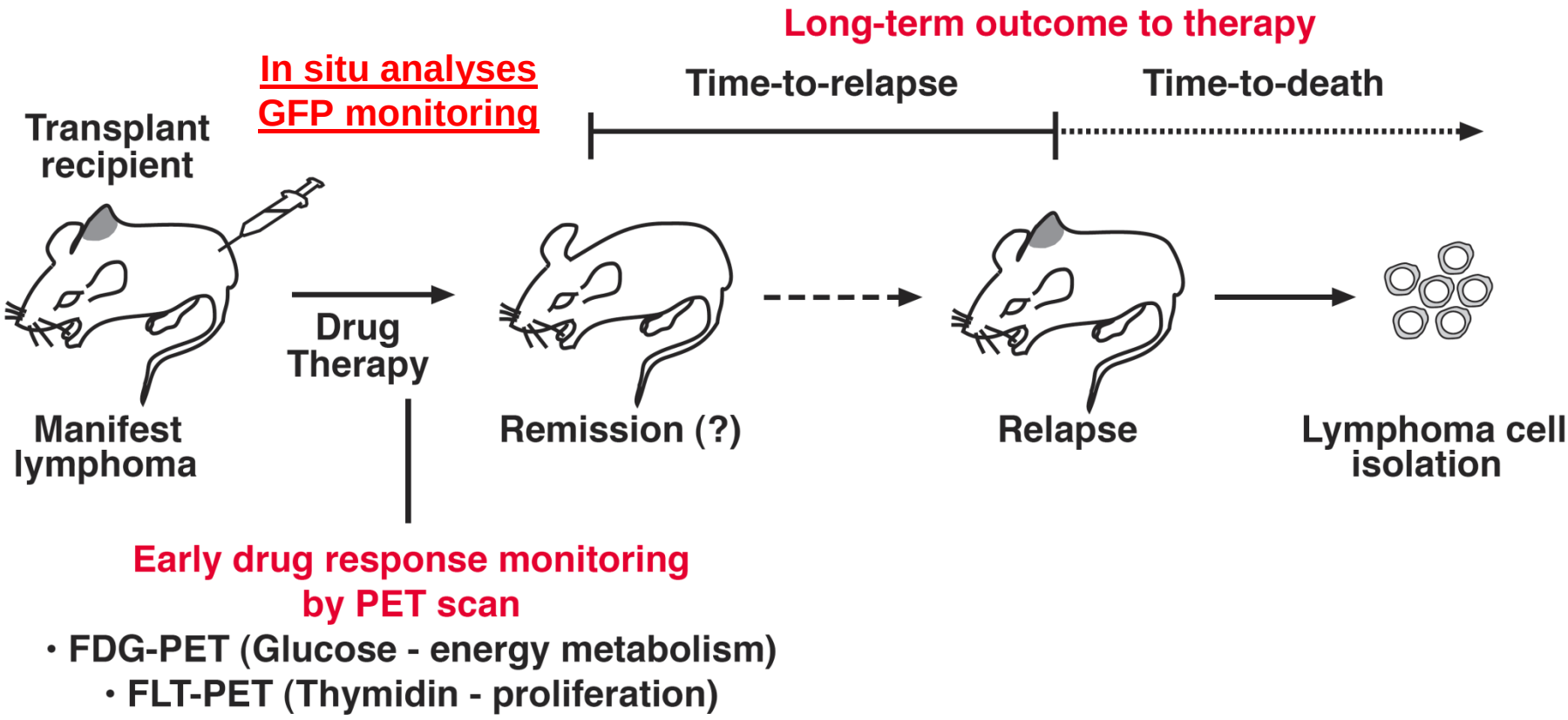
Oncogene induced senescence



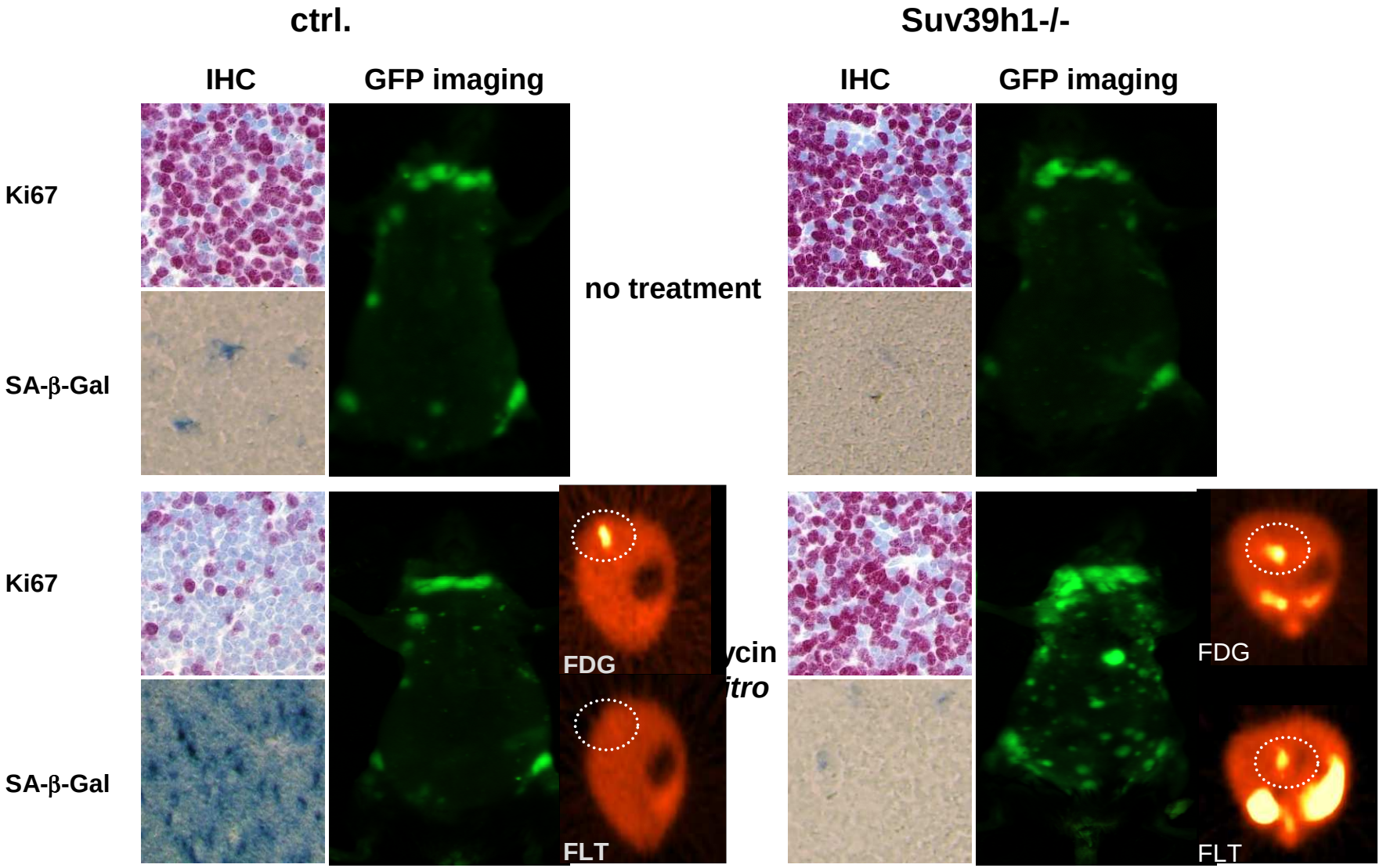
Monitoring drug responses in lymphoma

TRR54

Mice harboring transplanted primary lymphomas with defined genetic lesions undergo anticancer therapy in vivo



Therapy-induced senescence in bcl2-protected Eμ-myc lymphomas



Summary

- [^{18}F]FLT reflects (cell cycle-dependent) TK1- activity
- Enables non-invasive assessment of proliferative activity

- Accuracy of [^{18}F]FDG and [^{18}F]FLT for staging almost identical but [^{18}F]FLT superior regarding tumor grading

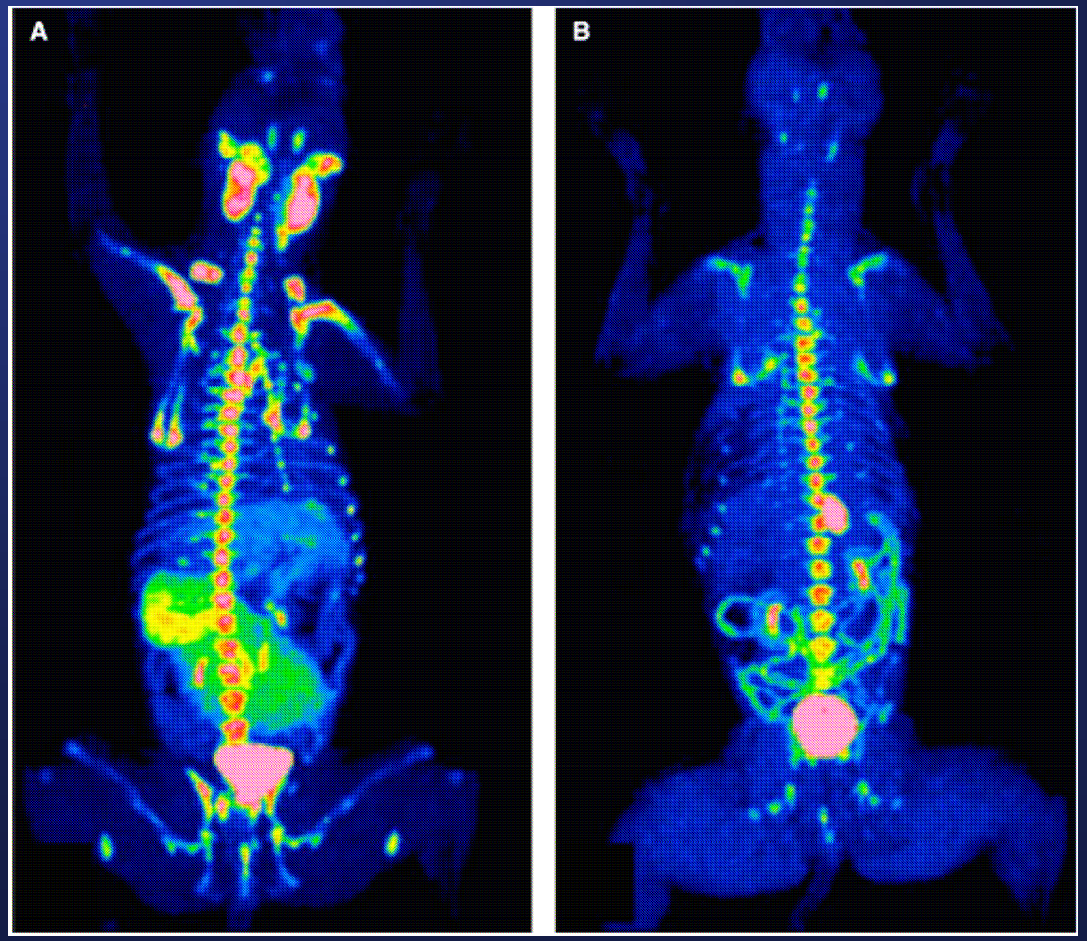
- anti-proliferative effects of chemotherapy early detectable with [^{18}F]FLT

- DNA-repair and resistance to treatment

- Therapy induced senescence

USE OF 3′-DEOXY-3′-[^{18}F]FLUOROTHYMIDINE PET/CT FOR EVALUATING RESPONSE TO CYTOTOXIC CHEMOTHERAPY IN DOGS WITH NON-HODGKIN'S LYMPHOMA

JESSICA LAWRENCE, MATTHEW VANDERHOEK, DAVID BARBEE, ROBERT JERAJ, DANIEL B. TUMAS, DAVID M. VAIL



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