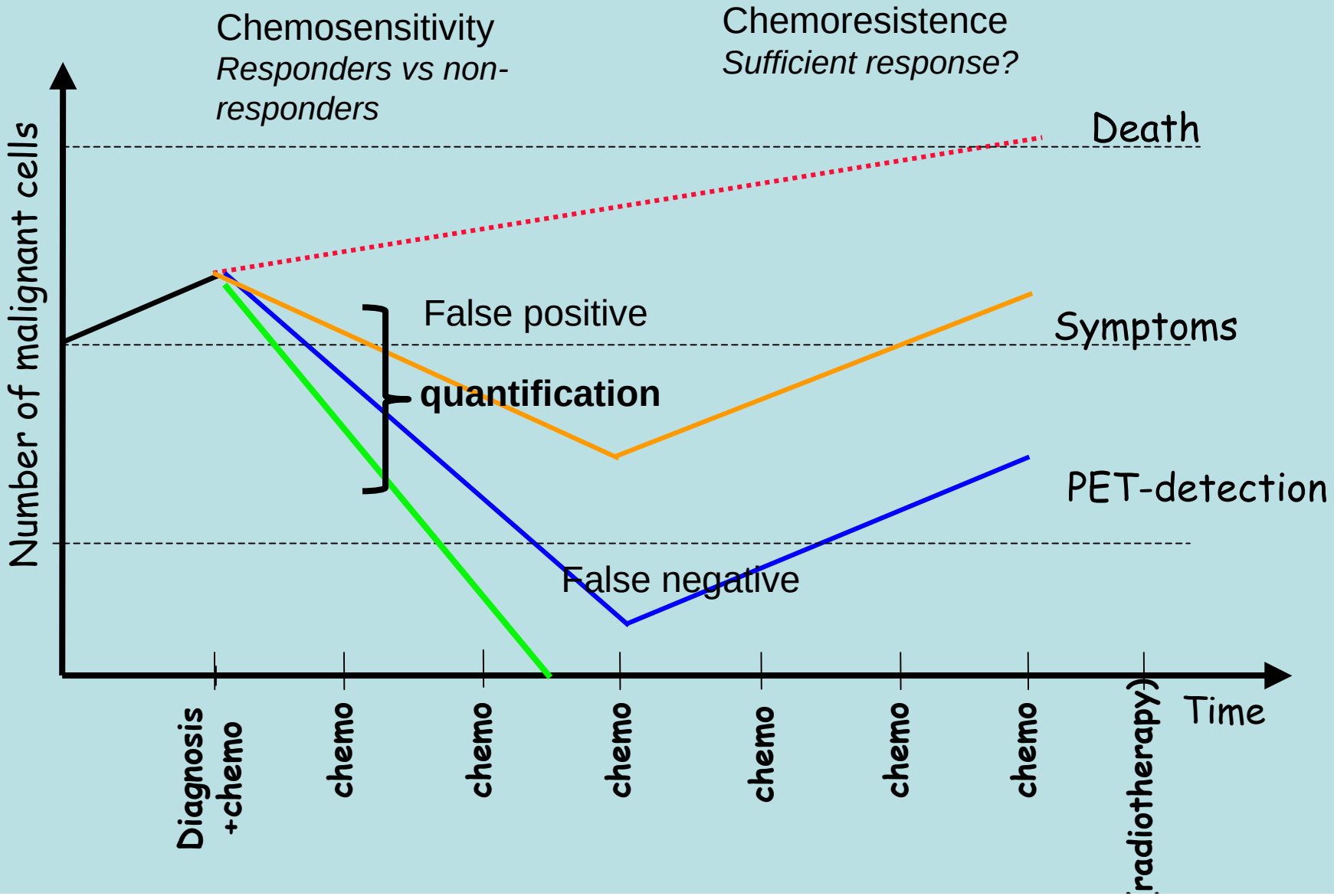
Interim PET with emphasis on the effect of drugs

What can we learn from animal studies?

L. Brepoels, S. Stroobants

Principles of response assessment



Early response assessment in DLBCL after 7 days of treatment

- Materials and methods
  - 29 patients
  - Newly diagnosed DLBCL
  - Treatment with R-CHOP
  - PET/CT after 7 days

Table V.1. Patients Characteristics

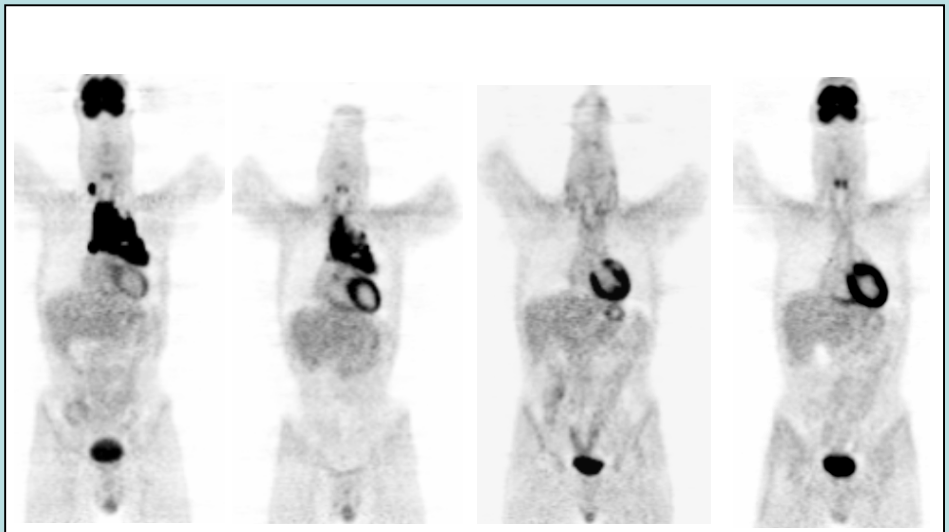
	Early PET negative (n=13)	Early PET positive (n=17)	Overall (n=30)
median age	63 yrs (range 34-79)	60 yrs (range 27-79)	61 yrs (range 27-7
gender			
man	4	12	16
women	9	5	14
IPI score			
low	3	6	9
low intermediate	3	3	6
high intermediate	3	4	7
high	4	4	8
bone marrow involvement			
yes	6	6	12
no	7	11	18
extranodal involvement (not bone marrow)			
yes	7	7	14
no	6	10	16
bcl-2			
>30%	11	11	22
<30%	2	4	6
not known	0	2	2
bcl-6			
>40%	11	7	18
<40%	1	7	8
not known	1	3	4
immunophenotype			
germinal center (GC	6	6	12
non-GC	6	8	14
unknown	1	3	4

Early response assessment in DLBCL after 7 days of treatment

- 29 patients
  - 17 patients positive on early PET
    - 2 refractory disease
      2 relapsed (12 and 23mths)
    - 13 disease free
      (follow-up 20 mths)
  - 12 patients negative on early PET
    - No relapses (21 mts)

Visual: NPV=100%, PPV=24%

Quantitative: NPV= 100%, PPV=29%



SUV_{mean_all} = 8.55 SUV_{max_all} = 18.34 Vol_{met_all} = 658 ml	SUV_{mean_all} = 5.66 SUV_{max_all} = 12.47 Vol_{met_all} = 361 ml	CR	CR

Despite a significant residual uptake on early PET, this patient obtained a complete remission at interim PET, and is still disease free after a follow-up of 29 months

Early response in DLBCL after 7 days

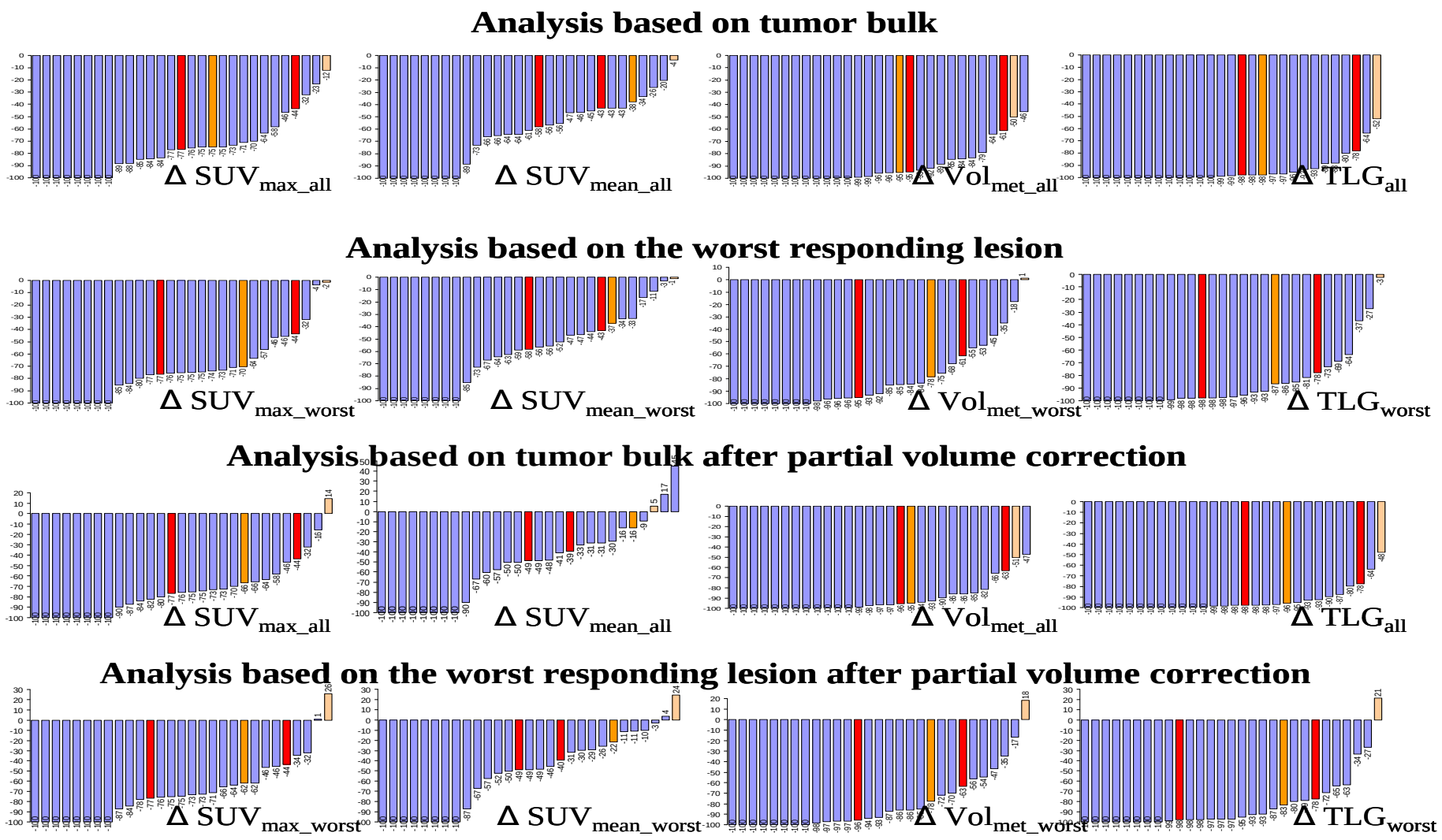
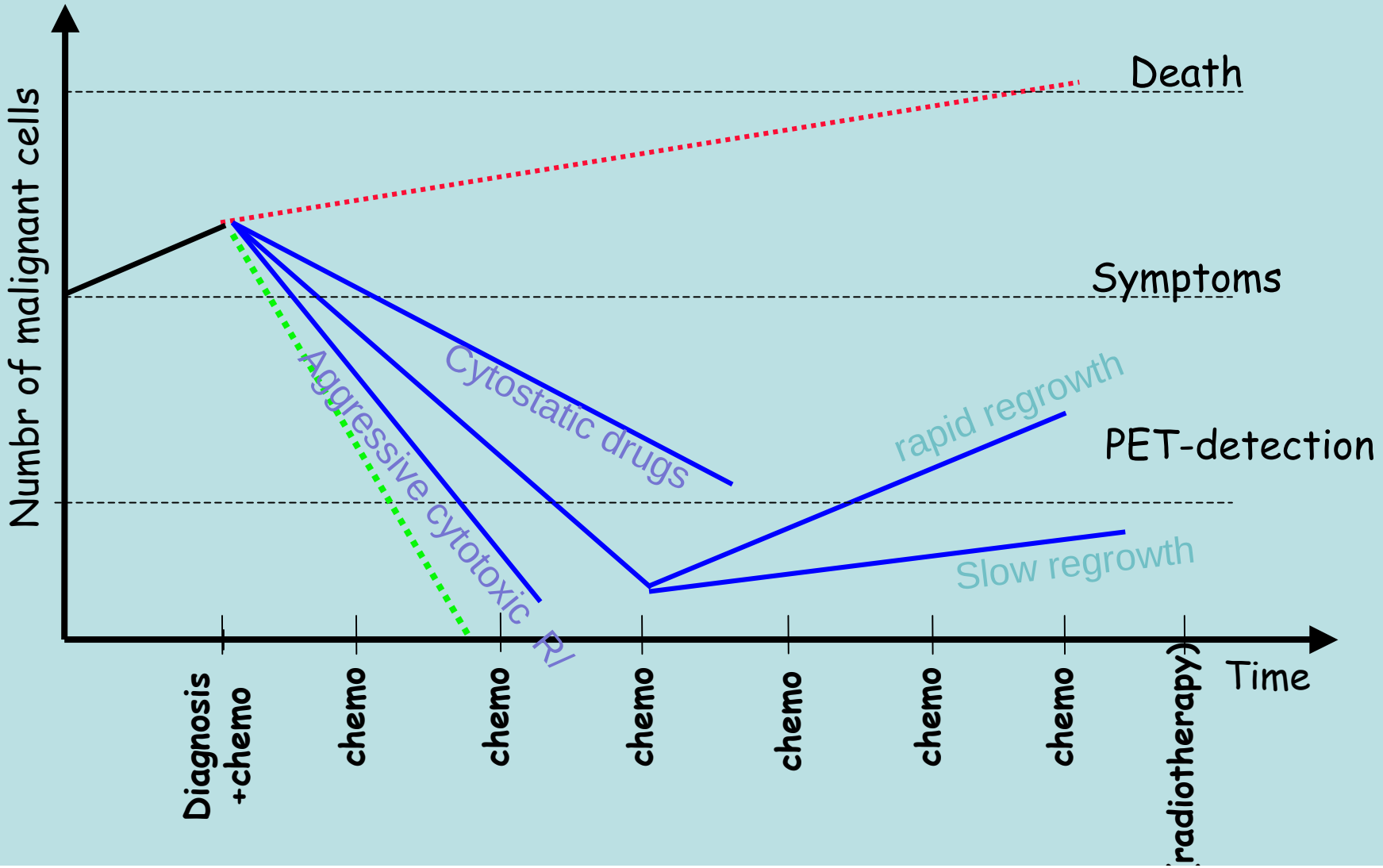


Figure IV.7. Overview of the different relative parameters of FDG-decrease for the different analyses with corresponding outcome of the patient.

No evidence of disease
Primary refractory disease
Relapse after 12mths
Relapse after 23 mths

Principle of response assessment: influence of different treatments



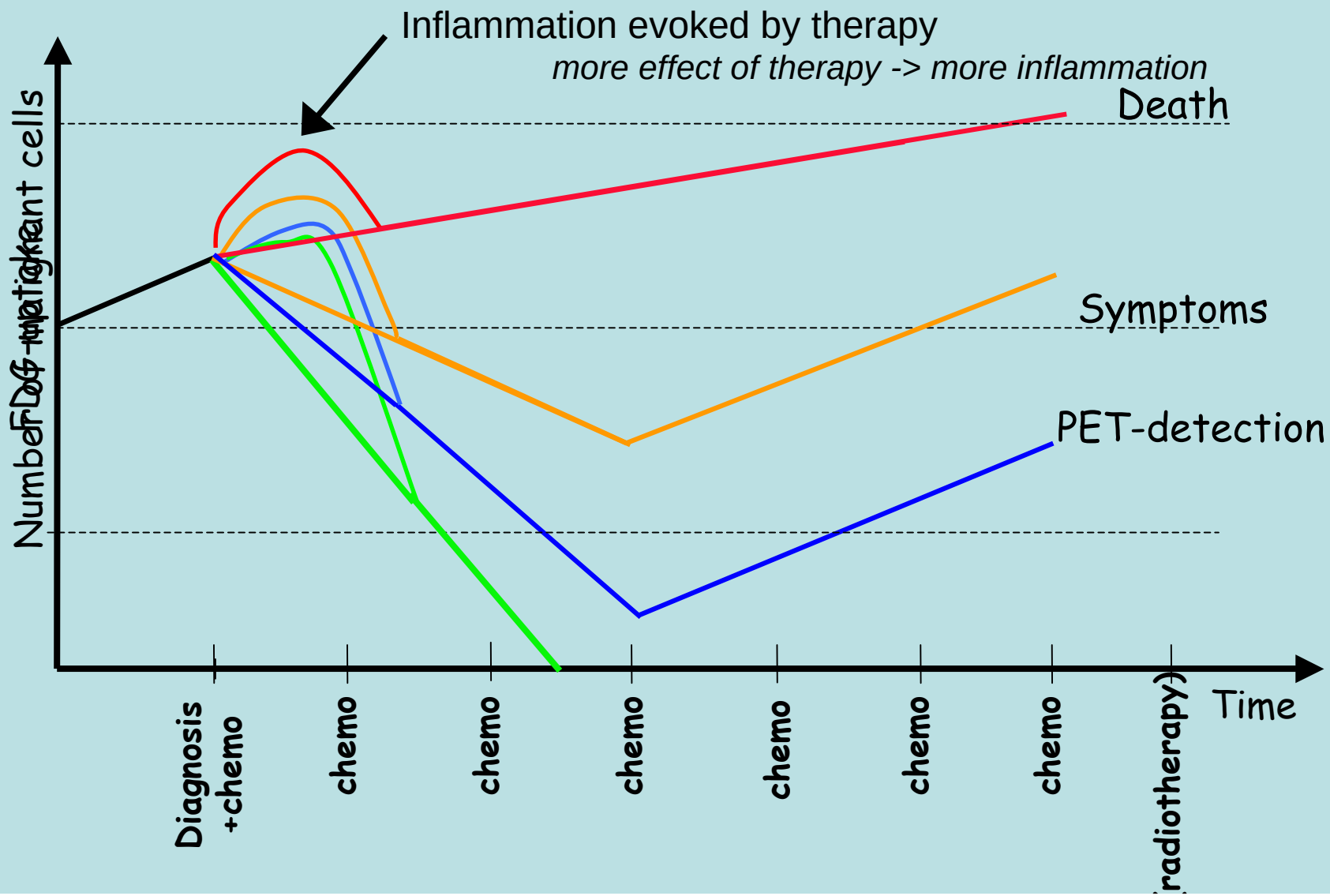
Intensified therapies are associated with a fast response, but…

- . Gallamini A, et al. Haematologica, 2007
  - 2xBEACOPPesc
  - Sens 50%, more false negative lesions
  - PPV 60%, more false positive lesions

- Avigdor A et al. Haematologica, 2007
  - 45 pt advanced staged HL
  - 2xBEACOPPesc, followed by 4x ABVD
  - Sens 60% spec 79% NPV 87%, PPV 45%

➔ a decrease in accuracy
more false negative results
more false positive results

Inflammation and its interference with early response assessment



Is inflammation important in clinical practice?

- High false positive rate after radiotherapy

- Jacene et al, *JNM 2009,*
  - RIT (Zevalin, Bexxar)
  - Continuous decrease in FDG-uptake 24 wks after therapy

➔ inflammatory changes with the recruitment of immune cells and high FDG-uptake

High incidence of false positive PET after rituximab in NHL

- Han et al, *Ann Oncol 2009*
  - 51 pt DLBCL+MCL,
  - Midtherapy (2-4 cycles): PPV= 33%, Sp 68%
  - Posttherapy: PPV=19%, Sp 80%

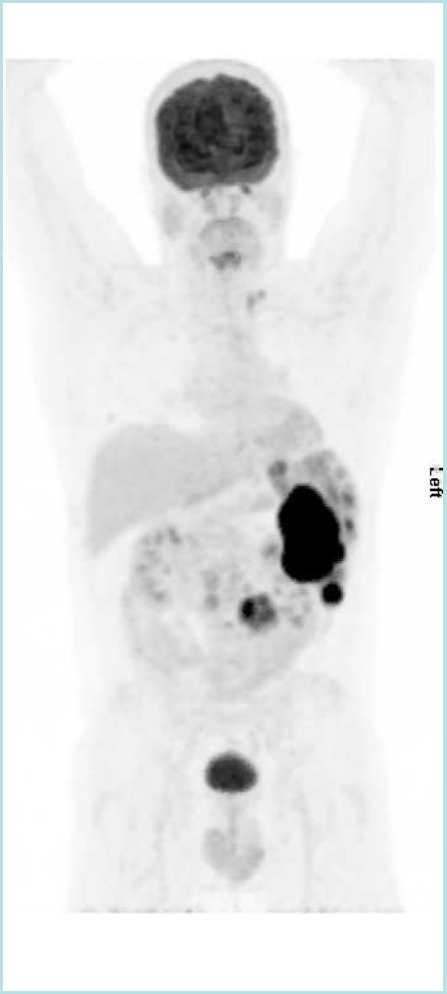
- Haioun et al, *Blood 2005*
  - 90 pt NHL, 37 rituximab, PPV 44%, Sp 70% after 2 cycles

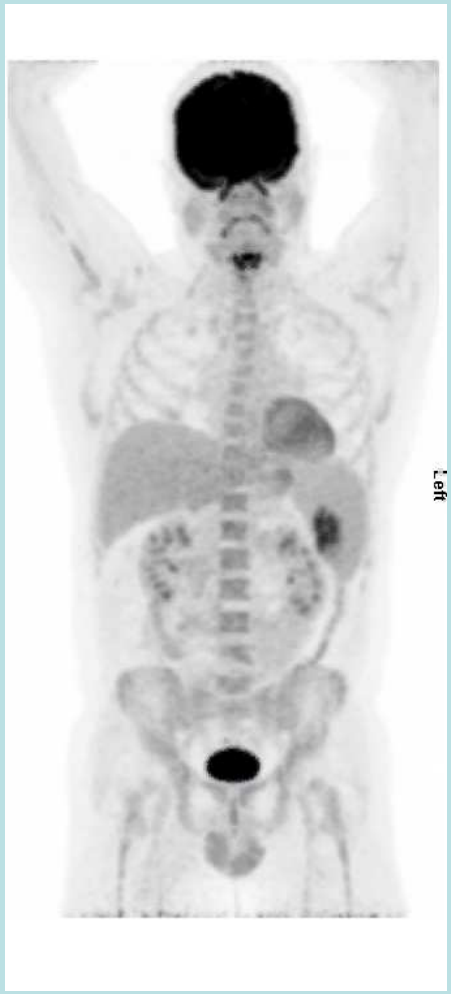
- Moskowitz et al, *JCO 2010*,
  - PET after intensified RCHOP4 in 97 patients
  - 59 PET neg – consolidation with ICE, excellent prognosis

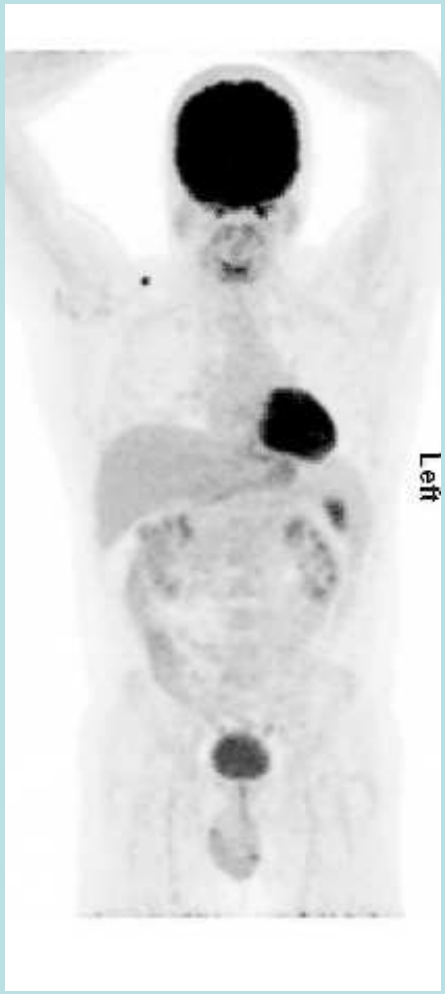
    ➔ midtreatment negative = excellent prognosis
  - 38 PET positive – 33 biopsy negative (2 sample error)

    ➔ high frequence of false positive midtreatment, outcome identical as PETnegative patients

False positive PET after rituximab in NHL





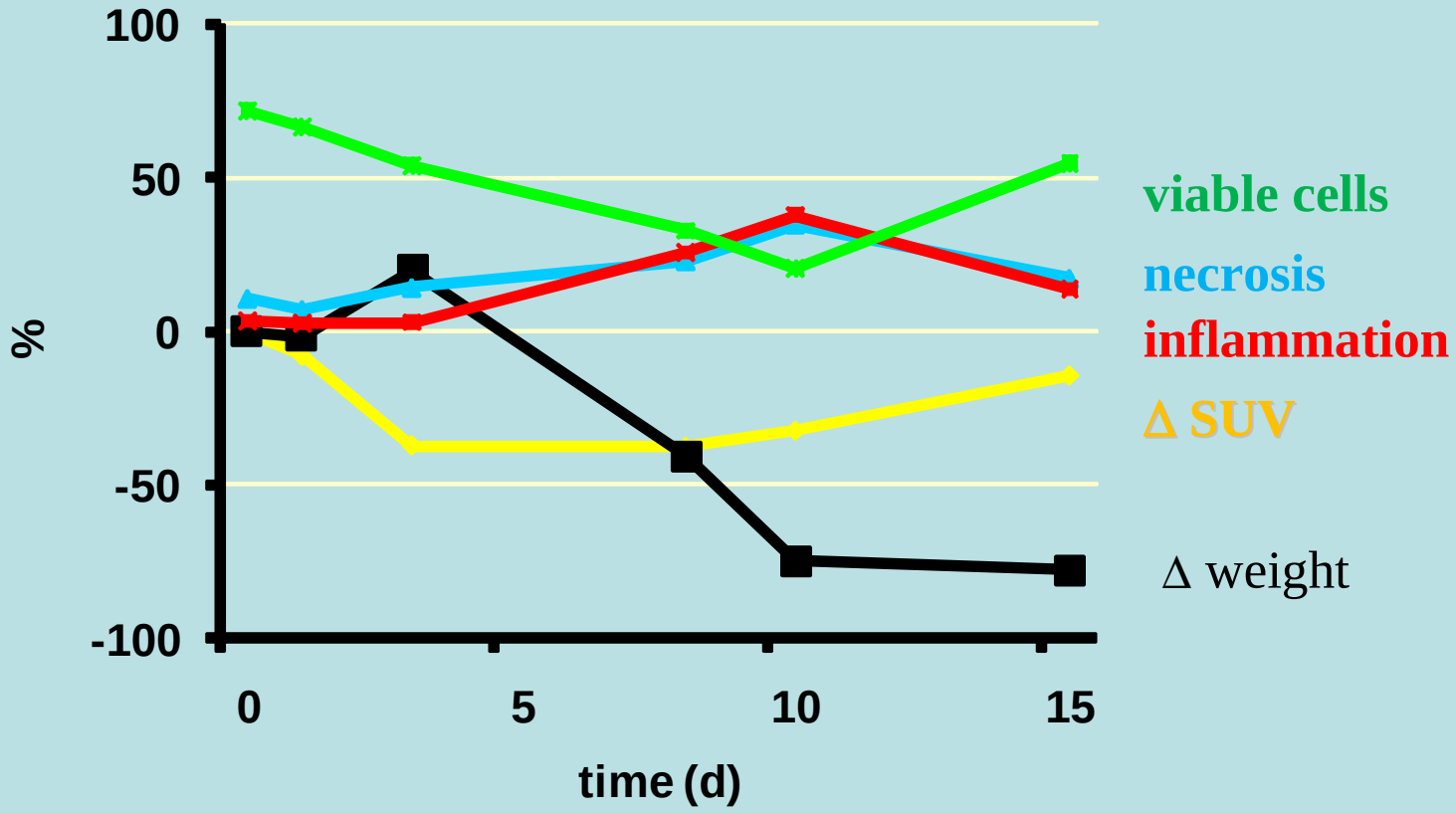


Baseline RCHOP 3 RCHOP 6

➔ inflammatory changes with the recruitment of immune cells ?

Inflammation and its interference with early response assessment

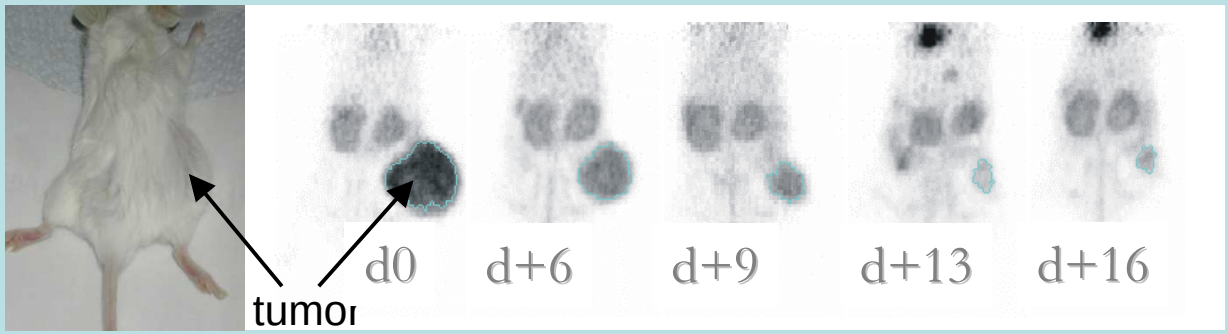
Spaepen, EJNM 2003
SCID mice with cyclophosphamide, ex-vivo measurements



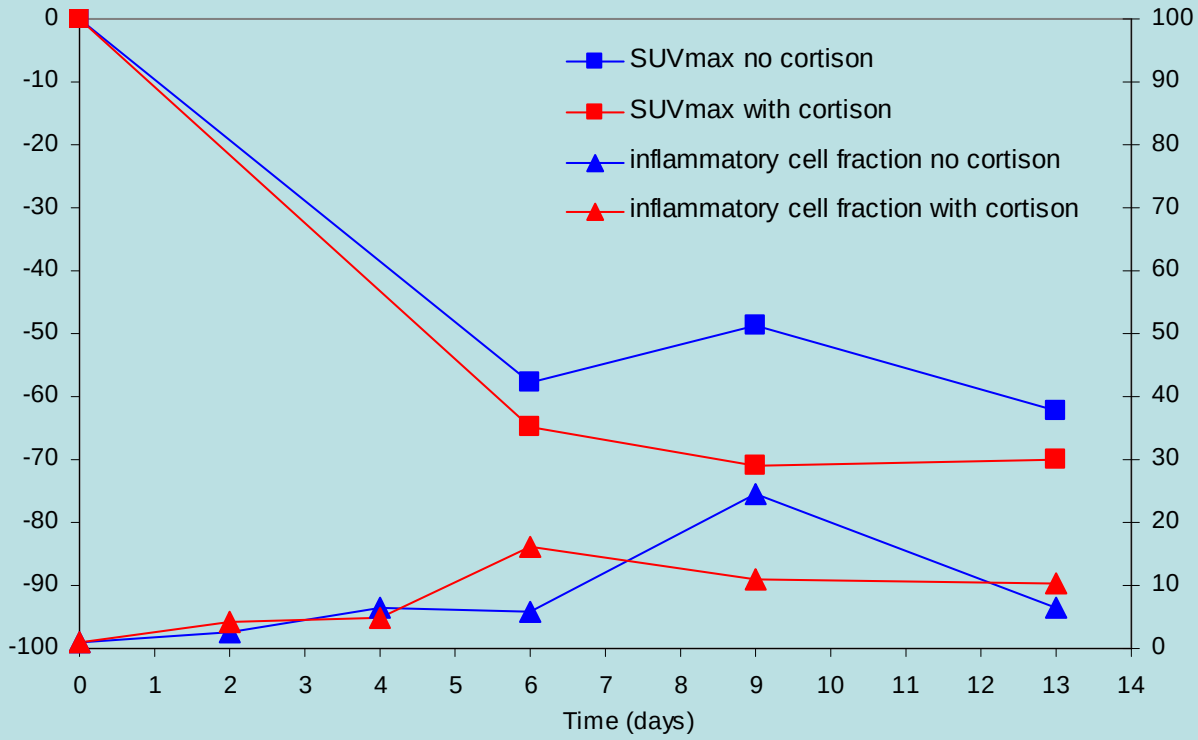
Inflammation and its interference with early response assessment

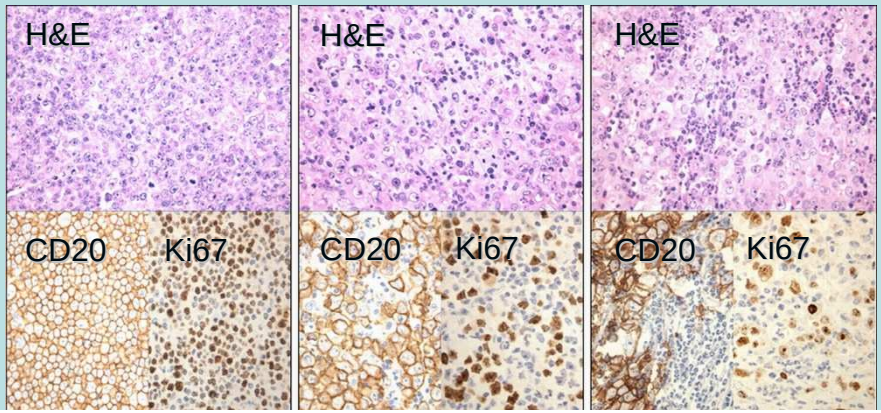
- Can we improve correlation of FDG-uptake with tumor response?
  1. By the administration of steroids?
  2. By the use of other PET-tracers: FLT as a marker of cellular proliferation ?

- Materials and methods
  - SCID-mouse subcutaneous injected with lymphoma cell line
  - Treatment with chemo at day 0, half the mice hydrocortisone
  - Measurements of tracer-uptake by microPET



Does the presence of anti-inflammatory drugs (corticosteroids) influences the FDG-uptake and the cellular respons after chemotherapy?





Cyclophosphamide

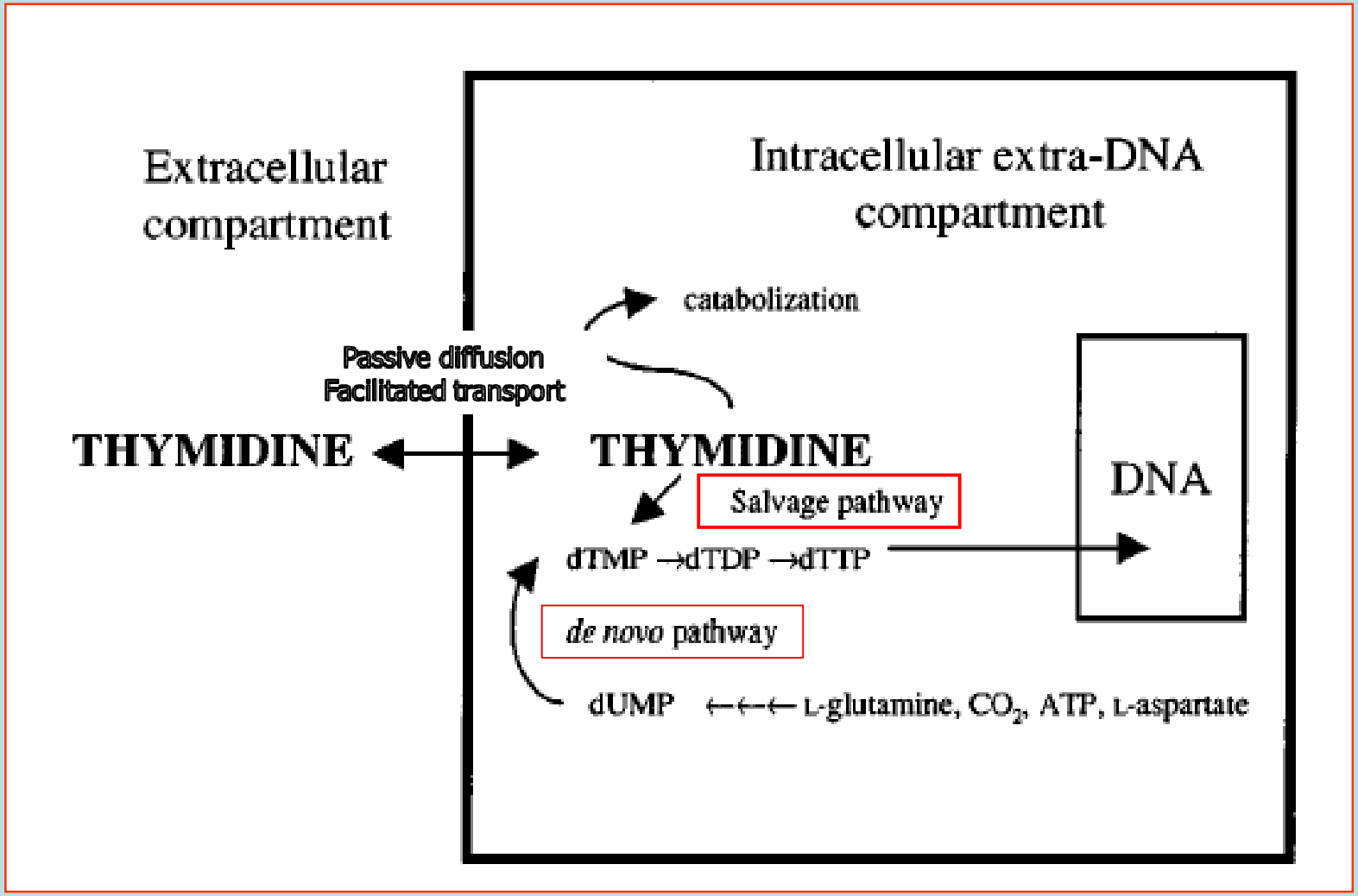
Cyclophosphamide + hydrocortisone

Brepoels L, Stroobants S, et al. J Nucl Med. 2007

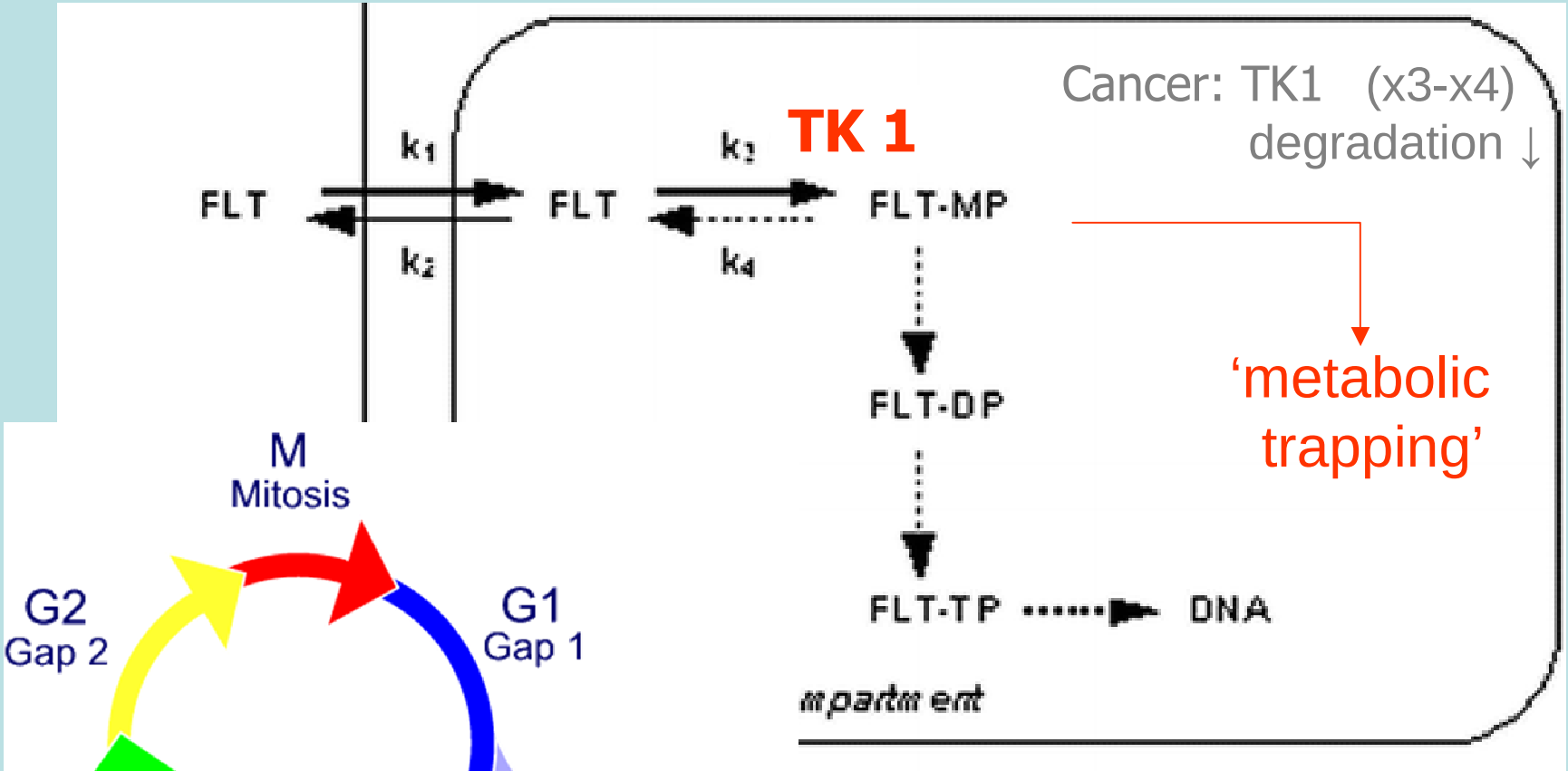
Alternatives for FDG? Proliferation tracers.

- Can we improve correlation of tracer uptake with tumor response by using FLT as a marker of *cellular proliferation* ?
  - Wagner, *Cancer Research 2003*
    - High uptake in murine model lymphoma, correlation with BrdU in mice
    - correlation with Ki67 in patients, high grade vs low grade lymphoma

Metabolism of Thymidine

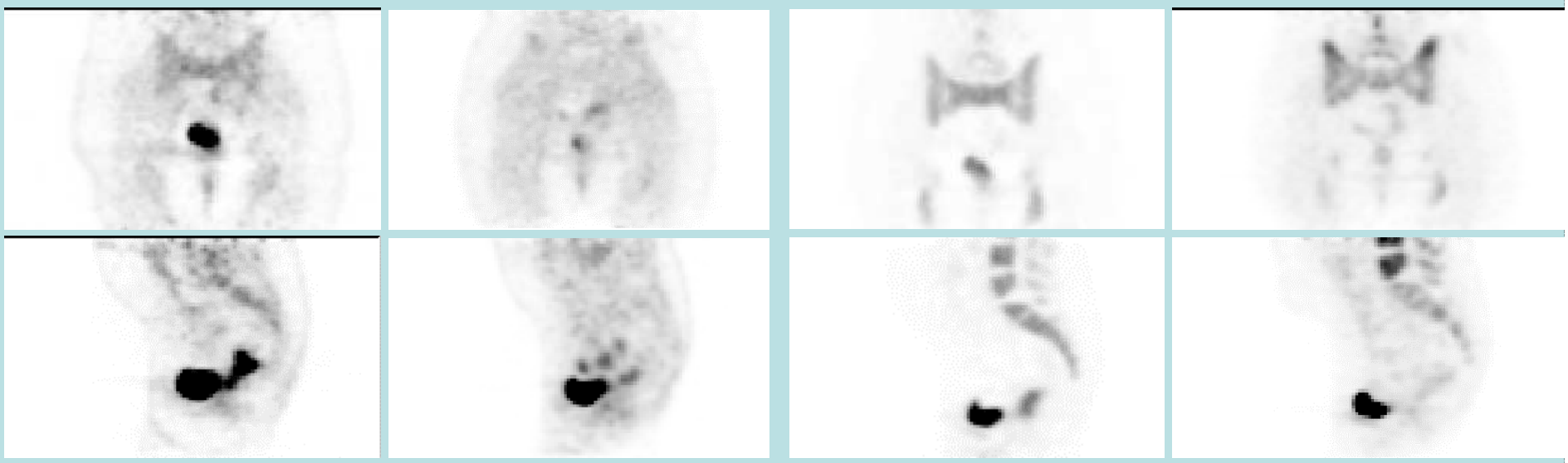


Metabolism of FLT: marker of proliferation



Response evaluation by FLT-PET

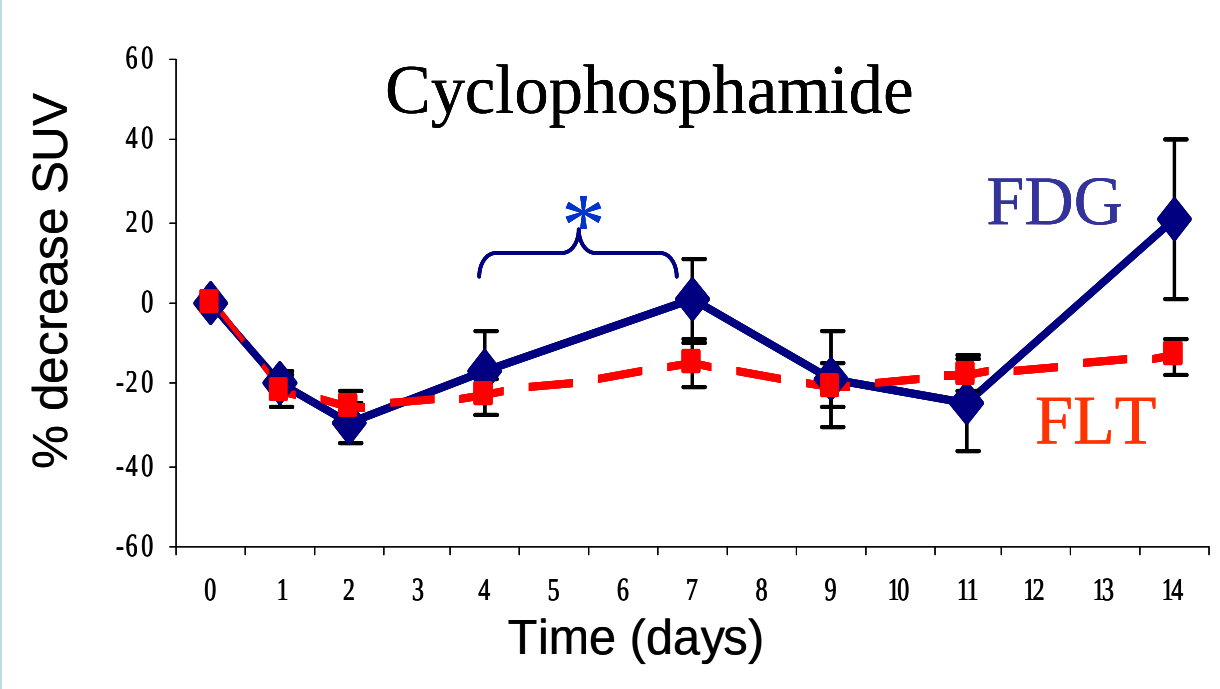
Rectumca: FDG + FLT before, during and after CRT



FDG d0 | FDG post CRT | FLT d0 | FLT post CRT

Inflammation and early response assessment: is FLT more accurate?

Granta cell line (Mantle cell lymphoma) in SCID mouse



FDG and FLT-uptake after cyclophosphamide

Brepoels et al. JNM 2007

Inflammation and early response assessment: is FLT more accurate?

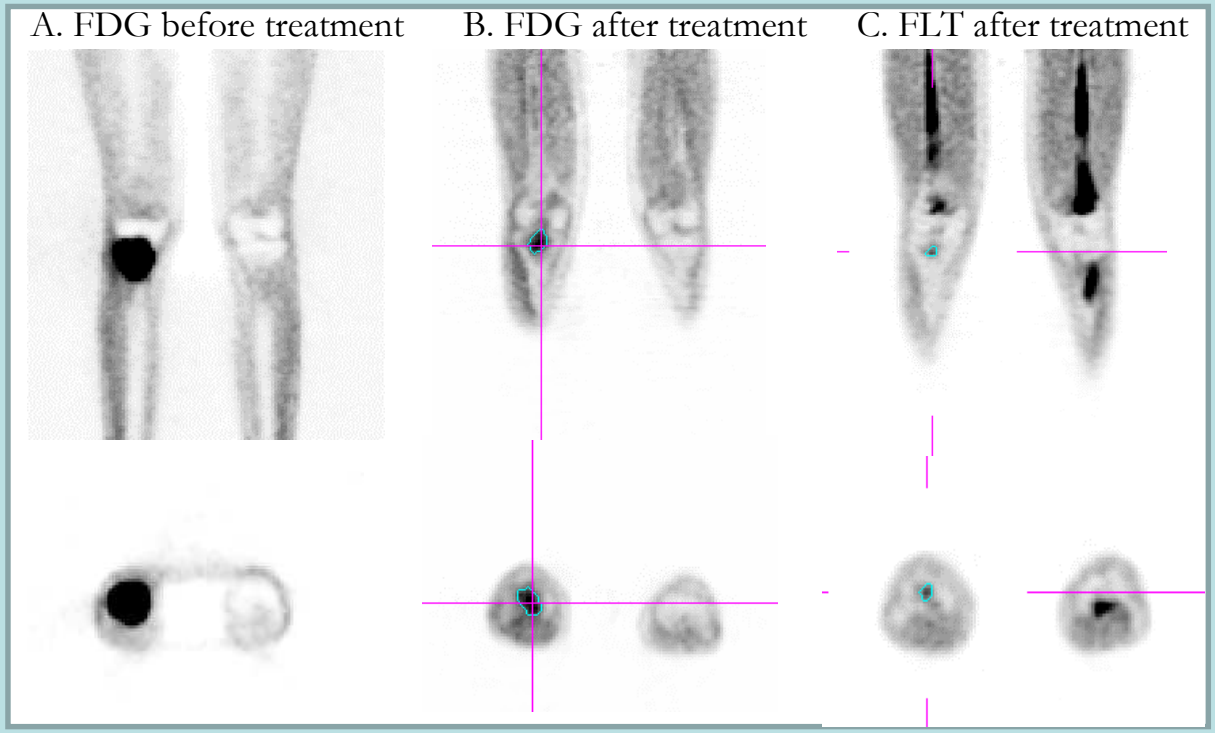


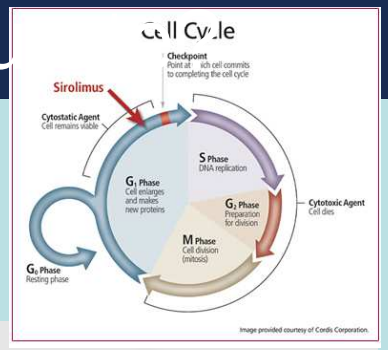
Illustration of the high specificity of FLT-PET compared to FDG-PET.
(A) PET before therapy shows an extensive lymphoma localization in the proximal tibia
(B) After chemotherapy and local radiotherapy, FDG-uptake is still clearly positive but post-radiotherapy changes can not be distinguished from persistent lymphoma
(C) FLT-PET after therapy shows a focal uptake in the proximal tibiae which suggests persistent lymphoma (mark the high FDG-uptake in the bone marrow in the non-pathological tibia).
The patient relapsed several months later.

Alternatives for FDG? Proliferation tracers.

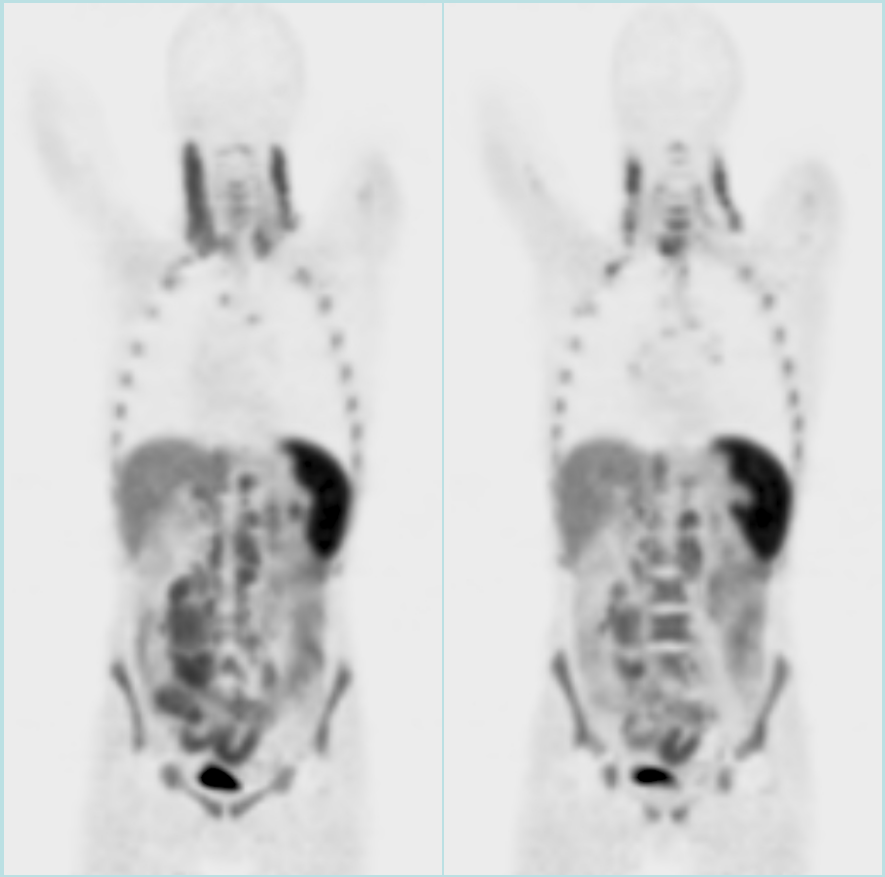
- *Can we improve correlation of tracer uptake with tumor response by using FLT as a marker of cellular proliferation ?*

- Metabolism ≠ proliferation: cytostatic and cell cycle *targeted agents?*
  - ➔ Is FLT more accurate in cell cycle targeting therapies?

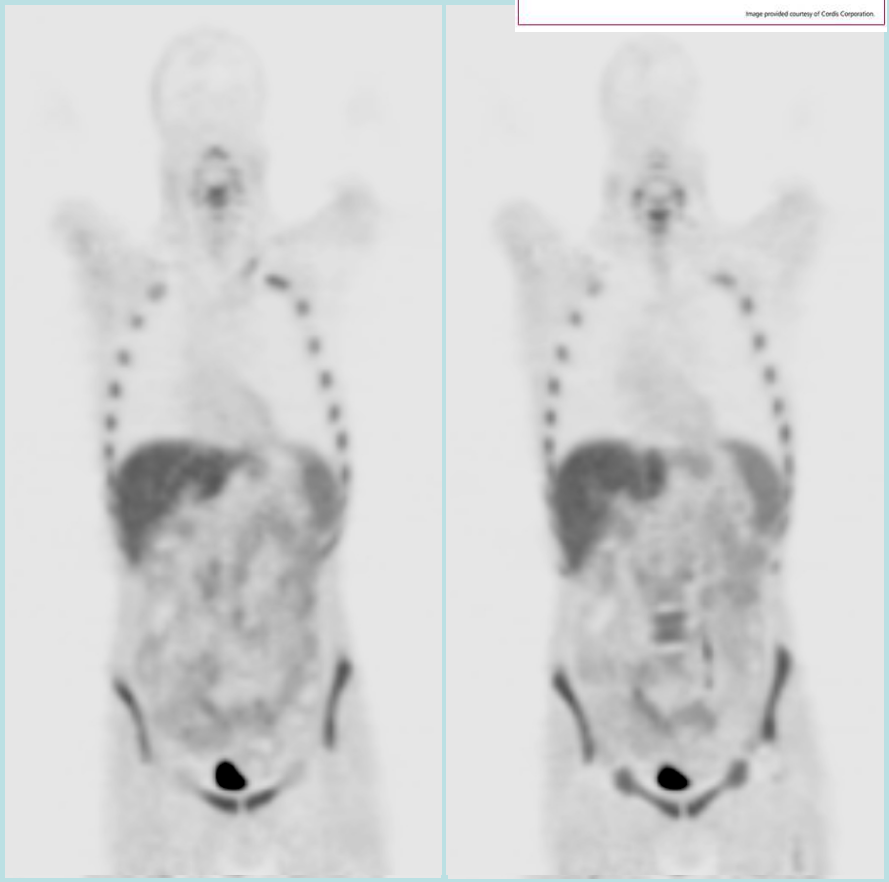
Inflammation and early response assessment: is FLT more accu



Mantel cell lymphoma R/mTOR inhibitor



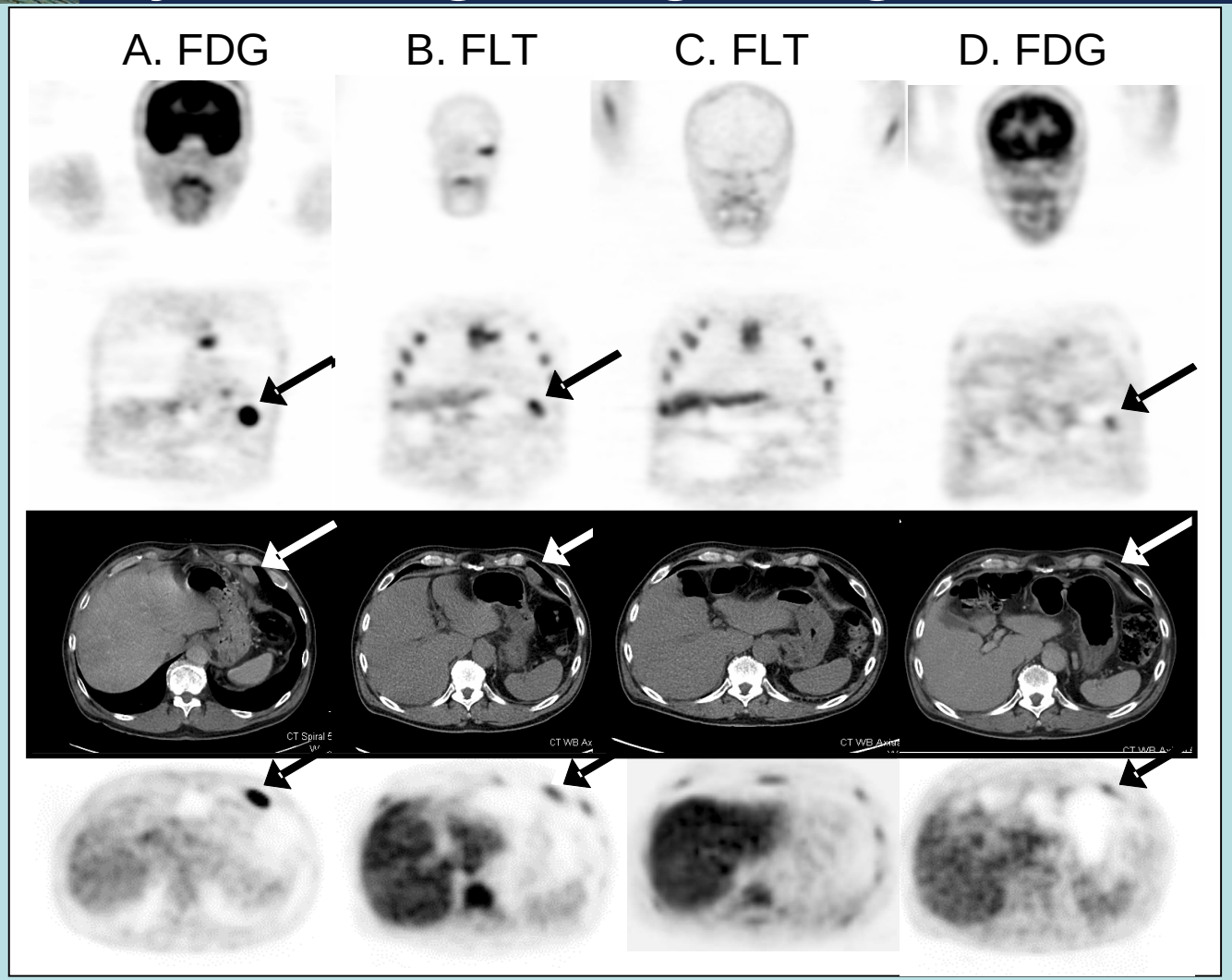
FLT d0



FLT d7

FDG d0

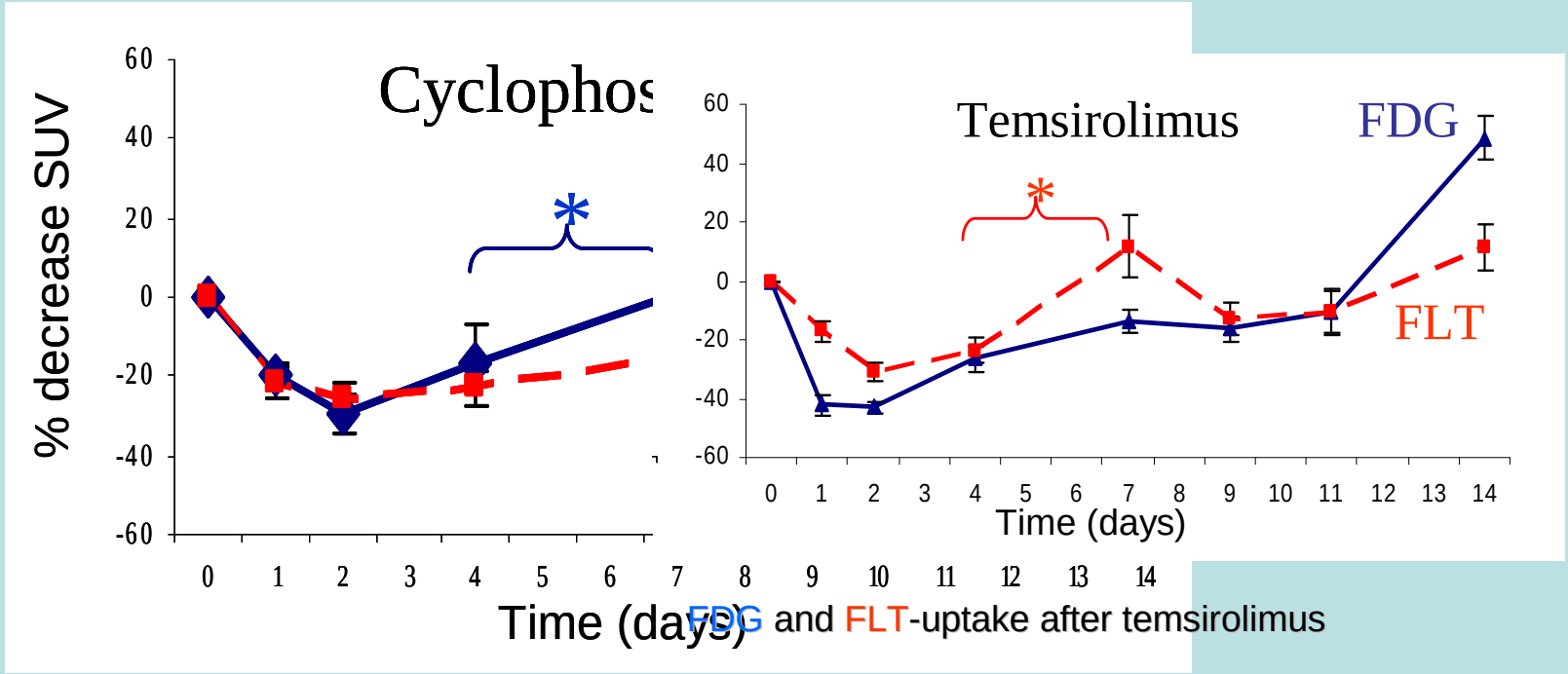
Is FLT more accurate in cell cycle targetting drugs?



Early response assessment after therapy with mTOR inhibition.
(A) FDG-PET/CT before therapy (B) FLT-PET/CT before therapy (C) FLT-PET/CT one week after the first administration and (D) FDG-PET/CT after 6 weeks of therapy
The patient obtained a disease free status after a few months of therapy and is still in complete remission (36 months)

Inflammation and early response assessment: is FLT more accurate?

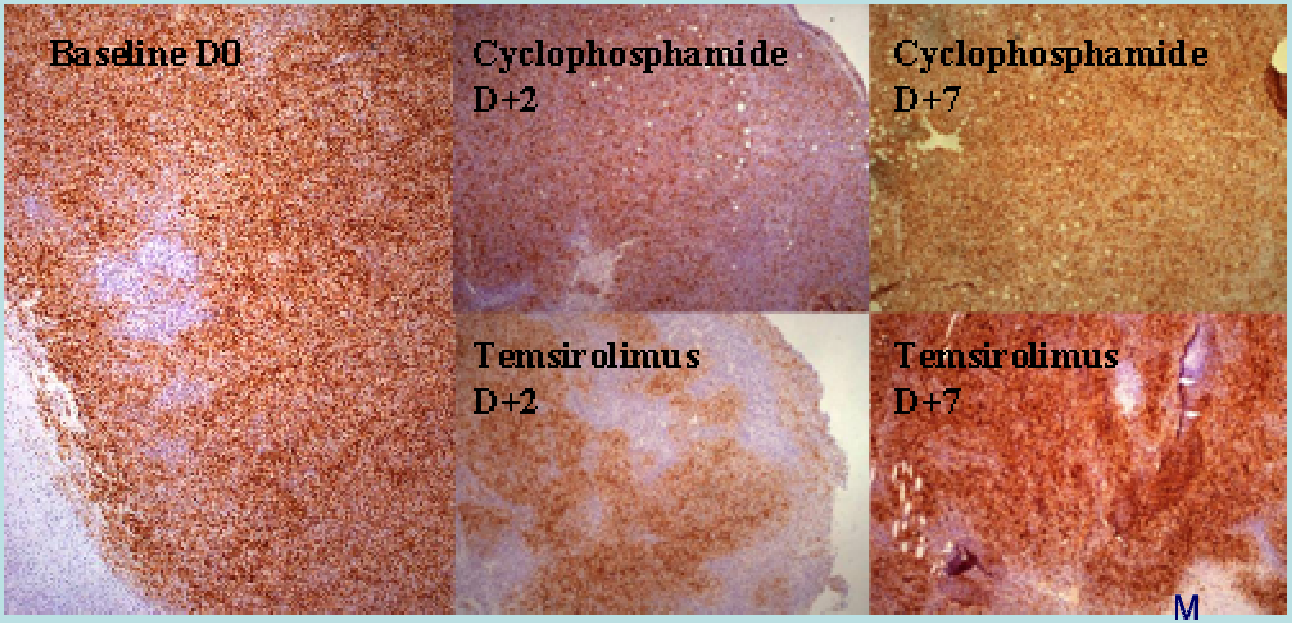
Granta cell line (Mantle cell lymphoma)



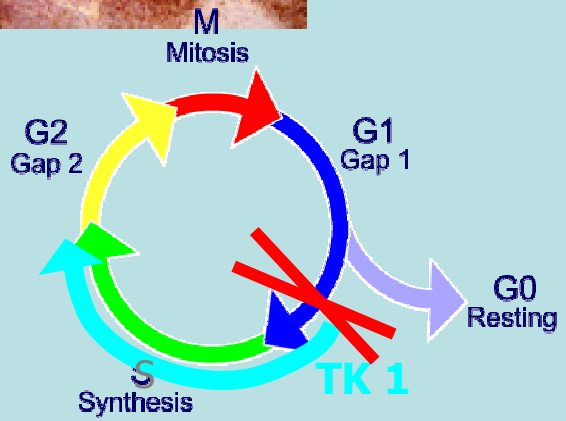
FDG and FLT-uptake after temsirolimus

FDG and FLT-uptake after cyclophosphamide

Explanation?



histology after mTOR treatment showed a decreased cyclin d1 expression shortly after therapy, which increased again on D+7



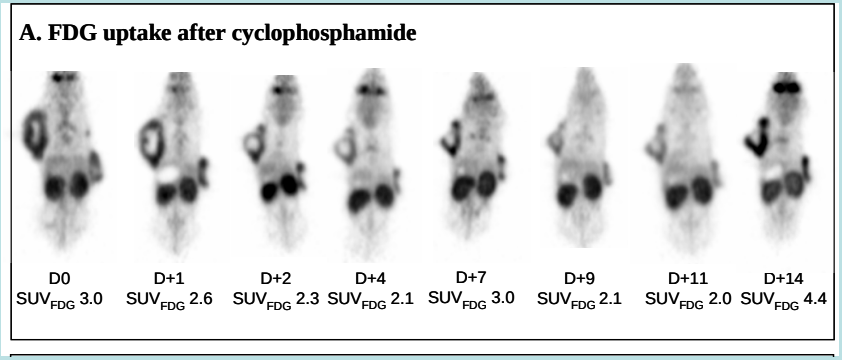
- ➔ Synchronization of the cells? Repair mechanisms?
- ➔ Close interactions of FLT uptake with cellular metabolism

Other more specific tracers?

- Apoptosis: annexin, caspase-3 ([18F]ICMT-11)
- Lymphoma specific tracers: Recombinant anti-CD20 antibody fragments,…
- ^{89}Zr-Zevalin
- Methionine
- FET

Opportunities of animal studies

- No limitations on numbers of scans, radiation protection: time course of tracer uptake
- Standardization
- Different treatment regimes, evaluation of the different components of a regimen
- Histological confirmation possible, ex vivo measurements of enzymes, ….



But…

- Evaluation of therapy response, not of “sufficient” response. Prognostic significance?
- Human cell lines in immunodeficient mice: interference with the immune system? HL?
- Syngeneic mice: growth of lymphoma-*like* pathology, potential to evaluate the effect of new treatment strategies (E.g. vaccination studies, Chaise, 2007, cancer immunol immunother)
- No new more accurate tracers compared to FDG have been developped, potential mainly because of their higher specificity

The future?

Animal studies allow the evaluation of

- Interaction of tracers with cellular metabolism
- Interaction of therapy with cellular metabolism
- Interactions of therapy with uptake of PET tracers