

L'imagerie fonctionnelle comme marqueur de substitution (« surrogate marker ») :
Généralités : *qu'entend-on par marqueur de substitution, quelle place pour l'imagerie ?*

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Inserm U877





Biomarqueur / Marqueur de substitution

CLINICAL PHARMACOLOGY & THERAPEUTICS
MARCH 2001

Biological marker (biomarker): A characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention.

Clinical endpoint: A characteristic or variable that reflects how a patient feels, functions, or survives.

Surrogate endpoint: A biomarker that is intended to substitute for a clinical endpoint. A surrogate endpoint is expected to predict clinical benefit (or harm or lack of benefit or harm) based on epidemiologic, therapeutic, pathophysiologic, or other scientific evidence.

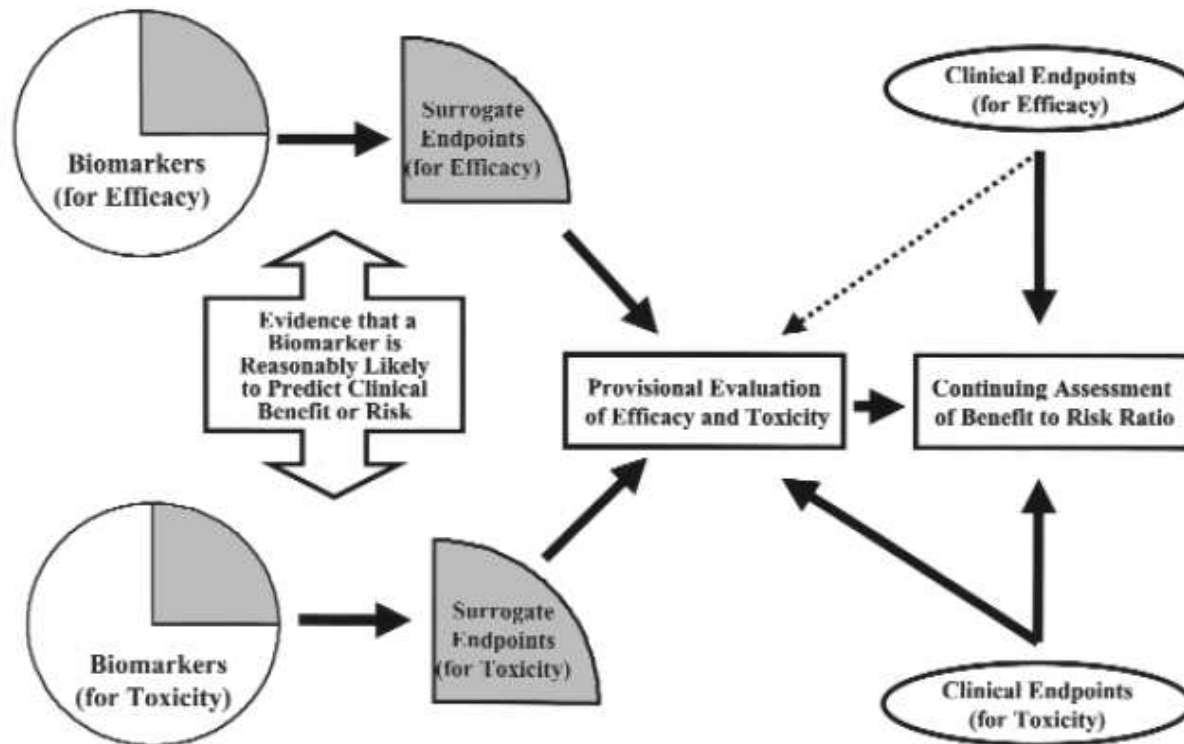


Fig 1. Conceptual model of the relationship of biomarkers, surrogate endpoints, and the process of evaluating therapeutic interventions.

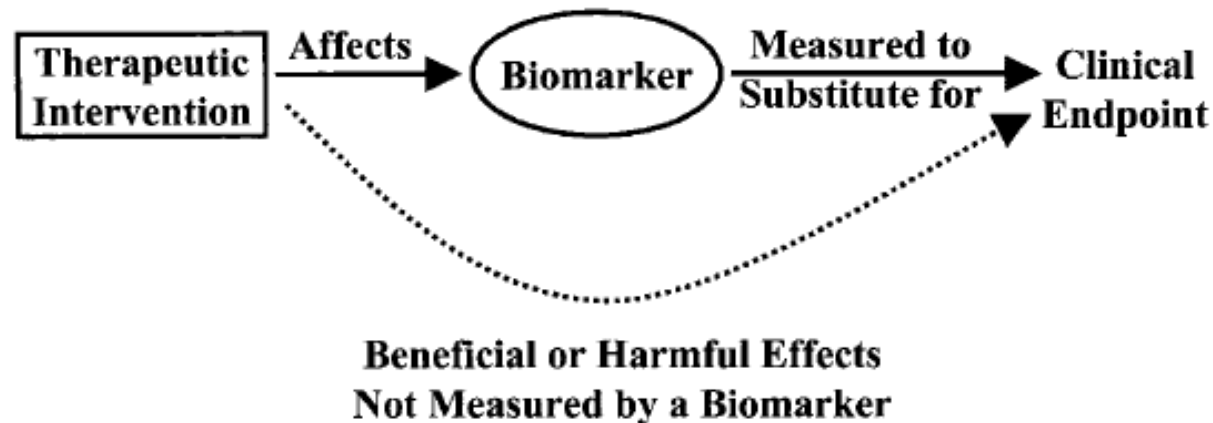


Fig 2. Effects of therapeutic interventions on biomarkers and clinical endpoints in clinical trials. In many circumstances, a therapeutic intervention will affect a clinical endpoint in a way that is not entirely accounted for by its effect on a biomarker. This is likely to occur in complex diseases in which a single biomarker may capture only a portion, or none, of the treatment effect. Interventions may also have unanticipated adverse consequences that diminish or completely offset the intended therapeutic benefits. The independent impact of these unanticipated beneficial or harmful effects of an intervention on clinical endpoints is represented by the *broken arrow*. Those biomarkers that do not account for a sufficient proportion of the treatment effect do not advance to surrogate endpoint status.



Une place pour l'imagerie ?

- Taux de réponse faibles : l'imagerie permet en routine clinique de décider de continuer, changer ou abandonner un traitement
- L'imagerie est une aide à la décision pour continuer le développement (phase 2 → phase 3) d'un nouveau médicament



A new era in drug development



Shorten time-lines, decrease attrition - seamless transitions, adaptive designs



Biomarkers, modeling, imaging, personalized medicine



- Right dose
- Right schedule
- Right drug combination
- Right patient

OR TERMINATE



FDA biomarker classes

- Predict the presence of disease or characterize it
- Predict response to therapy.


A **qualified imaging biomarker** is one that is established for some aspects of drug development providing data on safety or efficacy but which does not have specific labeling as an approved drug.

Unsealed source radiation dosimetry

RECIST/WHO morphology criteria for tumour response

A **validated imaging biomarker** is an approved drug with the corresponding indication to assure/improve safety and/or efficacy.

Whole body biodistribution of Zevalin® and Bexxar®

 **Validation = Commercialisation**



Que veut-on substituer ?

- Débat entre taux de réponse et survie
- Survie :
 - Brute
 - Sans progression
 - Sans rechute
 - Avant évènement...
- L'imagerie peut-elle être un marqueur de substitution de la survie
 - = prédictive de la survie ?



Imagerie comme marqueur/prédicteur de réponse tumorale

- WHO/RECIST/RECIST 0.1
- Imagerie métabolique : FDG
- Autres imageries moléculaires :
 - Drogues marquées (biodistribution, pharmacocinétique, pharmacodynamie...)
 - Traceurs de la cible du traitement



Imagerie comme marqueur prédictif de la survie

- FDG dans les lymphomes
- Perfusion/angiogenèse (IRM et gliomes)
- ...



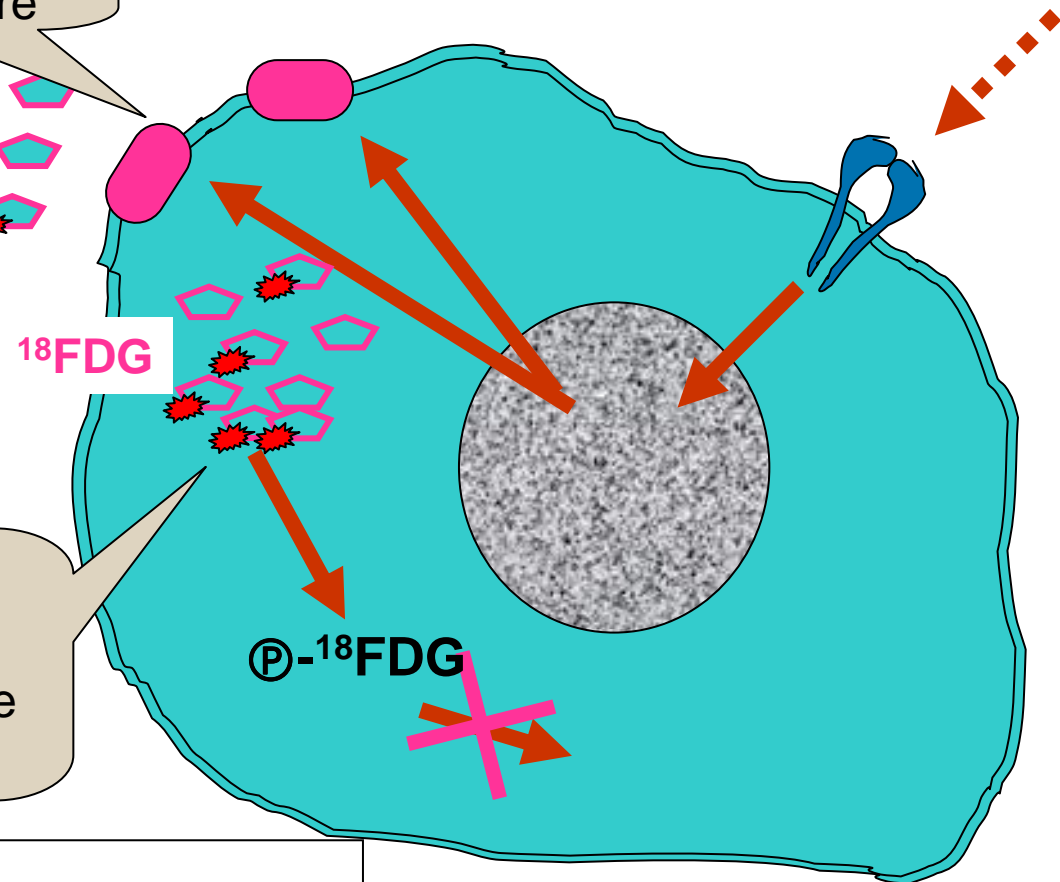
GLUT 1 :
Cycle cellulaire

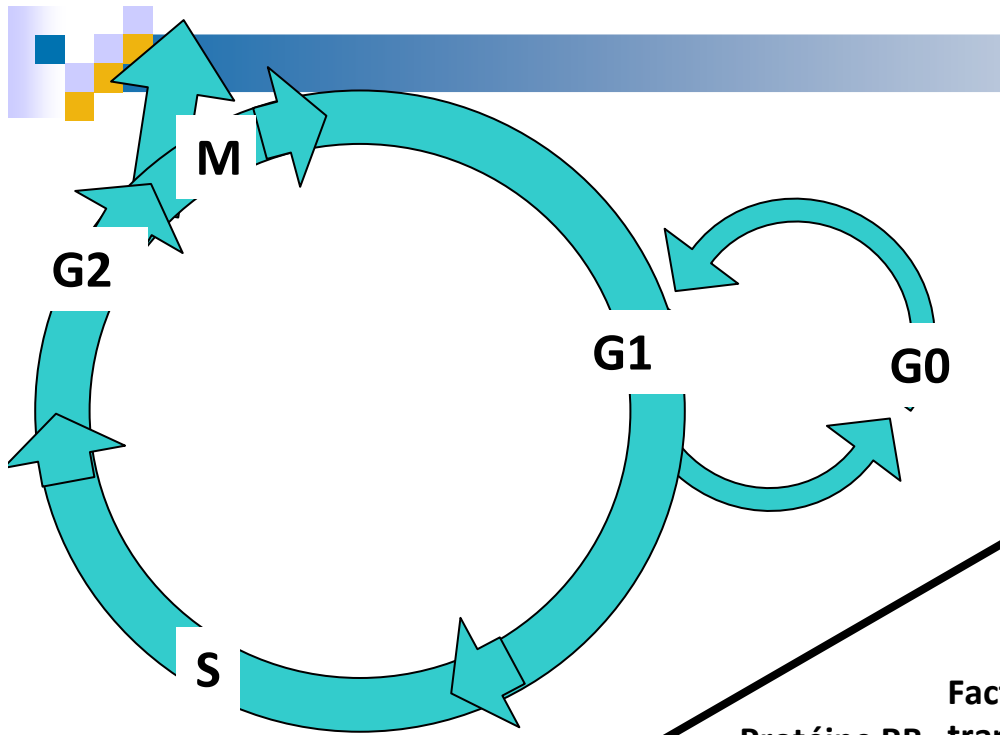
FDG et cellules tumorales (≠ FDG et tumeurs...)

Hexokinase :
Métabolisme,
hypoxie, synthèse
ADN...

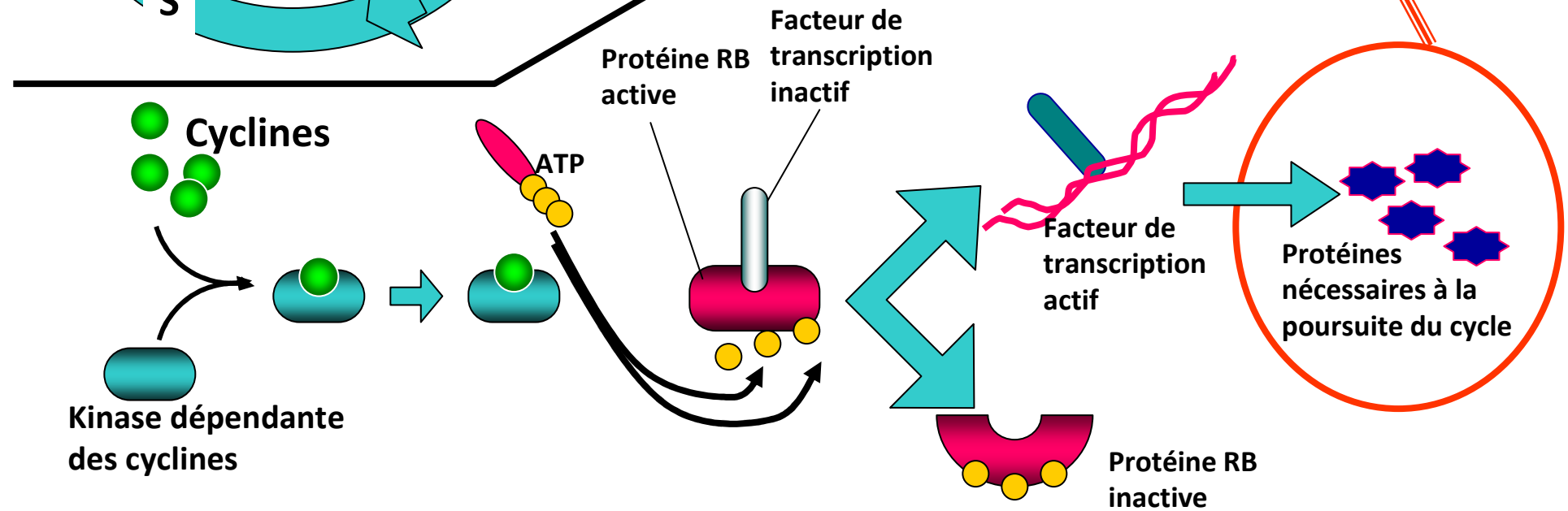
Paramètres explorés par le FDG...

- **Transport membranaire de glucose**
- **Phosphorylation**



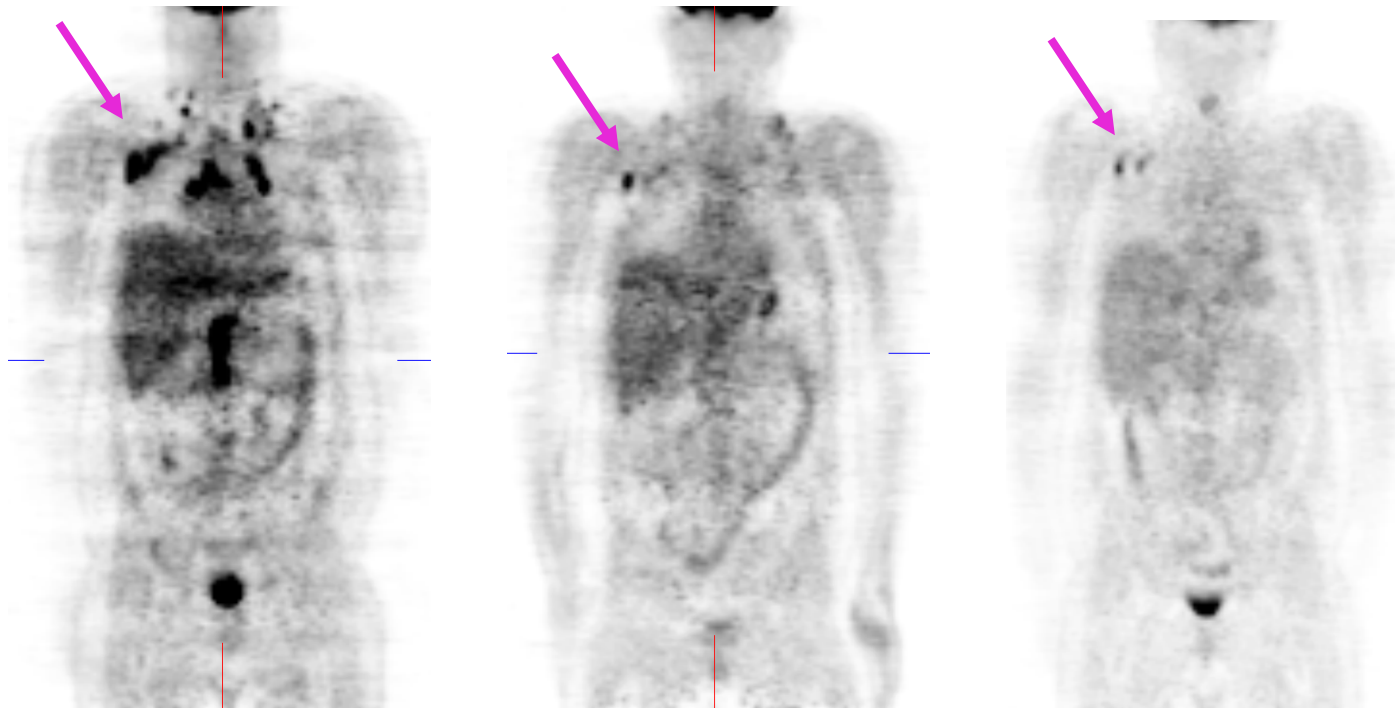


Protéines de compétence
C-myc
C-fos
GLUT1



Place de la TEP-FDG dans l'évaluation précoce de la réponse thérapeutique

Résultats de Grenoble (Céline Gallazzini-Crépin)



LNHBC

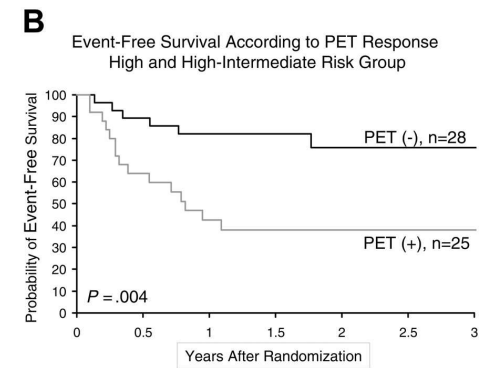
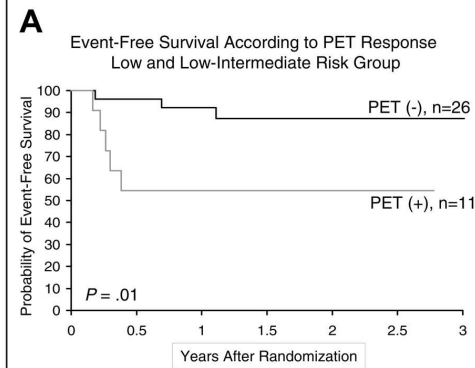
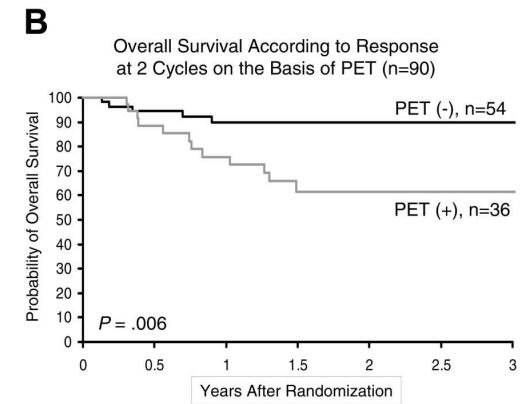
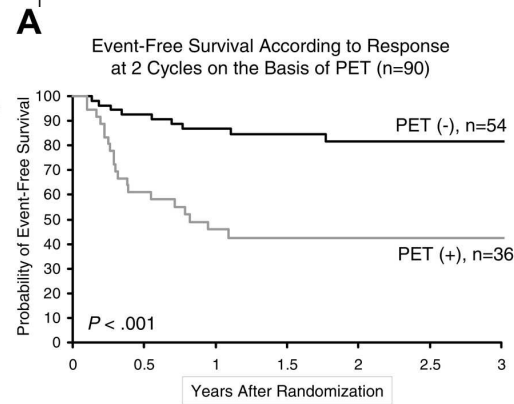
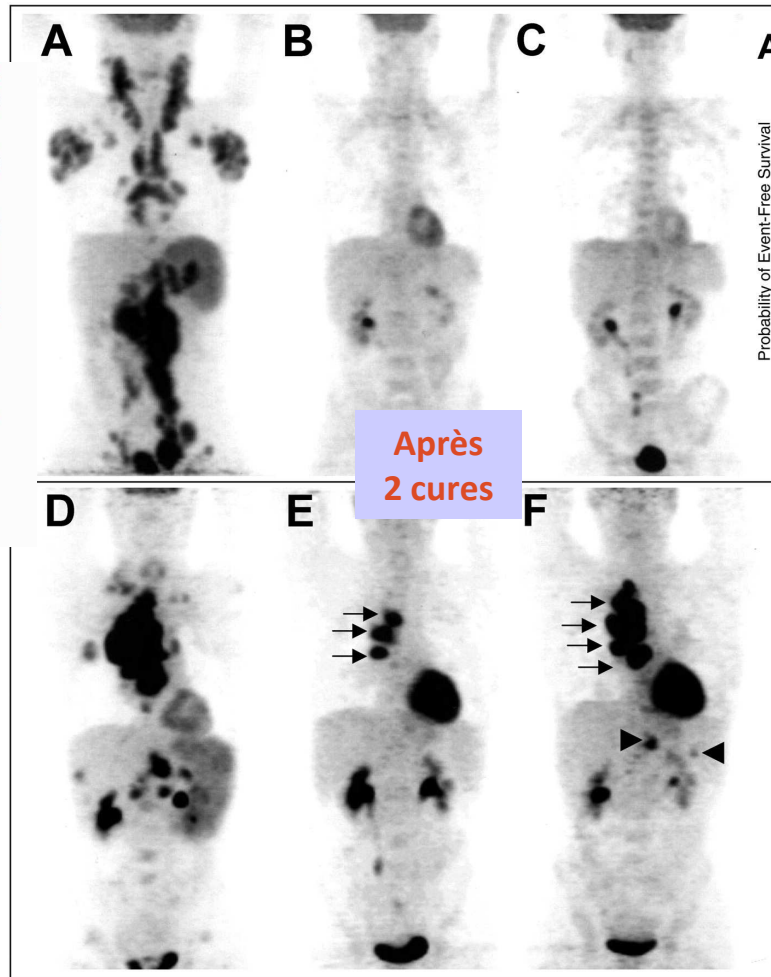
Coupes coronales corrigées d'atténuation d'un examen TEP-FDG diagnostique (1), précoce après 2 cures de chimiothérapie (2) et en fin de traitement (3). En (1) une hyperfixation des ganglions médiastinaux-hilaires, axillaires droits et cervicaux bilatéraux ; en (2) persistance d'hyperfixation cervicales bilatérales et axillaires droits ; en (3) présence de maladie résiduelle au niveau des ganglions axillaires droits.



Figure 2. Example of sequential FDG-PET findings in 2 patients

blood

JOURNAL OF
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SOCIETY OF
HEMATOLOGY



Haioun, C. et al. Blood 2005;106:1376-1381

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From RECIST to PERCIST: Evolving Considerations for PET Response Criteria in Solid Tumors

J Nucl Med 2009; 50:122S-150S

Richard L. Wahl^{1,2}, Heather Jacene¹, Yvette Kasamon², and Martin A. Lodge¹

SUV corrected for lean body mass (SUL)

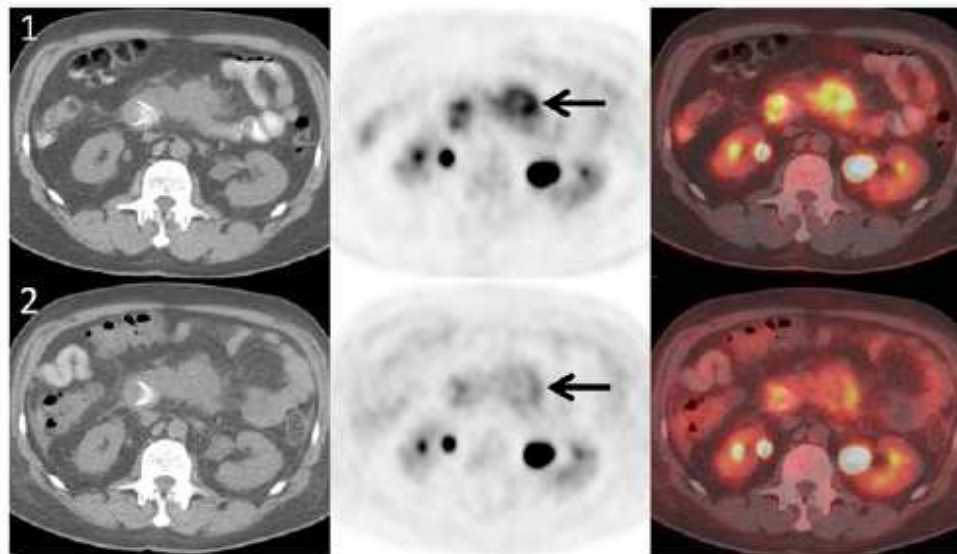


FIGURE 4. PET/CT images obtained before (1) and after (2) treatment of pancreatic carcinoma with experimental therapy targeting mammalian target of rapamycin. Note profound decline in SUL (~41%) despite stable pancreatic mass anatomically (arrows). This decline represents metabolic partial response by PERCIST (41% decline in marker lesion at 2 wk after therapy). Not all metabolic PMRs are clinically relevant; relevance will depend on the specific treatment.



Conclusion

- Les « clinical endpoints » sont de moins en moins applicables du fait de l'évolution de la cancérologie et des traitements...
- Nécessité de biomarqueurs +++
- Marqueurs de substitution : imposés par la pratique
- Rôle de l'imagerie :
 - Études « corps entier » / biopsie, non invasive
 - Suivi +++