PET/CT : van fysica en chemie naar moleculaire beeldvorming en behandelingen

Prof. Wim J.G. Oyen

HUMANITAS UNIVERSITY
Humanitas
University and Clinical and Research Center, Milan, Italy
wim.oyen@hunimed.eu

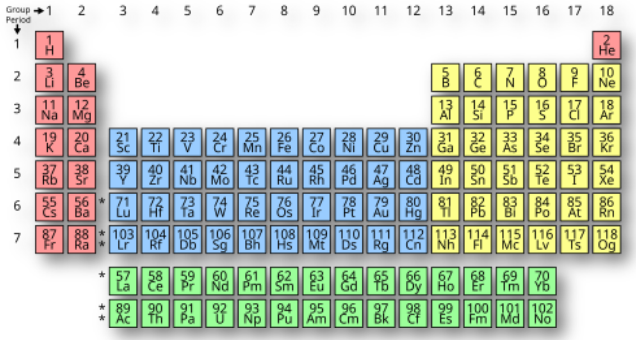
Rijnstate Hospital
Arnhem, The Netherlands
woyen@rijnstate.nl

Radboudumc
Radboudumc,
Nijmegen, The Netherlands

1

Nuclear Medicine

Medical specialty that uses **open, radioactive sources** for **imaging** and **treatment**



2

Nuclear Medicine

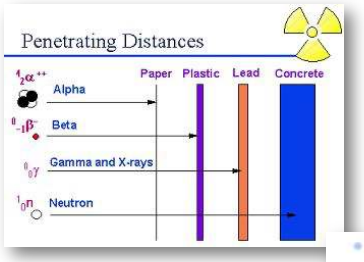
Imaging
ɣ (~100-400 keV)
→ single photon emission computed tomography (SPECT)
β^+ (511 keV)
→ positron emission computed tomography (PET)

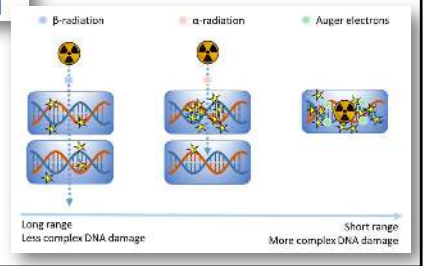
Treatment
β^- (electron)
α (helium nucleus)
Auger (electron)

NUCLEAR MEDICINE = DIAGNOSIS + THERAPY = THERANOSTICS

3

Therapy : inducing DNA damage





4

The theranostics principle in nuclear medicine

Image adapted from: Yordanova A et al. Oncotargets and Ther. 2017;10:4821-4828.

5

The theranostics principle in nuclear medicine

Image adapted from: Yordanova A et al. Oncotargets and Ther. 2017;10:4821-4828.

6

The theranostics principle in nuclear medicine

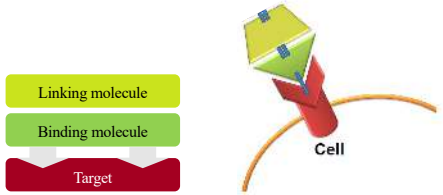


Image adapted from: Yordanova A et al. Oncotargets and Ther. 2017;10:4821-4828.

7

The theranostics principle in nuclear medicine

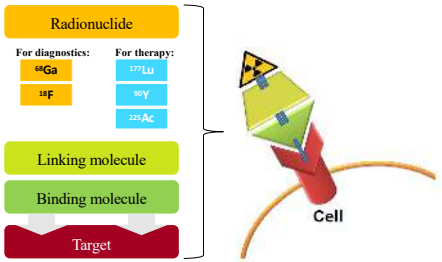


Image adapted from: Yordanova A et al. Oncotargets and Ther. 2017;10:4821-4828.

8

Nuclear Medicine

Imaging function, physiology and target expression in almost every organ system or disease entity:

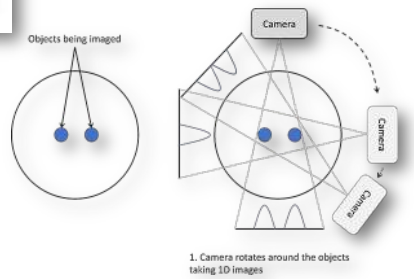
bone, heart, lungs, brain, thyroid, lymphatics, kidneys, lungs, liver, pancreas, GI, cancer, infection/inflammation

Selective, personalized treatment of benign and malignant conditions:

cancer, hyperthyroidism, inflamed joints

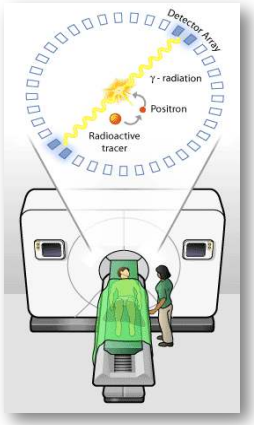
9

SPECT



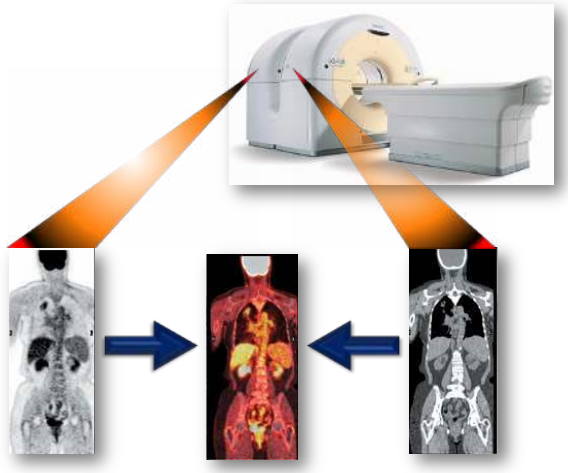
10

PET



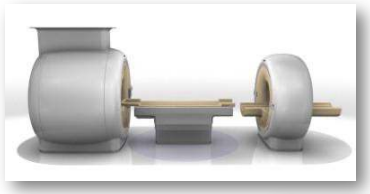
11

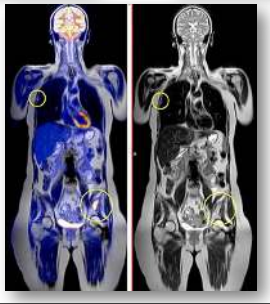
Combined molecular and anatomical imaging



12

Combined molecular and anatomical imaging





13

The imaging landscape

Cross-sectional imaging is *multimodal* (CT, MRI, SPECT, PET)

Knowledge of *anatomy* and *physiology* and *pathology*
(and *immunology, molecular biology, genetics* and …)

Understand *strengths*, *weaknesses* and *complemetarity*

Always consider and understand the clinical question or dilemma and *answer the question*

Appropriate use :
more imaging ≠ better, but insufficient imaging = worse

Last, but not least : use radiation consciously and wisely

14

Nuclear imaging

Scintigraphy

SPECT

Molecular imaging

PET

Precision imaging

Targeted radionuclide therapy

Targeted molecular radiotherapy

Systemic radiotherapy

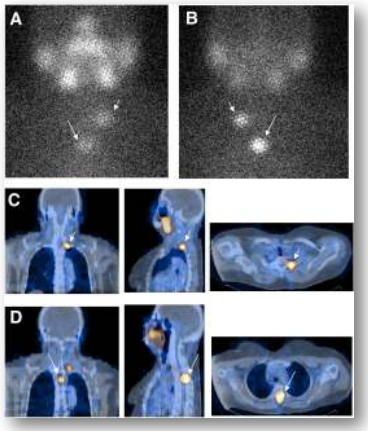
Radioligand therapy

Personalized radiotherapy

15

When Molecular Imaging still was Nuclear Medicine …

Saul Hertz 1940



Spanu et al. JNM 2009

16

Focus on oncology - imaging

"Modern imaging techniques detect, delineate and characterize lesions for tailored clinical management of individual patients" (*1992*)

Henry N. Wagner Jr. (1927–2012)

17

Molecular Imaging

Discovery (radiochemistry)

Preclinical development (biology)

Translation (radiopharmacy)

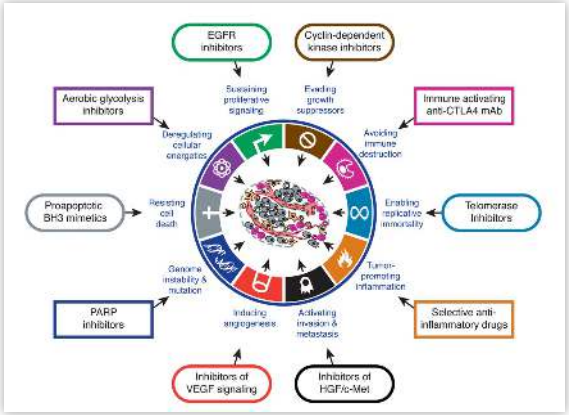
Early clinical studies **(nuclear medicine)**

Large(r) scale clinical studies (clinic)

Guidelines / Clinical Practice (policy)

18

Hallmarks of Cancer



Hanahan & Weinberg 2011

19

Molecular Imaging

Yesterday's Challenges, Today's Practice
- implementation -

Today's Challenges, Tomorrow's Practice
-translation-

20

Potential impact of cancer imaging

- **Staging**
- **Tumor delineation**
- **Characterization of tumors**
  - prognostic biomarkers
  - features indicating radioresistance
  - heterogeneity (intra & intertumoral)
- **Therapy response monitoring and prediction**
  - predictive biomarkers
  - early adaptation of ineffective treatment
  - interactions in multi-modality treatment
- **Follow-up / Relapse detection**

21

Why Molecular Imaging

- Presence of the target : *is it there ?*
- Heterogeneity of expression *: is it on all lesions ?*
- Accessibility of the target : *does the drug reach it ?*
- Dose dependency : *how much drug is needed ?*
- Modulation of the target : *does expression change ?*
- Drug interactions : *impact of combination therapy ?*

22

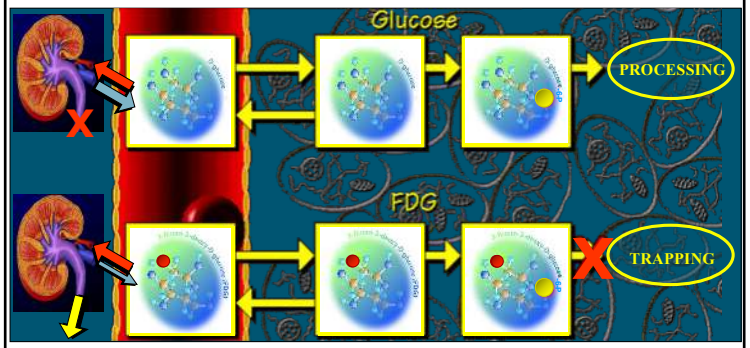
Pivotal Questions

~~Descriptive statistics (sensitivity / specificity)~~

- ***Impact on patient management***
- ***Impact on patient outcome***
- ***Impact on patient quality of life***
- ***Impact on costs of healthcare***

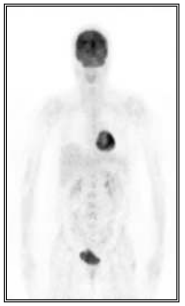
23

[^{18}F]-Fluoro-deoxyglucose (FDG) the most important PET-radiopharmaceutical

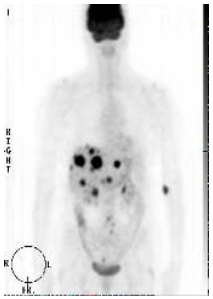


24

FDG-PET in oncology



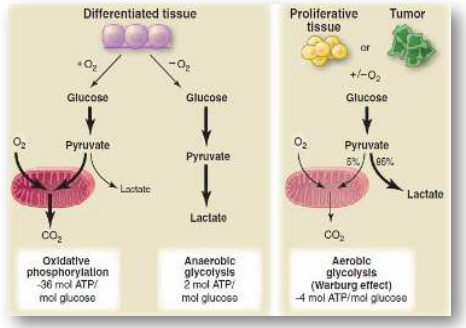
Normal FDG-PET

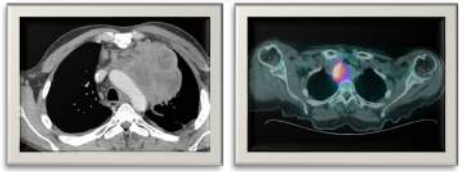


Metastases in
liver and lymphnodes

25

The Warburg effect



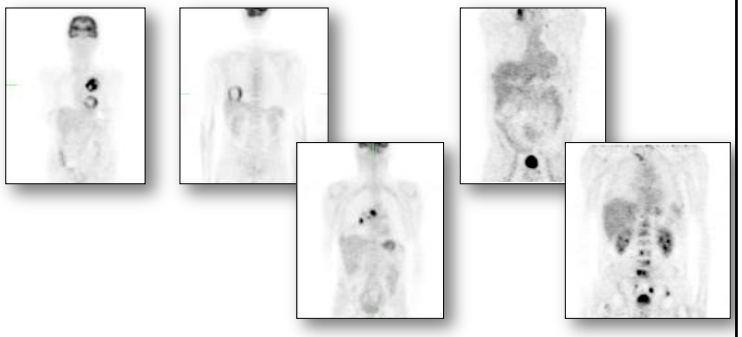


Science **324**, 1029 (2009)

26

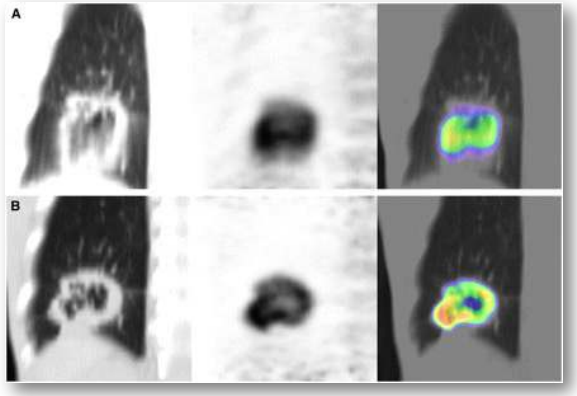
FDG-PET in lung cancer : Setting the stage

LOCAL REGIONAL DISTANT



27

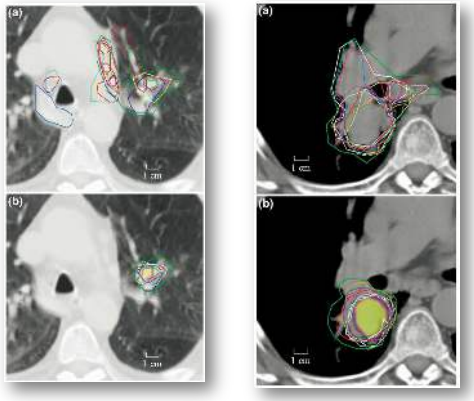
Respiratory motion artifact



Kawano 2008

28

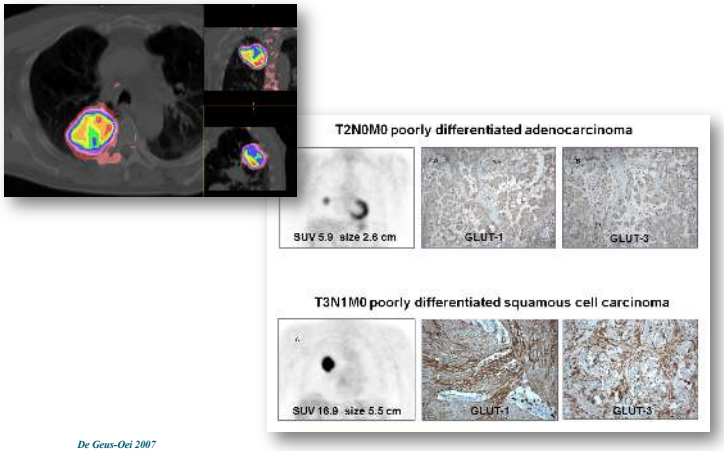
Tumor delineation



Steenbakkers et al. IJROBP 2006

29

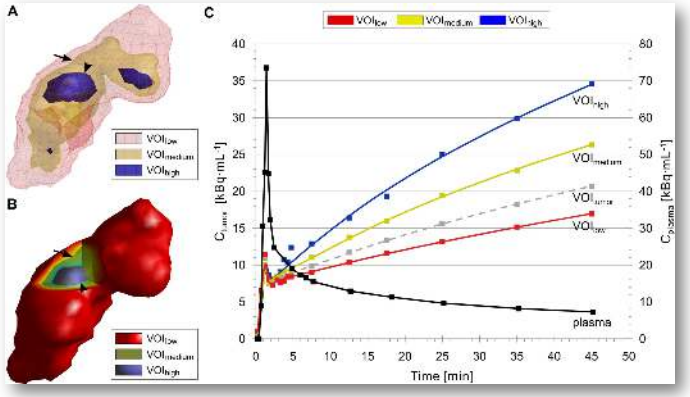
Understanding tumor biology : *Heterogeneity*



De Geus-Oei 2007

30

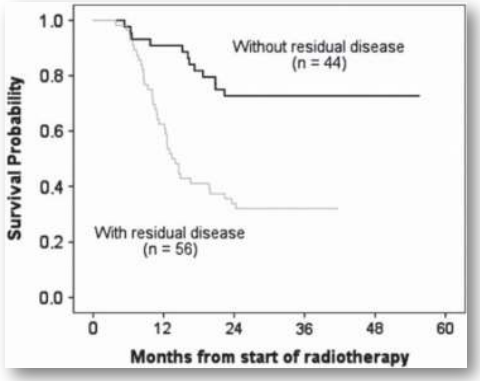
Understanding tumor biology : *Heterogeneity*



Vriens et al. IJROBP 2012

31

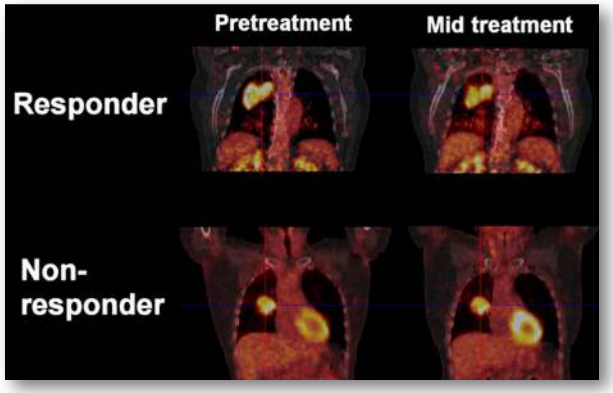
End of treatment FDG-PET in NSCLC



Velasquez 2010

32

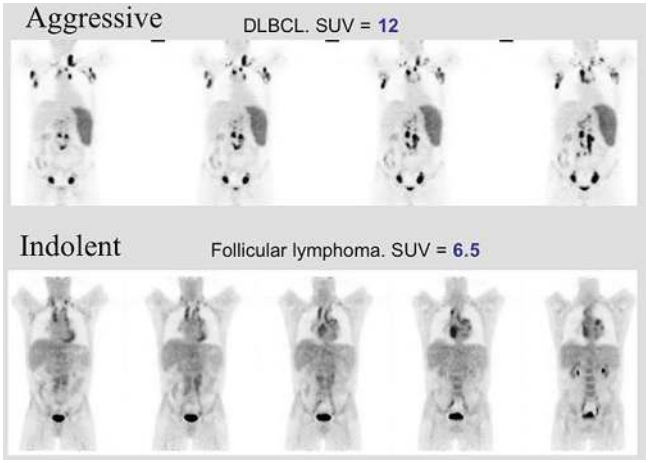
Early FDG-PET during radiotherapy in NSCLC



Van Elmpt JNM 2012; 53: 1514-1520

33

FDG-PET/CT in malignant lymphoma



34

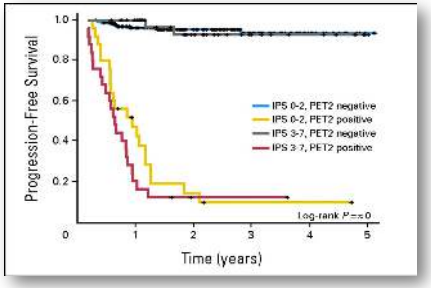
Assets of FDG-PET/CT

- FDG-PET more sensitive and specific than CT
  - positive nodes of normal size, negative enlarged nodes
  - organ localizations (liver, spleen)
  - bone marrow involvement (replacement of biospy in HD, DLBCL)
- Reclassification of stage in ~20% of patients (10-50%) (upstaging > downstaging)
- Early response assessment
- Follow-up after end of treatment

35

Prognostic superiority of early interim FDG-PET in advanced HL

Progression-free survival according to IPS and PET after two cycles of ABVD (doxorubicin, bleomycin, vinblastine, and dacarbazine)



Gallamini, A. et al. J Clin Oncol 2007; 25:3746-3752

36

Reduce if possible, intensify if needed

- A substantial number of patients are not cured with standard therapy
  ➔ change / intensification / combination of therapy might improve outcome
- Late treatment related morbidity and mortality especially after combination chemoradiation
  ➔ reduce therapy without compromising outcome
- Individualized patient management strategies
  ➔ risk adapted
  ➔ response adapted

37

Modified Deauville Criteria (2009 and following)

DEVELOPED FOR INTERIM PET/CT

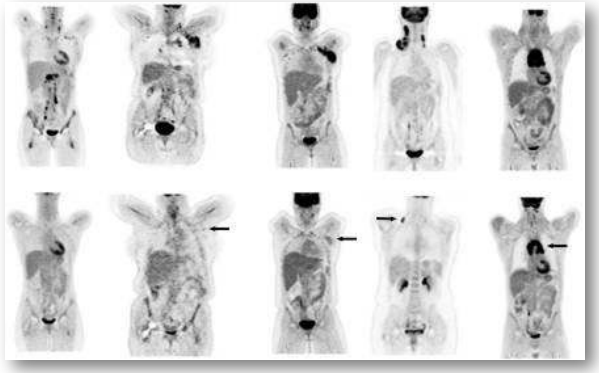
1 : No uptake above background
2 : Uptake ≤ mediastinum
3 : Uptake > mediastinum but ≤ liver
4 : Uptake moderately increased compared to the liver at any site
5 : Uptake markedly increased compared to the liver at any site
X : New areas of uptake unlikely to be related to lymphoma

38

Deauville Score

Staging

Response



1 **2** **3** **4** **5**

Barrington et al. EJNMI 2017; 44(Suppl 1): 97-110

39

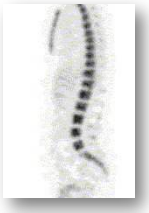
Modified Deauville Criteria (2009 and following)

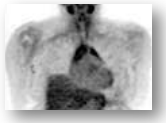
- Deauville score 1&2 → negative
- Deauville score 4&5 → positive
- Deauville score 3 usually indicates good prognosis with standard treatment → consider with clinical context
- Consider verification biopsy when second-line therapy is considered (exclude false positive FDG-uptake)

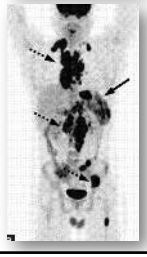
40

Pitfalls and caveats

- Impact of patient preparation, timing and scanning protocols
  - Growth factors and bone marrow repopulation
- Treatment induced changes (thymus, inflammation)
- Active infection /inflammation



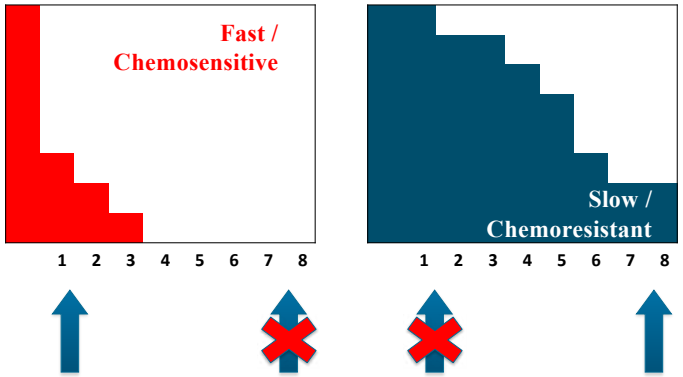




Jeph et al. IJNM 2014; 29: 102

41

Timing of imaging response



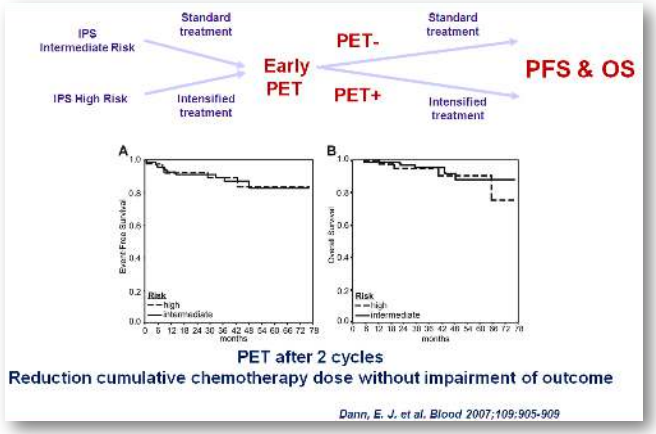
42

Focus of clinical trials

- **De-escalation strategies**
  - Decrease the number of chemotherapy cycles
  - Omitting bleomycin
  - Switching to less potent chemotherapy
- **Limiting or omitting radiotherapy**
- **Criteria for escalating to more potent chemotherapy:**
  - which patients ?
  - when ?

43

iPET2 / Ga-67 risk-adapted treatment of early unfavorable and advanced HL

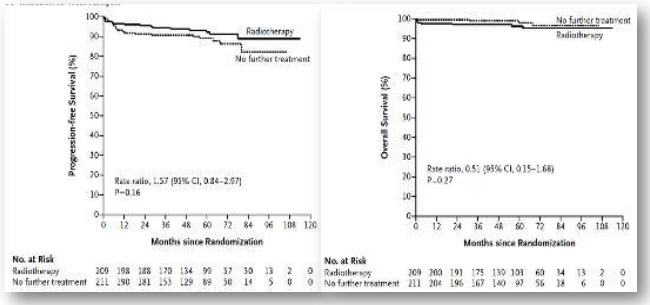


PET after 2 cycles
Reduction cumulative chemotherapy dose without impairment of outcome

Dann, E. J. et al. Blood 2007;109:905-909

44

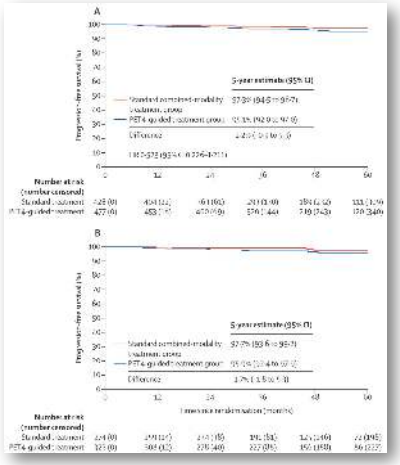
iPET3 guided treatment in early HL (RAPID)



Radford et al. NEJM 2015; 372: 1598

45

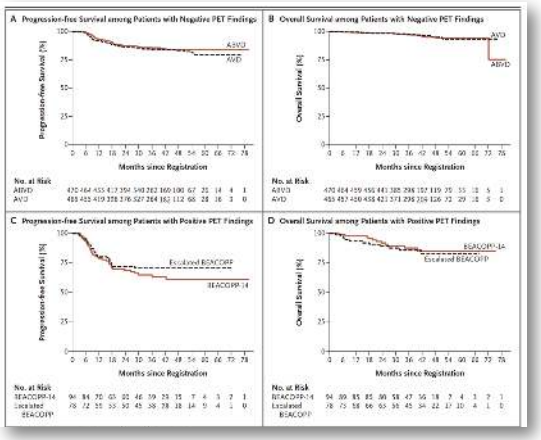
iPET4 guided treatment of unfavorable early-stage HL after 2xeBEACOPP + 2xABVD (GHSG HD17)



Borchmann et al. Lancet Oncol 2021; 22: 223

46

iPET2 guided treatment in advanced HL (RATHL)



Johnson et al. NEJM 2016; 374: 2419

47

Evidence in advanced HL

"A change to the treatment paradigm is appropriate"

iPET-adapted treatment approach after 2 ABVD should become the standard of care for all patients

- Positive iPET2 ABVD → (e)BEACOPP (?)
- Negative iPET2 ABVD → stop bleomycin

- Higher IPS and more advanced stage : lower NPV of a iPET2 [-] ABVD, not of iPET2 [-] eBEACOPP
- iPET2 [-] : 4 = 6 eBEACOPP
- iPET2 [+] D5 : higher risk of treatment failure, ABVD → eBEACOPP not sufficient.

Amitai et al. Acta Oncologica 2018; 57:765

48

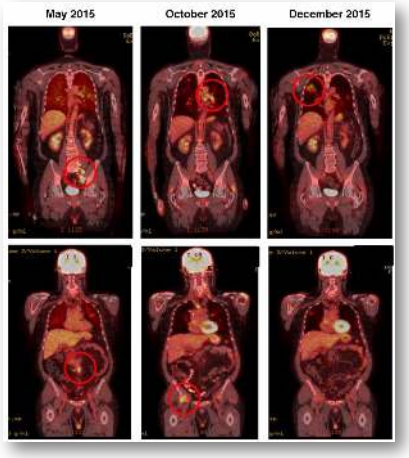
Role of iPET in NHL

- an effective predictive biomarker (DLBCL), but not accepted as standard of care : prediction of treatment success not sufficient for treatment modification (no availability of more effective therapies for iPET [+] patients)
- Inconsistencies in timing of iPET, therapeutic regimen, and/or PET reporting criteria (DS, IHP, SUV).
- metabolic CR : 15%-20% DLBCL and almost all FL will relapse.
- False[+] due to inflammation and tumor necrosis.
- iPET is better than iCT to predict prognosis and to exclude progression.
- changing of standard treatment on iPET is NOT recommended, unless clear evidence of progression.

Barrington te al. Lancet Haemat ol 2021; 8: e80
Cheson SNM 2018; 48: 76
Zijlstra et al. Hematologica 2016; 101: 1279

49

Immunotherapy in HD
- pseudoprogression on nivolumab -



Cheson et al. Blood 2016; 128: 2489

50

FDG-PET/CT in lymphoma

- FDG-PET/CT provides important clinically relevant information before, during and after treatment for malignant lymphoma
- Malignant lymphoma is by far the most advanced field in oncology, utilizing PET-driven changes in systemic treatment of cancer
- Body of evidence is largest in Hodgkin's lymphoma, NHL still rather scattered landscape
- On-going trials based on FDG-PET/CT that will answer important clinical questions

51

Monitoring of disease activity
after systemic treatment with FDG-PET

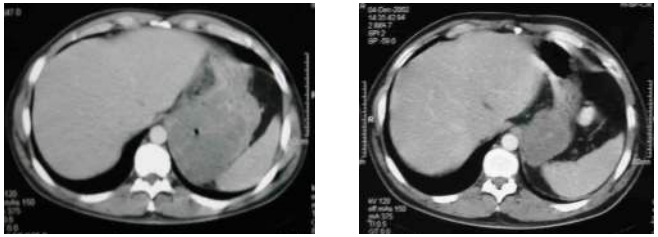
Therapy with signal transduction modifiers:
→ role model : imatinib treatment of GIST

- imatinib inhibits proliferation and induces apoptosis in GIST cells, which express an activating c-kit mutation
- **Kit receptor signaling regulates glucose uptake as well as glucose metabolism (strong decrease of hexokinase and glucose-6-phosphate 1-dehydrogenase activity) → FDG-PET**

52

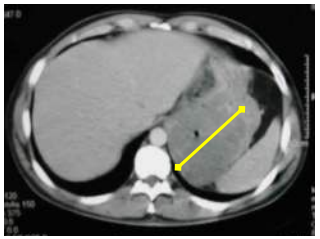
What you see is what you get

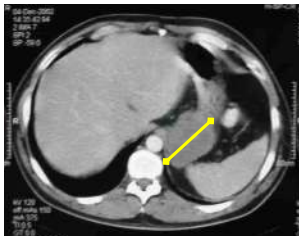
Pretreatment **12 wks Imatinib**



53

RECIST ?





- Unidimensional
  - CR
  - PR > 30% decrease
  - SD
  - PD > 20% increase
- **Tumor volume**
  - CR
  - PR > **66% decrease**
  - SD
  - PD **> 73% increase**

54

Targeted anticancer drugs in GIST

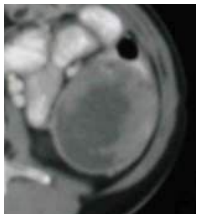
- Size reduction is late sign of response in GIST treated with Imatinib
- Increase in lesion size in responders due to therapy-associated hemorrhage or myxoid degeneration
- Clinical benefit in patients without major volume reduction

55

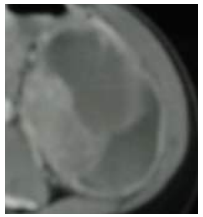
Beyond RECIST ?

- Analysis of tumor size and density (HU) on CT
- Decrease in tumor size of more than 10% or a decrease in tumor density of more than 15%

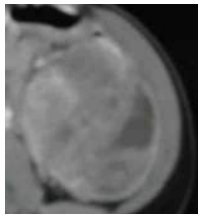
Pretreatment



8 wks Imatinib



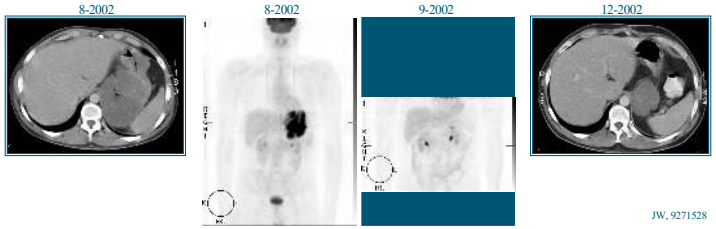
16 wks Imatinib



Choi et al. JCO 2007; 25:1753-9:

56

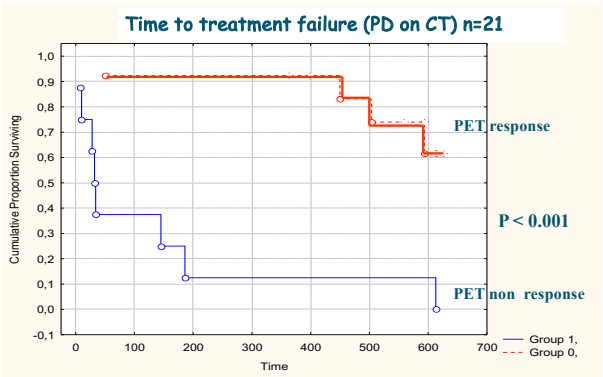
Monitoring of disease activity after imatinib treatment with FDG-PET



- Very early prediction of response (days)
- Indication for effective dosing
- Costs for PET less than approx. 1 week of treatment with Gleevec
- From *morphological* to *molecular* monitoring of response to treatment

57

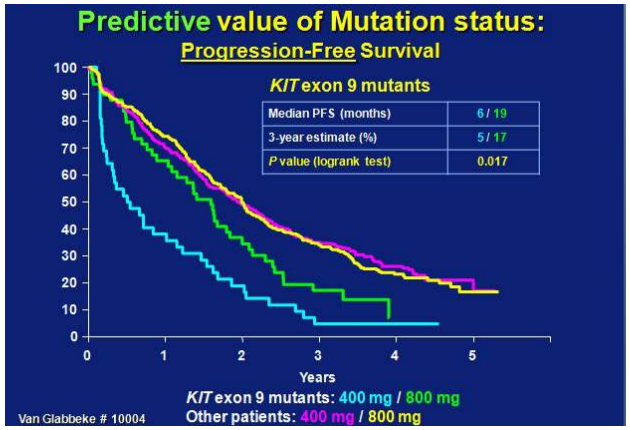
FDG-PET response after 8 days of imatinib



Stroobants et al. (Eur J Cancer 2003)

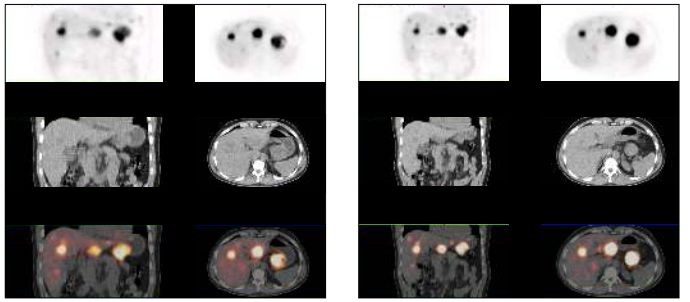
58

Imatinib-resistant GIST - relevance of exon 9 mutation -



59

Imatinib-resistant GIST - exon 9 mutation -



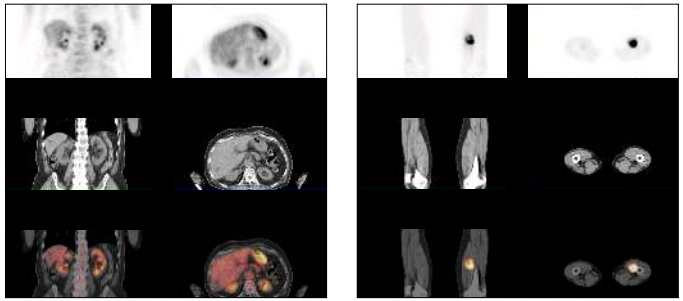
Before imatinib

During imatinib (2 weeks)

4502391

60

GIST
- heterogeneity of metastases -



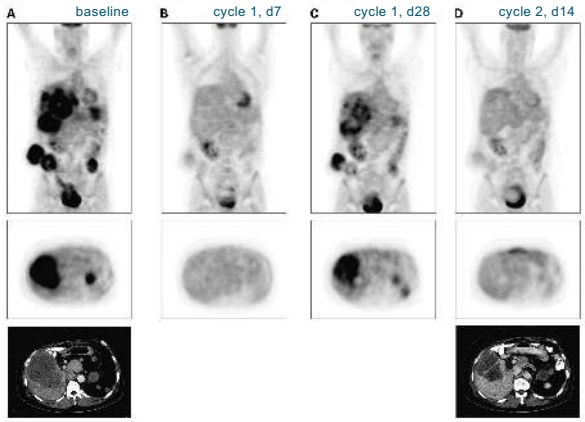
Liver metastasis,
imatinib sensitive

Soft tissue metastasis,
imatinib resistant

1515414

61

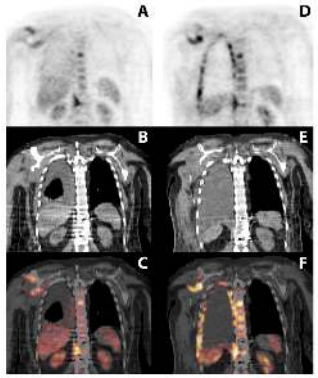
FDG-PET in GIST during sunitinib (2 wks on / 2 wks off)



Demetri et al. CCR 2009;15:5902-5909

62

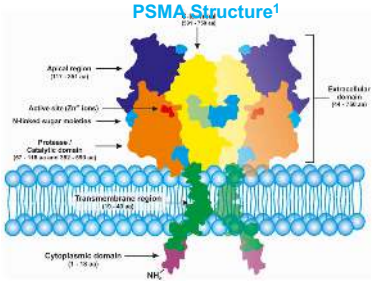
Treatment beyond progression
- Imaging nonresponse: flare-up -



63

Prostate cancer imaging through PSMA

PSMA Structure[1]



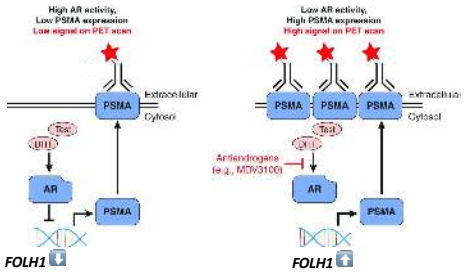
Prostate-Specific Membrane Antigen[1]

- Type II membrane bound glycoprotein
- Expressed in all forms of prostate tissue
- Overexpressed in carcinoma
- Also found in the neovasculature of most solid tumors

PSMA, prostate-specific membrane antigen.
Evans JC, et al. Br J Pharmacol. 2016;173(21):3041-3079.

64

Noninvasively measuring AR signaling pathway output with a radiotracer targeting PSMA



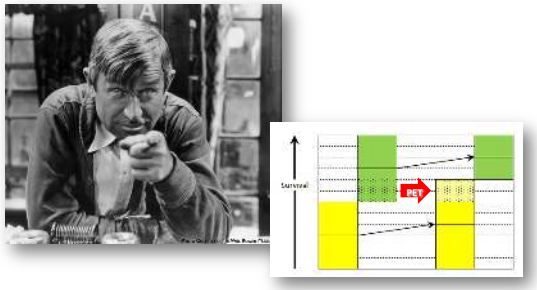
AR, androgen receptor; DHT, dihydrotestosterone; PET, positron emission tomography; PSMA, prostate-specific membrane antigen.; Test, testosterone.

Evans JM et al. Cancer Discov. 2012;2:985-994.

65

66

Will Rogers' phenomenon



"When the Okies left Oklahoma and moved to California, they raised the average intelligence level in both states."

67

- Ga-68-PSMA-11
- F-18-DCFPyL
- F-18-PSMA-1007
- F-18-rh-PSMA-7.3
- Ga-68-PSMA-I&T
- Cu-64-PSMA-I&T
- Ga-68-THP-PSMA
- F-18-CTT1057
- Tc-99m-MIP1404

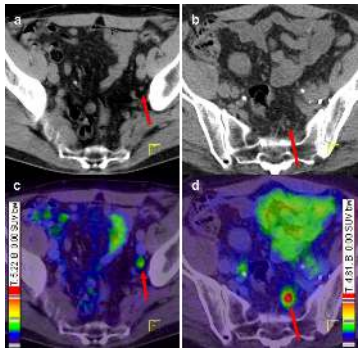
68

PSMA-PET/CT in HSPC

Primary staging :

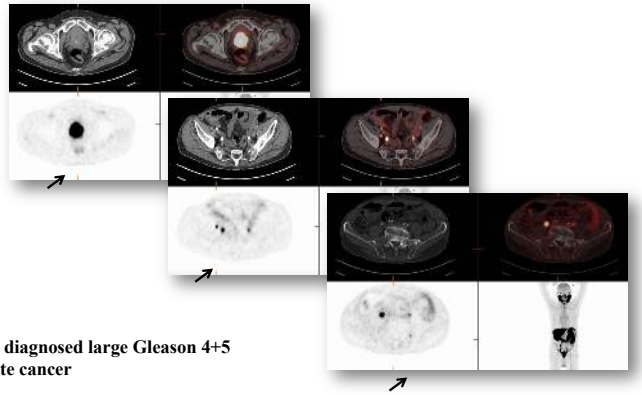
- Primary tumor : MRI leading, role PSMA-PET/CT remains to be established
- Detecting metastatic disease (upstaging from N0M0)
- Establishing more extensive metastatic disease
- Preventing invasive diagnostic procedures
- PSMA-PET/CT N0M0 low likelihood of disease, but not zero (micrometastases)

69



Afshar-Oromieh et al. EJNMMI 2015; 42:197-209

70



Newly diagnosed large Gleason 4+5 prostate cancer

PSMA-PET/CT : small right iliac node
small bone metastasis sacrum

Change of management : include bone met the in radiotherapy plan

71

*

Definition			
Low-risk	**Intermediate-risk**	**High-risk**	
PSA < 10 ng/mL	PSA 10-20 ng/mL	PSA > 20 ng/mL	any PSA
and GS < 7 (ISUP grade 1)	or GS 7 (ISUP grade 2/3)	or GS > 7 (ISUP grade 4/5)	any GS (any ISUP grade)
and cT1-2a	or cT2b	or cT2c	cT3-4 or cN+
Localised			**Locally advanced**

72

US multicenter phase III

- prospective multi-centre study ^{68}Ga-PSMA-11 PET/CT vs. surgery
- 764 patients with intermediate/high-risk Pca; 277 radical prostatectomy + LND (36%)
- 75 of 277 patients (27%) had pelvic nodal metastases
- Pelvic nodal metastases : sensitivity 0.40 (95% CI, 0.34-0.46), specificity 0.95 (95% CI, 0.92-0.97), positive predictive value 0.75 (95% CI, 0.70-0.80), negativepredictive value 0.81 (95% CI,0.76-0.85), respectively.
- "False-positives" : these lymph nodes were not removed → histopathology reference standard inaccurate *Hope et al. JAMA Oncology, 2021. 7: 1635.*
- 487 (64%) no prostatectomy, of which 108 were lost to follow-up. Patients with follow-up instead → radiotherapy (262/379; 69%), systemic therapy (82/379; 22%), surveillance (16/379; 4%), or other treatments (19/379; 5%).

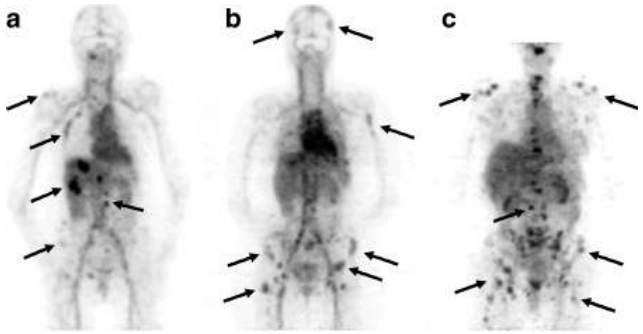
73

PSMA imaging in prostate cancer

- Introduction of very sensitive diagnostics like PSMA-PET/CT changes TNM classification
- PSMA-PET/CT may prevent the need for invasive procedures
- Impacts on the link TNM <-> therapeutic choices <-> outcome
- Improved (re)staging / earlier detection ≠ survival benefit
- CT / bone scan obsolete for staging, but established position as prognostic imaging biomarkers remains …. for now (mainly relevant for systemic treatments)

74

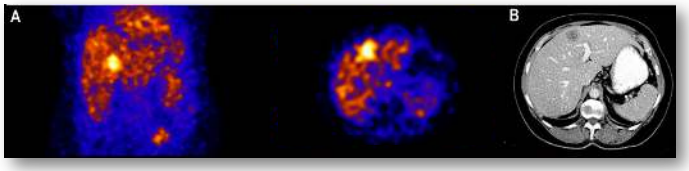
Target expression - trastuzumab



Dijkers et al. Clin Pharmacol Ther. 2010;87:586

75

Target expression - bevacuzimab

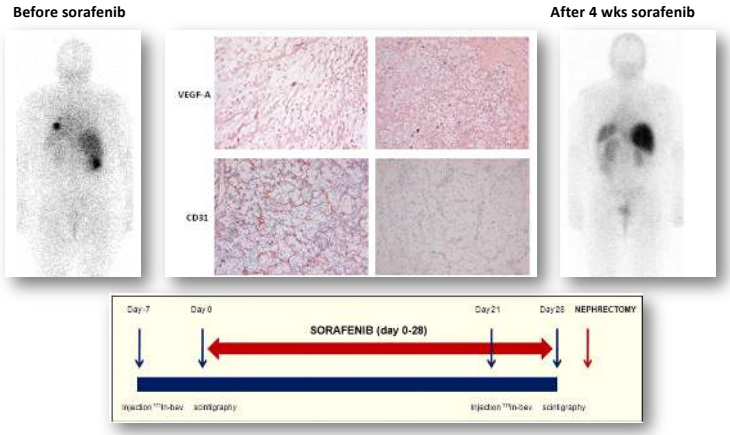


- no correlation between the VEGF in liver mets and VEGF in plasma (ρ=0.13, p=0.76)
- no correlation between VEGF in plasma and In-111-bevacizumab targeting of liver metastases (r=0.06, p=0.89)
- no correlation between the VEGF in liver mets and In-111-bevacizumab targeting of liver mets (ρ=0.43, p=0.19)

Scheer et al. EJC 2008;44(:1835

76

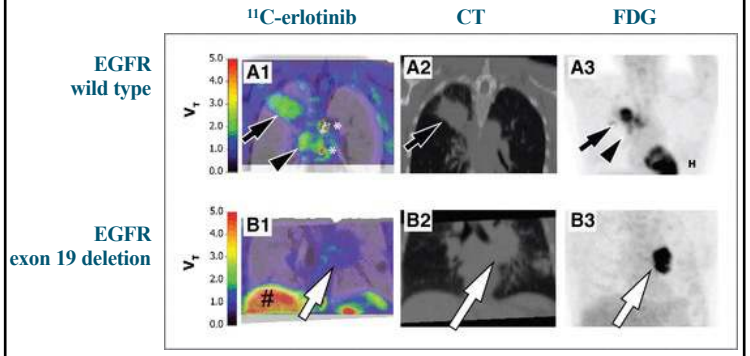
Target accessibility - bevacuzimab



Desar et al. J Nucl Med 2010;51:1707

77

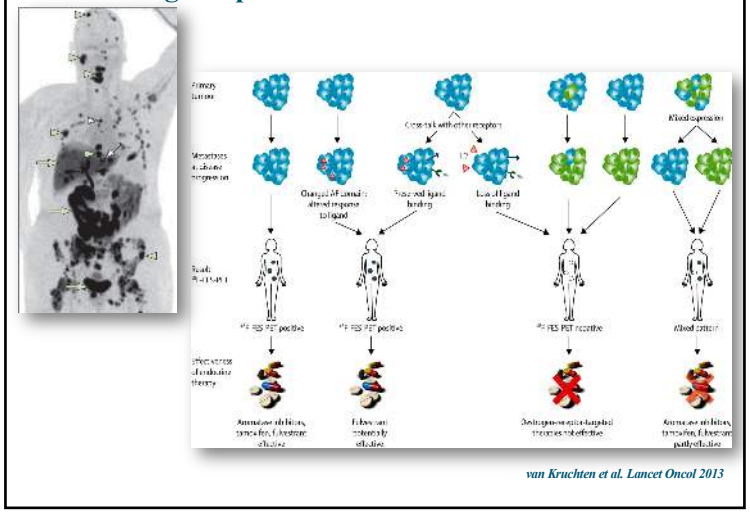
Targeting of TKIs



Bahce et al. CCR 2013; 19:183

78

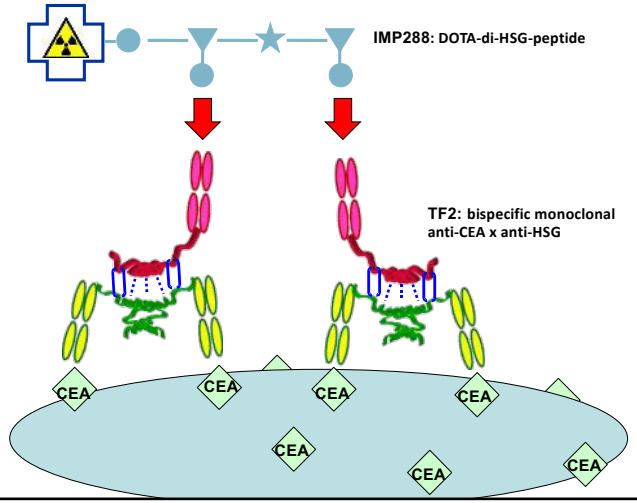
Target expression and modulation - FES



van Kruchten et al. Lancet Oncol 2013

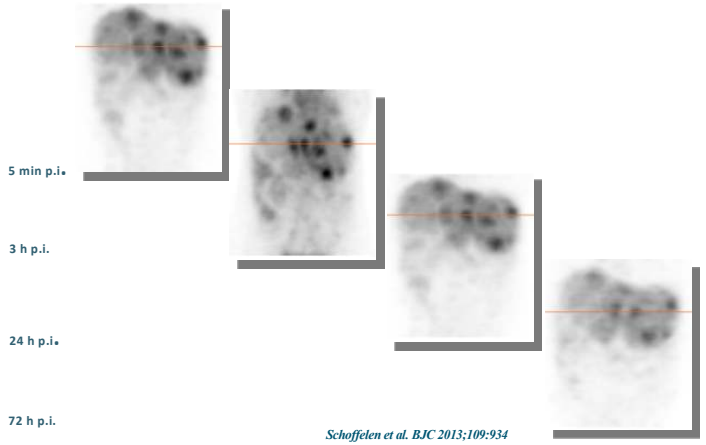
79

Pretargeted antibody targeting



80

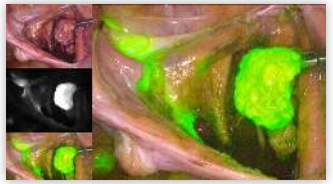
Pretargeted anti-CEA antibody: 150 mg TF2, 25 µg IMP288, 1-day interval



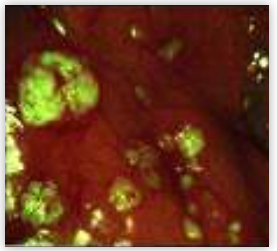
Schoffelen et al. BJC 2013;109:934

81

A open mind for new domains



Leitao et al. MSKCC 2014

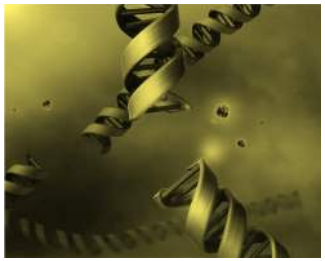


van Dam et al. Nature Med 2011

82

Focus on oncology - Therapy

β particles



α particles

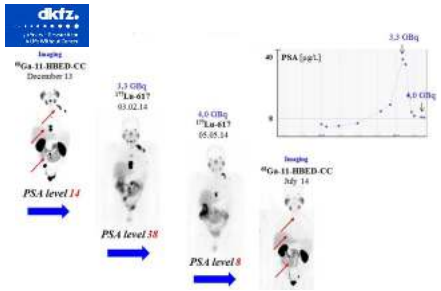
83

From diagnostics to therapy

- **Changing the radioisotope : ɣ / β^+ → β^- / α**
  - **Modifying the carrier molecule**
  - **Modifying the linker**
- **Establishing the theranostic principle :**
  - **Matching of PET/CT images with the therapeutic images (tumor targeting, pharmacokinetics, normal organ targeting, etc.)**
- **Clinical development of the radiopharmaceutical**

84

Theranostics:
Linked molecular imaging and radioligand therapy



Afshar-Oromieh, Kratochwil. et al, Department of Nuclear Medicine, University Hospital Heidenlberg.

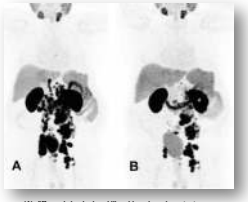
85

^{68}Ga / ^{177}Lu – PSMA theranostics

First study to retrospectively analyse safety and efficacy:[1]

- Heavily pretreated patients with extensively metastatic progressive CRPC (n=10)
- Mean ^{177}Lu-PSMA-617 5.6 GBq (range 4.1–6.1 GBq)
- No serious clinical adverse events due to ^{177}Lu-PSMA-617
- Grade 3/4 myelotoxicity observed in only 1 patient
- No relevant nephrotoxicity
- Large PSA decrease in 7/10 patients after 8 weeks of therapy

PSMA PET/CT before and after RLT[1]

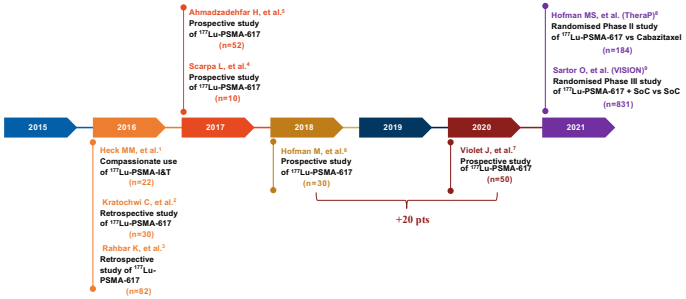


(A) diffuse abdominal and iliacal lymph node metastases
(B) a partial response 7 weeks after RLT with 63 % PSA decline

Ahmadzadehfar H, et al. EJNMMI Res. 2015 Dec;5(1):114.

86

Development of PSMA theranostics over time



1. Heck MM, et al. J Urol. 2016;196(2):382-91; 2. Kratochwil C, et al. J Nucl Med. 2016;57(8):1170-6; 3. Rahbar K, et al. J Nucl Med. 2016;57(9):1334-8; 4. Scarpa L et al. Eur J Nucl Med Mol Imaging. 2017;44(5):788-800; 5. Ahmadzadehfar H et al. Eur J Nucl Med Mol Imaging. 2017;44(9):1448-1454; 6. Hofman M, et al. Lancet Oncol. 2018;19(6):825-833; 7. Violet J, et al. J Nucl Med. 2020;61(6):857-865; 8. Hofman MS, et al. Lancet. 2021;27;397(10276):797-804; 9. Sartor O, et al. N Engl J Med 2021; 385:1091-1103.

87

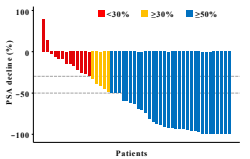
^{68}Ga / ^{177}Lu – PSMA Theranostics
First prospective trial

A prospective, open-label, single-arm, single-center, Phase 2 trial[1,2]

- Patients with mCRPC pretreated (n=30) with ≥1 line of prior chemotherapy and/or abiraterone/enzalutamide
- An additional cohort of 20 patients were enrolled[2]
- Up to 4 cycles of 7.5 GBq ^{177}Lu-PSMA at 6 weekly intervals
- 56% objective response in measurable soft-tissue disease
- 37% ≥10 point improvement in global health score by the 2nd cycle[1]
- Median OS: 13.3 months (95% CI, 10.5–18.7)
  - Significantly longer survival of 18.4 months (95% CI, 13.8–23.8) in patients achieving a PSA decline of ≥ 50%
- Grade1 dry mouth (66%), grade 1-2 transient nausea (48%), Grade 3-G4 thrombocytopenia (10%), and grade 3 anemia (10%)[2]

Best PSA response from baseline[2]

64% achieved ≥50% decrease
44% achieved ≥80% decrease



The two dashed lines represent PSA response >30% and >50%

1. Hofman M, et al. Lancet Oncol. 2018;19(6):825–833;
2. 2. Violet J, et al. J Nucl Med. 2020;61(6):857-865.

88

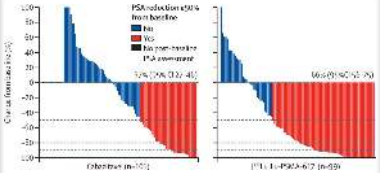
^{68}Ga / ^{177}Lu – PSMA Theranostics

First randomised trial: TheraP

An open-label, randomised, multicenter, Phase 2 trial to evaluate and compare the activity and safety of ^{177}Lu-PSMA-617 vs cabazitaxel

- Patients with mCRPC (n=200), PSMA-positive by ^{68}Ga-PSMA and ^{18}F-FDG-PET/CT
- Up to 6 cycles of 7.5 GBq ^{177}Lu-PSMA at 6 weekly intervals vs. cabazitaxel (20 mg/m2 iv every 3 weeks up to 10 cycles)
- Primary endpoint: PSA reduction of at least 50% from baseline
- Grade 3–4 adverse events: 33% in ^{177}Lu-PSMA-617 group vs. 53% in cabazitaxel group

Primary endpoint: PSA50 response rate[1]



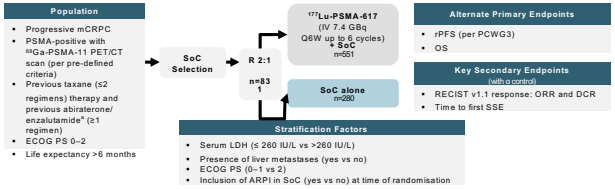
PSA decline met in 66% vs 37% by intention to treat; difference 29% (95% CI, 16–42; *p*<0·0001)

1. Hofman MS, et al. Lancet. 2021;27;397(10276):797-804.

89

VISION: ^{177}Lu-PSMA-617 pivotal Phase III trial

Study Design[1]



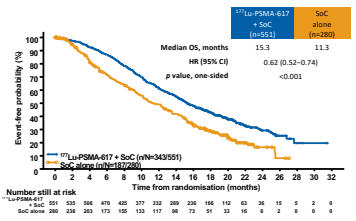
Sartor O, et al. N Engl J Med 2021; 385:1091-1103.

90

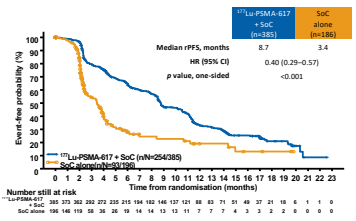
VISION: ^{177}Lu-PSMA-617 pivotal Phase III trial

VISION met both primary endpoints of OS and rPFS[1]

OS: 38% risk reduction for death[1]



rPFS: 60% risk reduction for progression/death[1]

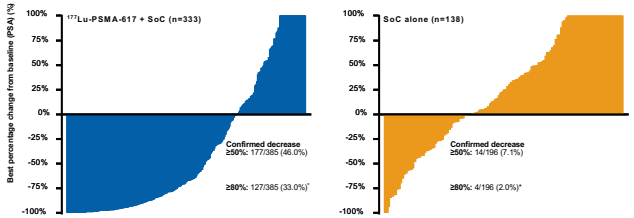


Sartor O, et al. N Engl J Med 2021; 385:1091-1103.

91

VISION: ^{177}Lu-PSMA-617 pivotal Phase III trial

PSA response[1]



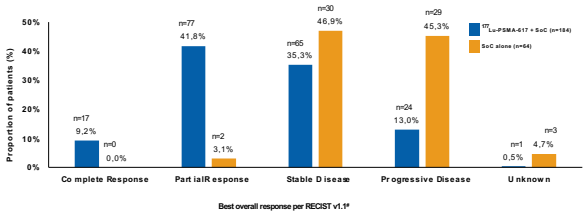
Sartor O, et al. N Engl J Med 2021; 385:1091-1103.

92

VISION: ^{177}Lu-PSMA-617 pivotal Phase III trial

Best overall response[1]
(per RECIST v1.1, patients with measurable disease)

ORR*: 51.1% of patients experienced a CR or PR in the ^{177}Lu-PSMA-617 + SoC arm vs 3.1% in the SoC only arm; DCR‡ was 86.4% vs 50.0%



Sartor O, et al. N Engl J Med 2021; 385:1091-1103.

93

VISION: ^{177}Lu-PSMA-617 pivotal Phase III trial

Safety and tolerability[1]

Event	Safety Set (N=734) All Grades ^{177}Lu-PSMA-617 + SoC (n=529) n (%)	All Grades SoC alone (n=205) n (%)	Grade 3–5# ^{177}Lu-PSMA-617 + SoC (n=529) n (%)	Grade 3–5# SoC alone (n=205) n (%)
Any TEAE	519 (98.1)	170 (82.9)	279 (52.7)	78 (38.0)
TEAEs occurring in ≥12% of patients*, n (%)				
Fatigue	228 (43.1)	47 (22.9)	31 (5.9)	3 (1.5)
Dry mouth	205 (38.8)	1 (0.5)	0	0
Nausea	187 (35.3)	34 (16.6)	7 (1.3)	1 (0.5)
Anaemia	168 (31.8)	27 (13.2)	68 (12.9)	10 (4.9)
Back pain	124 (23.4)	30 (14.6)	17 (3.2)	7 (3.4)
Arthralgia	118 (22.3)	26 (12.7)	6 (1.1)	1 (0.5)
Decreased appetite	112 (21.2)	30 (14.6)	10 (1.9)	1 (0.5)
Constipation	107 (20.2)	23 (11.2)	6 (1.1)	1 (0.5)
Diarrhea	100 (18.9)	6 (2.9)	4 (0.8)	1 (0.5)
Vomiting	100 (18.9)	13 (6.3)	5 (0.9)	1 (0.5)
Thrombocytopaenia	91 (17.2)	9 (4.4)	42 (7.9)	2 (1.0)
Lymphopaenia	75 (14.2)	8 (3.9)	41 (7.8)	1 (0.5)
Leukopaenia	66 (12.5)	4 (2.0)	13 (2.5)	1 (0.5)
TEAE leading to dose reduction in ^{177}Lu-PSMA-617	30 (5.7)	0	10 (1.9)	0
TEAE leading to interruption of ^{177}Lu-PSMA-617‡	85 (16.1)	2 (1.0)[b]	42 (7.9)	0
TEAE leading to discontinuation of ^{177}Lu-PSMA-617‡	63 (11.9)	1 (0.5)[b]	37 (7.0)	0
TEAE leading to death	19 (3.6)	6 (2.9)	19 (3.6)	6 (2.9)

Sartor O, et al. N Engl J Med 2021; 385:1091-1103.

94

VISION: ^{177}Lu-PSMA-617 pivotal Phase III trial

Post-protocol therapies[1]

Treatment	OS Analysis Set (n=831) ^{177}Lu-PSMA-617 + SoC (n=551) n (%)	SoC only (n=280) n (%)
Treatment type		
Radiotherapy	49 (8.9)	31 (11.1)
Medication	155 (28.1)	97 (34.6)
Medications received by ≥1% of patients		
Taxane	99 (18.0)	61 (21.8)
Cabazitaxel	82 (14.9)	53 (18.9)
Docetaxel	27 (4.9)	10 (3.6)
Paclitaxel	4 (0.7)	2 (0.7)
Platinum compound	40 (7.3)	27 (9.6)
Monoclonal antibodies	16 (2.9)	22 (7.9)
Therapeutic radiopharmaceuticals	16 (2.9)	23 (8.2)
^{223}Ra	14 (2.5)	15 (5.4)
^{177}Lu-PSMA-617	2 (0.4)	3 (1.1)
^{225}Ac-PSMA-617	1 (0.2)	0 (0.0)
Other/various	0 (0.0)	5 (1.8)
ARPI and Anti-androgens	23 (4.2)	13 (4.6)
Enzalutamide	12 (2.2)	7 (2.5)
Darolutamide	5 (0.9)	3 (1.1)
Apalutamide	4 (0.7)	2 (0.7)
Proxalutamide	2 (0.4)	1 (0.4)
Bicalutamide	1 (0.2)	1 (0.4)
Abiraterone acetate	13 (2.4)	3 (1.1)

Sartor O, et al. N Engl J Med 2021; 385:1091-1103.

95

VISION: ^{177}Lu-PSMA-617 pivotal Phase III trial

Trial	Comparison	OS (months)	HR for OS	OS Difference
Post-Docetaxel mCRPC				
TROPIC[1]	Cabazitaxel/prednisone vs Mitoxantrone/prednisone	15.1 vs 12.7	0.70	2.4 months
COU-AA-301[2]	Abiraterone/prednisone vs Placebo/prednisone	15.8 vs 11.2	0.74	4.6 months
AFFIRM[3]	Enzalutamide vs Placebo	18.4 vs 13.6	0.63	4.8 months
Front-line and Post-Docetaxel mCRPC				
ALSYMPCA[4]	SoC +/- Radium-223	14.9 vs 11.3	0.70	3.6 months
Post-Abiraterone/Enzalutamide or Post-Abiraterone/Enzalutamide/Docetaxel mCRPC (*BRCA1/BRCA2/ATM* subset)				
PROfound[5]	Olaparib vs Abiraterone/enzalutamide second line	19.1 vs 14.7	0.69	4.4 months
Post-Abiraterone/Enzalutamide and Post-Docetaxel mCRPC				
VISION[6]	SoC +/- ^{177}Lu-PSMA-617	15.3 vs 11.3	0.62	4.0 months

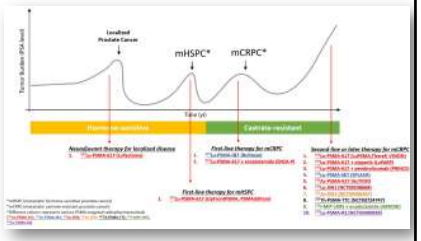
1. de Bono JS, et al. Lancet. 2010;376(9747):1147-1154; 2. Fizazi K, et al. Lancet Oncol. 2012;13(10):983-992; 3. Scher HI, et al. N Engl J Med. 2012;367(13):1187-1197; 4. Parker C, et al. N Engl J Med. 2013;369(3):213-223; 5.. Hussain M, et al. N Engl J Med. 2020;383(24):2345-2357; 6. Sartor O, et al. N Engl J Med 2021; 385:1091-1103.

96

What's next ?

On-going clinical trials with various concepts :

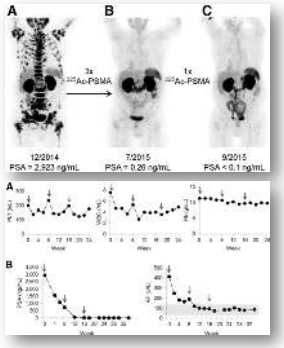
- Earlier than after 2nd line in mCRPC: towards hormone-sensitive metastatic prostate cancer (… or even earlier ?)
- **Alternative ligands, e.g. PSMA-I&T**
  (… me too, or real, clinical improvement ?)
- **Alternative radionuclides : use of α-emitters (… too toxic or or real, clinical improvement ?)**
- **Combination therapies**



July 2021 from : Zhang H et al. Cancers 2021, 13(16), 402

97

Ga-68 / Ac-225 – PSMA Theranostics



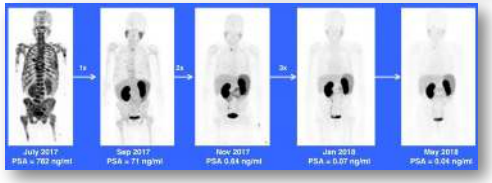
- Large PSA decline (CR) in heavily pretreated, extensively metastasized patients
- No safety issues
- Xerostomia

Kratochwil et al. JNM 2016; 57:1941-44

98

Ga-68 / Ac-225 – PSMA Theranostics

- 15/17 pts. large PSA decline in metastatic patients; upto 4 cycles of AC-225-PSMA
- No safety issues; xerostomia in all pts; worsening of kidney failure in 1 patient



Sathekge et al. EJNMMI 2019; 46:129-138

99

Ga-68 / Ac-225 – PSMA Theranostics

- 20 heavily pretreated pts. with end-stage prostate cancer
- Insufficient response to Lu-177-PSMA → 1 cycle of Ac-225-PSMA, followed by further Lu-177-PSMA
- 65% best biochemical response of PSA decline > 50%
- Median PFS 19 weeks, median OS 48 weeks
- No grade G3/4 xerostomia

Khreish et al. EJNMMI 2020; 47:721-728

- 28 pts. with and without Lu-177-PSMA pretreatment
- 1-7 (median 3) cycles of 100kBq/kg Ac-225-PSMA at 8 weekly intervals
- >50% decline in PSA :
  - 25% @ 8th week of post 1st cycle
  - 39% end of follow-up
- CMR 9%, PMR 45%, SMD 9%, PMD 36%
- transient fatigue 50%, G1/2 xerostomia 29%

Yadav et al. Theranostics 2020; 10: 9364

100

PSMA therapy in prostate cancer

- The concept of theranostics is at the core of nuclear medicine therapy
- ^{177}Lu-PSMA-617:
  - *Significant gain in OS and rPFS*
  - *Excellent safety and tolerability characteristics*
- Objective responses (biochemical, molecular imaging, RECIST), manageable adverse events, improvement of QoL
- Mandatory theranostic approach: 10–15% intrinsically PSMA-negative
- Manageable logistics for work-up and delivery of treatment
- First Lu-177-PSMA therapy approved in Europe, phase 3 trials for other indications and other agents

101

Nuclear Medicine

- Multidisciplinary and collaborative
- Clinical medicine and technical challenges
- Innovation and creativity
- Dynamic : evolution and revolutions

102

Nuclear Medicine

103