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MOLECULAR IMAGING: CONTRIBUTION TO PERSONALISED ONCOLOGY

Molecular imaging biomarkers in solid tumours

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Patrick Flamen, MD, PhD

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Educational Portal for Oncologists

WHAT IS MOLECULAR IMAGING?

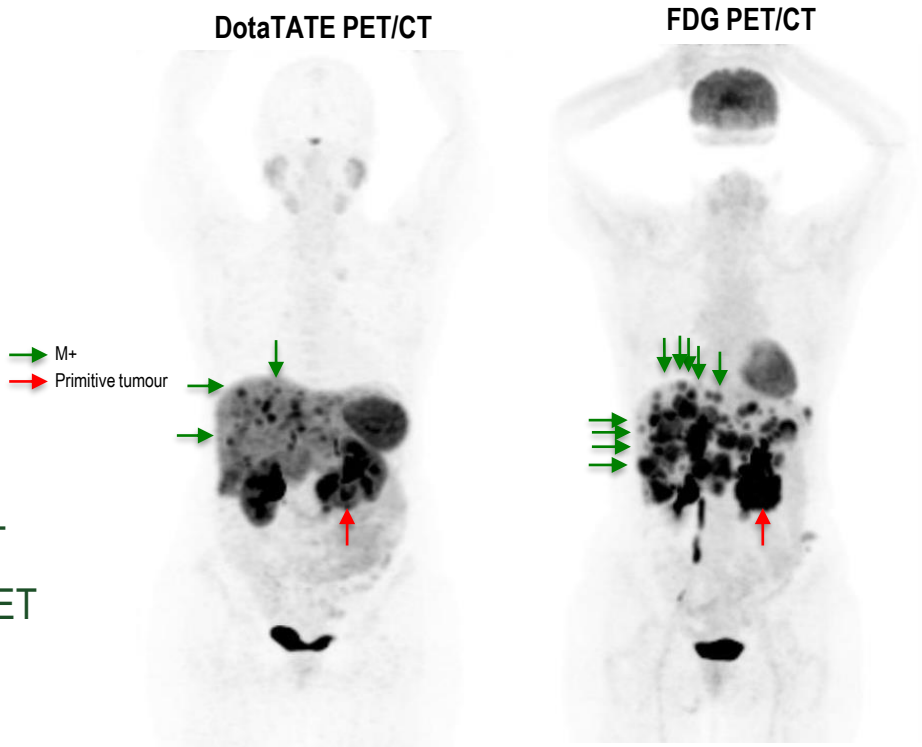
Imaging of molecular/metabolic processes:

- glucose metabolism: ^{18}F-Glucose (FDG)-PET
- amino acids: ^{18}F-Ethyl-Tyrosine (FET)-PET
- hypoxia: ^{18}F-Misonidazole (FMISO)-PET
- proliferation: ^{18}F-Thymidine (FLT)-PET
- …

Imaging of molecular targets:

- **Oestrogen** receptors: ^{18}F-Estradiol (FES)-PET
- Somatostatin receptors: ie ^{68}Ga-DOTATATE-PET
- Prostate-Specific Membrane Antigen (PSMA): 68Ga-PSMA-PET
- …

Images Courtesy of Institut Jules Bordet

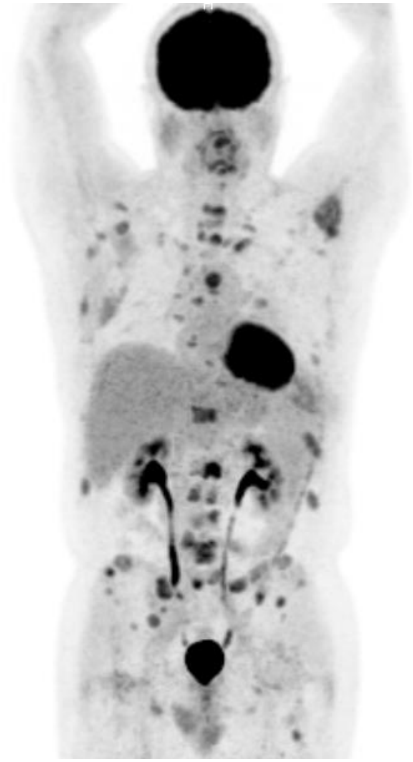


Dual molecular PET imaging: patient with pancreatic NET G2 showing mismatch between SSTR expression (DotaTATE PET) and metabolic activity (FDG PET)

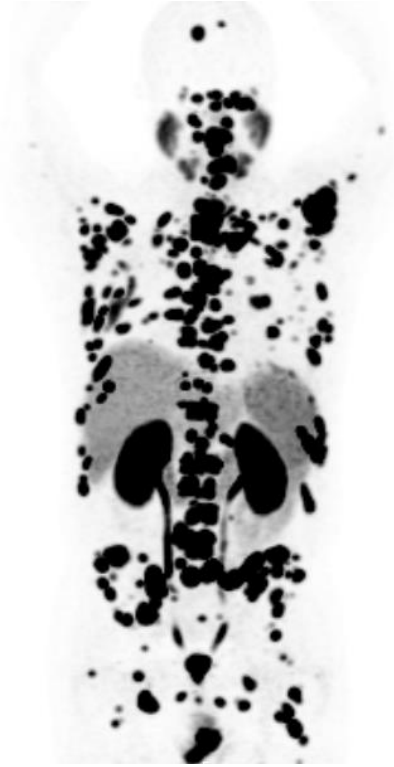
EXAMPLES OF DUAL MOLECULAR IMAGING

Recurrent prostate cancer

^{18}F-FDG



^{68}Ga-PSMA-11



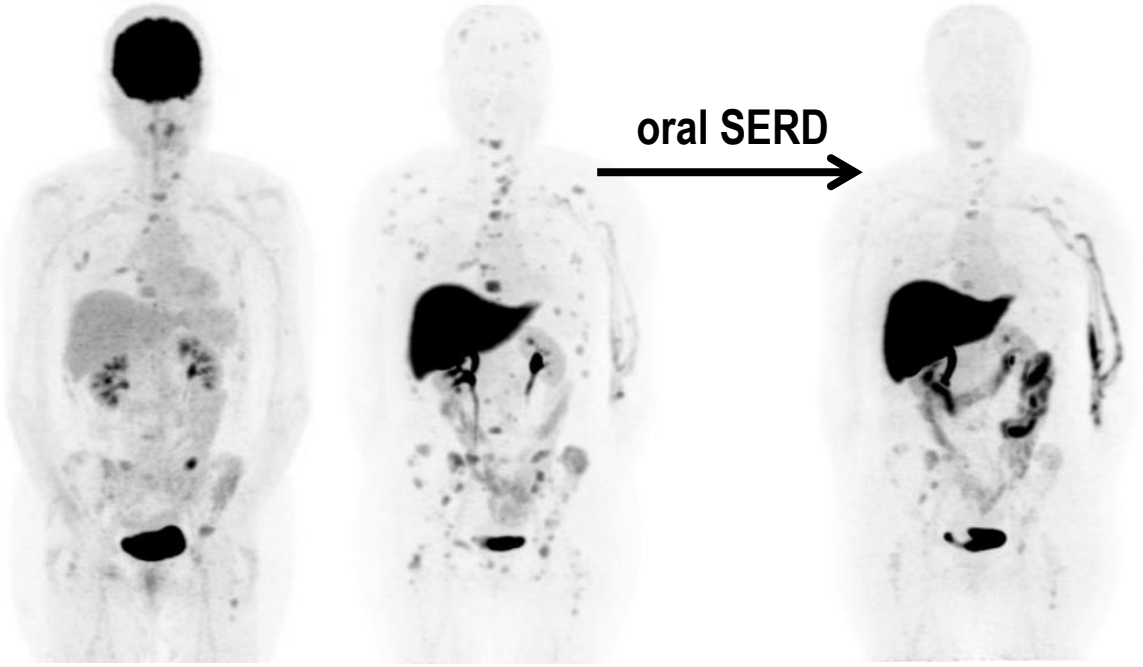
Images Courtesy of Institut Jules Bordet

Patient with prostate cancer showing no mismatch between expression of PSMA (Prostate Specific Membrane Antigen) and metabolic activity (FDG): all FDG-positive lesions express PSMA

PSMA PET/CT provides image of disease extent (Staging) whereas FDG-PET/CT provides a grading of the disease (i.e. amplification of glycolytic activity of the tumour is a sign of malignant transformation coupled to infaust prognosis)

EXAMPLES OF DUAL MOLECULAR IMAGING

Drug target imaging



Baseline FDG PET **Baseline FES PET** **Cycle 2 FES PET**

Images Courtesy of Institut Jules Bordet

Patient with metastatic breast cancer, showing no FDG uptake and a positivity for FES PET. Disappearance of FES-positive lesions after treatment by SERD (selective oestrogen receptor degrader)

FES PET shows the target expression for targeted therapy

WHY DO WE NEED BIOMARKERS IN MODERN ONCOLOGY?

Need of biomarkers predictive of the presence of a drug target and predictive of response to therapy

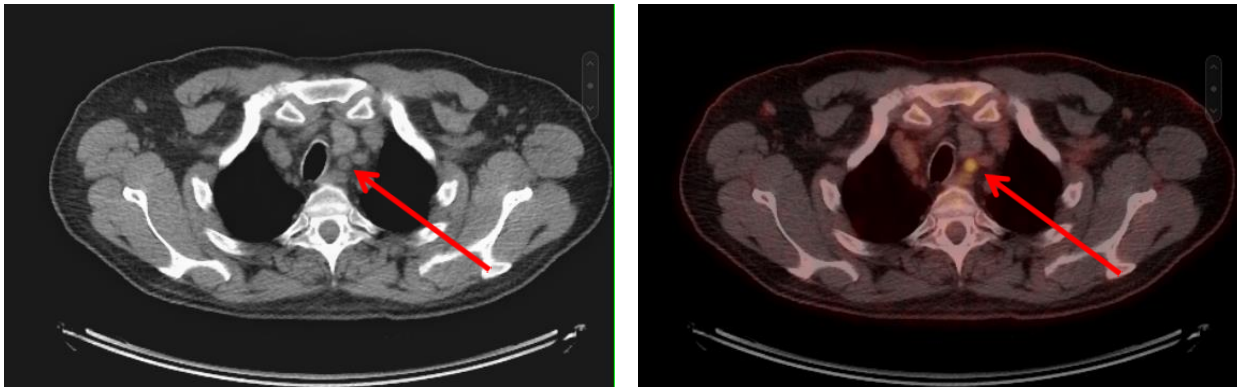
Molecular imaging could help personalise oncological care by providing tools able to identify the patients **unlikely to benefit** from a targeted treatment:

1. by detecting a drug target's presence/absence
2. by identifying the non-responding patients early after the therapy onset

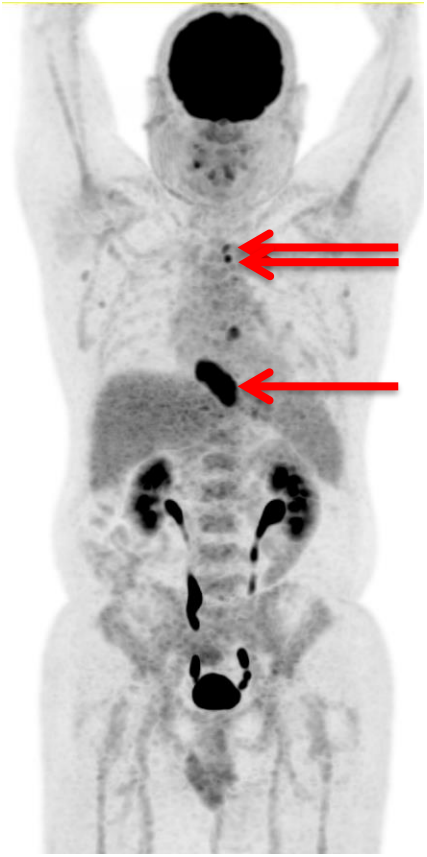
Molecular imaging provide additional prognostic information on tumour stage & grade (FDG-PET) and burden (Metabolic Active Tumour Volume (MATV))

ROLE OF METABOLIC IMAGING: PREOPERATIVE STAGING

FDG PET's currently accepted indication: exclude distant dissemination in case of locoregional advanced gastro-esophageal cancer (Tumour cartography)



Left Paratracheal LN metastasis (11 mm)



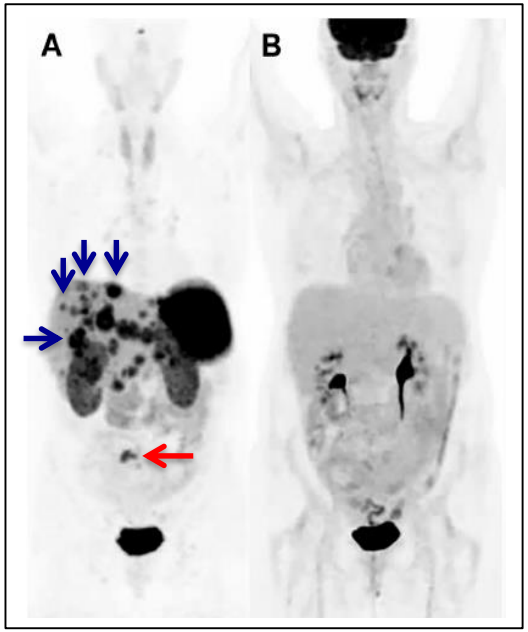
GEJ adenocarcinoma with mediastinal, left paratracheal & retroclavicular metastatic lymph nodes

Images Courtesy of Institut Jules Bordet

ROLE OF METABOLIC IMAGING: PRETHERAPEUTIC GRADING

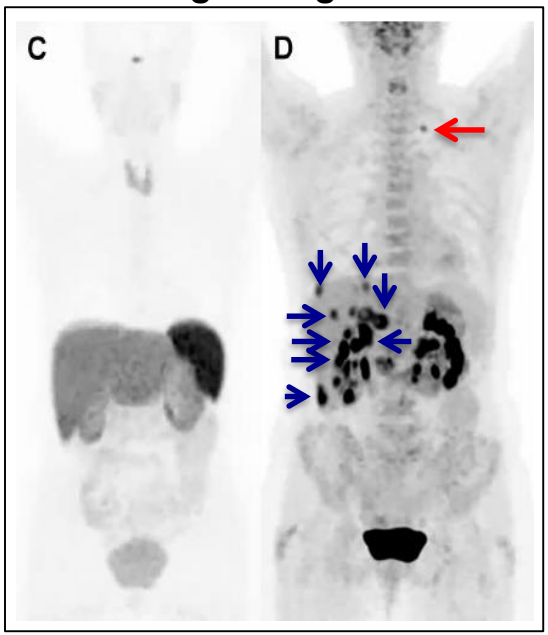
Use of dual metabolic imaging to define NENS phenotype

Ileal GEP-NET grade I



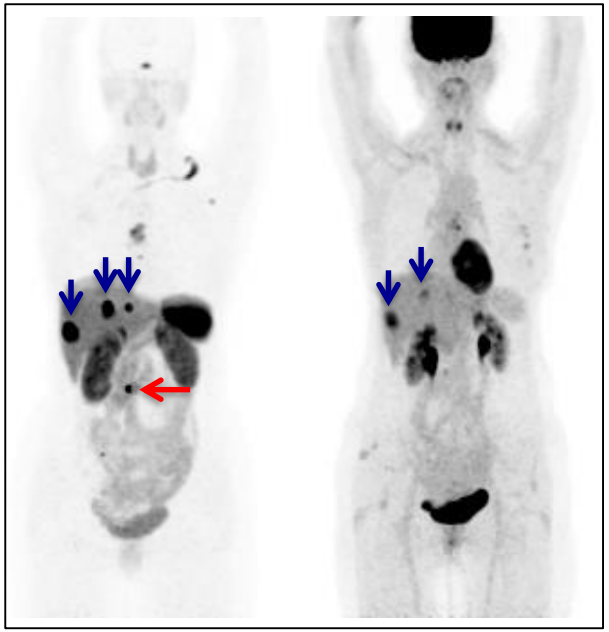
Ileal tumour (red) & liver M+ (blue) express SSTR2 No avidity for FDG

Lung NET grade 3



Lung tumour (red) & liver M+ (blue) don't express SSTR2 but are avid for FDG

Duodenal NET grade 1



Intestinal tumour (red) & liver M+ (blue) express SSTR2 and some liver lesions are avid for FDG, without mismatch

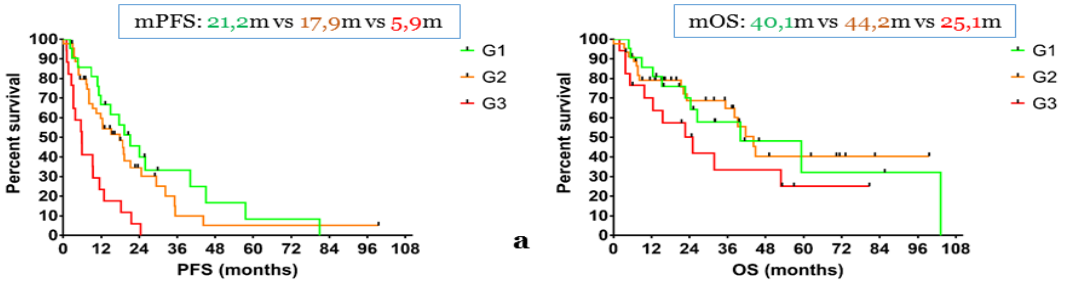
Images Courtesy of Institut Jules Bordet

ROLE OF METABOLIC IMAGING: PRETHERAPEUTIC GRADING

Use of dual metabolic imaging: the PET score

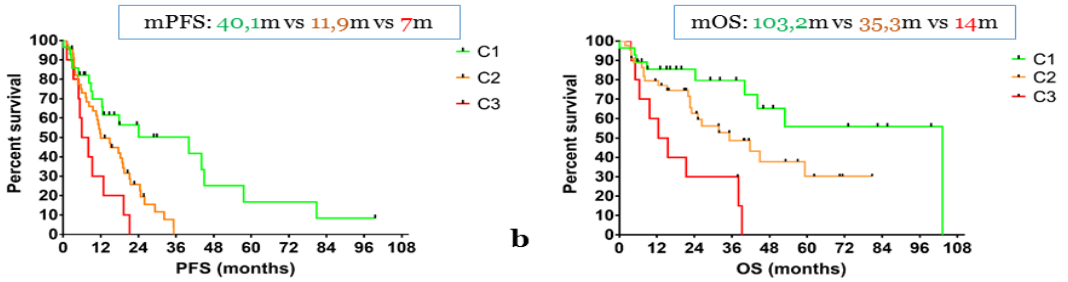
Pathological grade (ENETS)

G1: Ki-67 <2%
G2: Ki-67 2-20%
G3: Ki-67 >20%



Dual PET (FDG- and Octreo-PET) **Imaging score**

C1: all lesions OctreoPET+ & FDGPET-
C2: all lesions OctreoPET+ some FDGPET+
C3: mismatch of at least 1 lesion FDGPET+ is OctreoPET-

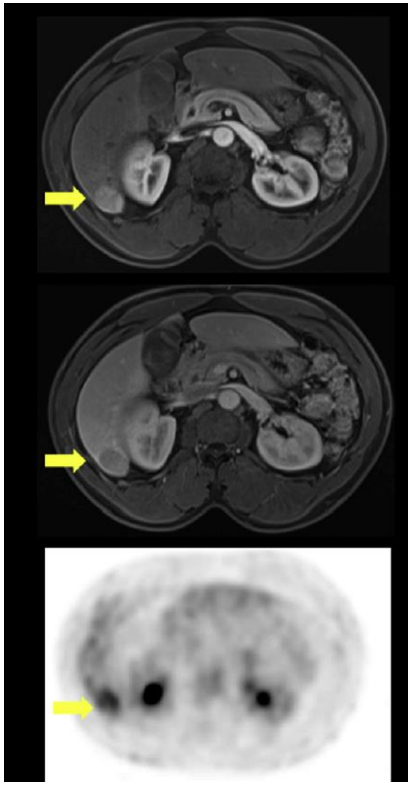


Dual PET-based imaging score seems to allow better classification of outcome as compared to classical pathological grade

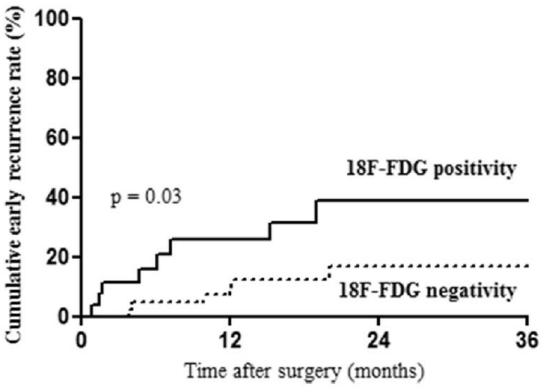
This research was originally published in JNM, Karfis I, *et al.* J Nucl Med May 1, 2019 vol. 60 no. supplement 1 1523. © SNMMI.
http://jnm.snmjournals.org/content/60/supplement_1/1523

ROLE OF METABOLIC IMAGING: PRETHERAPEUTIC GRADING

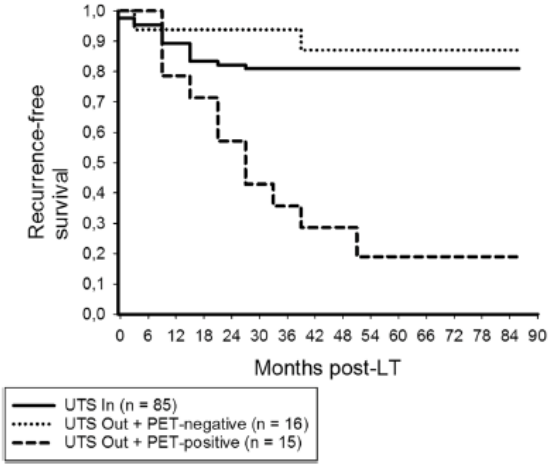
Defining hepatocellular carcinoma phenotype



FDGPET as a prognostic factor for recurrence after **liver surgery**[1]



FDGPET as a independent prognostic factor for recurrence after **liver transplantation**[2]

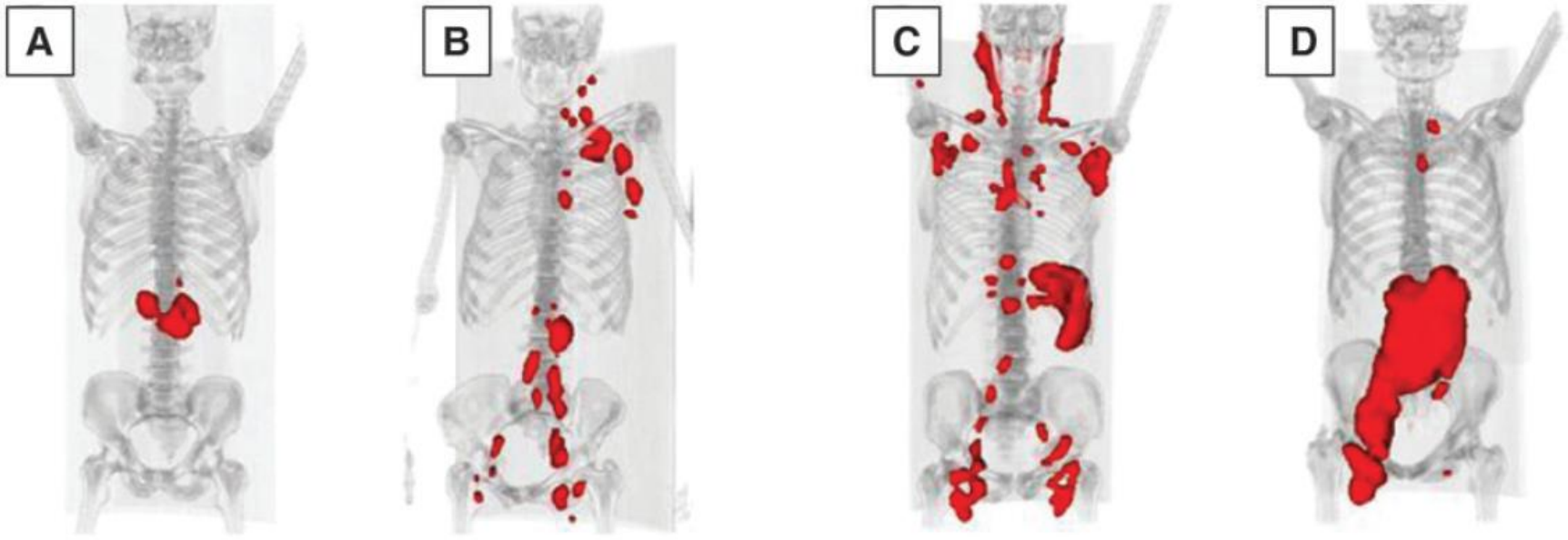


High negative prognostic value of FDGPET in HCC

(1) Reprinted from HPB Journal, 21(6), Lim C, *et al.* 18F-FDG PET/CT predicts microvascular invasion and early recurrence after liver resection for hepatocellular carcinoma A prospective observational study, 739-747., Copyright (2019), with permission from Elsevier. 2. Kornberg A, et al. Sci Rep 2017: 14176 Open Access This article is licensed under a Creative Commons Attribution 4.0 International License.

ROLE OF METABOLIC IMAGING: PROGNOSIS ASSESSMENT

Baseline Metabolically Active Tumour Volume (MATV) as a prognostic biomarker

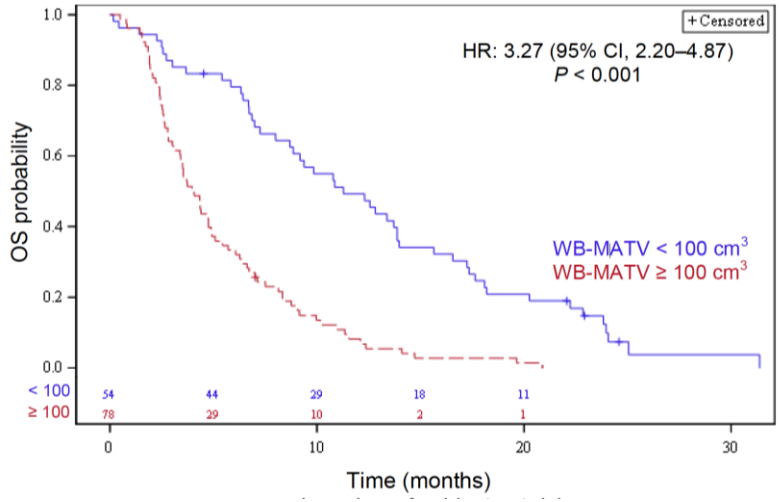


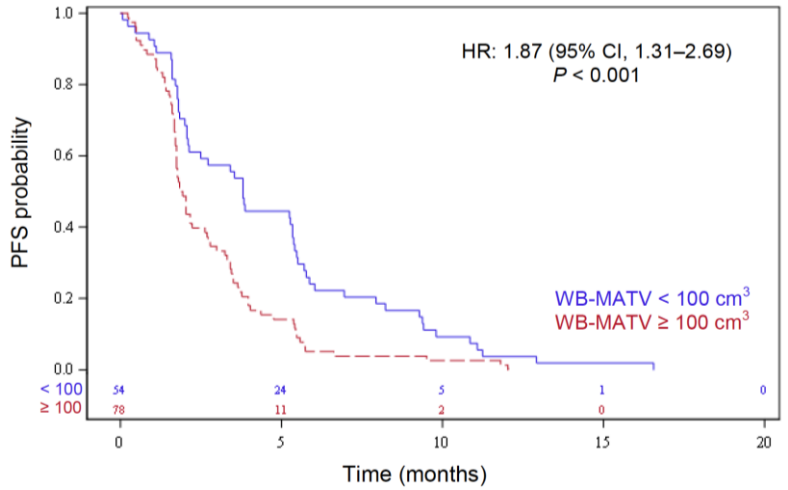
Examples of patients with diffuse large B-cell lymphoma with low baseline MATV (<300 cm^3); patients A and B, and patients with high MATV (>300 cm^3); patients C and D.

Reprinted (or adapted) from Clinical Cancer Research, 2016, 22(15), 3801-9, Cottereau A-S, *et al.* Molecular Profile and FDG-PET/CT Total Metabolic Tumor Volume Improve Risk Classification at Diagnosis for Patients with Diffuse Large B-Cell Lymphoma, with permission from AACR.

ROLE OF METABOLIC IMAGING: PROGNOSIS ASSESSMENT

Metabolically Active Tumour Volume (MATV) at baseline defines prognosis in metastatic chemorefractory colorectal cancer

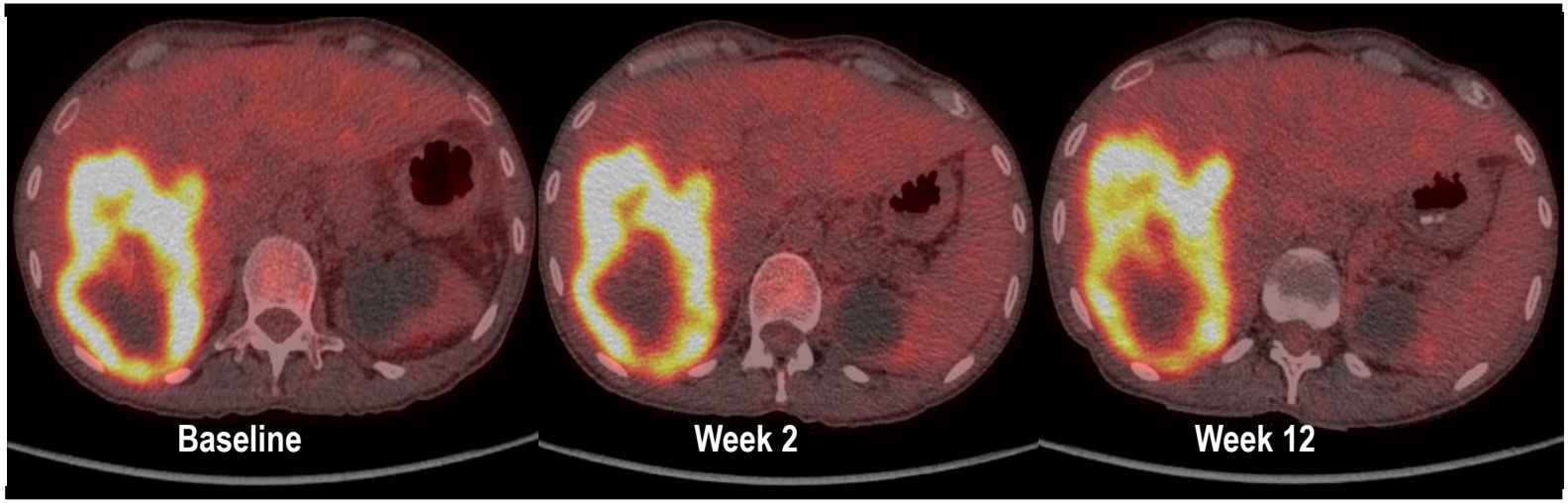




This research was originally published in JNM. Woff E, *et al.* J Nucl Med 2019;60(10):1366-72. © SNMMI. http://jnm.snmjournals.org/content/60/10/1366. .

ROLE OF METABOLIC IMAGING IN RESPONSE PREDICTION

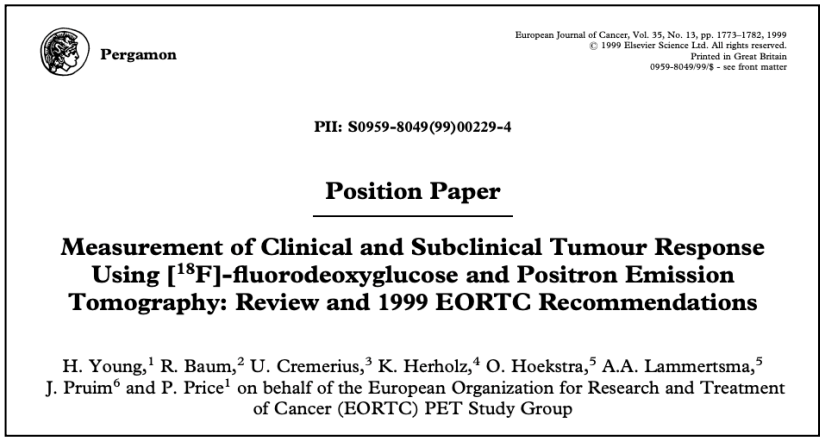
Dynamic information during therapy



1. Tissue metabolic activity is affected in damaged cells before their death leads to changes in tumour size
2. A treatment that does not induce tumoural metabolic changes will probably not lead to a significant tumoural shrinkage

1. Hendlisz A, *et al.* Ann Oncol 2012, 23(7): 1687-1693. 2. Woff E, *et al.* Eur J Nucl Med Mol Imaging 2016

METABOLIC RESPONSE CRITERIA FOR SOLID TUMOURS



Pergamon

European Journal of Cancer, Vol. 35, No. 13, pp. 1773–1782, 1999

Printed in Great Britain
0959-8049/99/$ - see front matter

PII: S0959-8049(99)00229-4

Position Paper

Measurement of Clinical and Subclinical Tumour Response Using [^{18}F]-fluorodeoxyglucose and Positron Emission Tomography: Review and 1999 EORTC Recommendations

H. Young,[1] R. Baum,[2] U. Cremerius,[3] K. Herholz,[4] O. Hoekstra,[5] A.A. Lammertsma,[5] J. Pruim[6] and P. Price[1] on behalf of the European Organization for Research and Treatment of Cancer (EORTC) PET Study Group

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

Richard L. Wahl[1,2], Heather Jacene[1], Yvette Kasamon[2], and Martin A. Lodge[1]

[1]Division of Nuclear Medicine, Department of Radiology, Johns Hopkins University School of Medicine, Baltimore, Maryland; and [2]Department of Oncology, Johns Hopkins University School of Medicine, Baltimore, Maryland

There is a current international standardisation effort leading to improved usability of metabolic imaging response assessment for clinical and research purposes

Young H, *et al.* Eur J Cancer 1999. Wahl RL, *et al.* J Nucl Med 2009.

METABOLIC RESPONSE ASSESSMENT (MRA)

In locally advanced solid tumours – Oesophageal cancer (1/2)

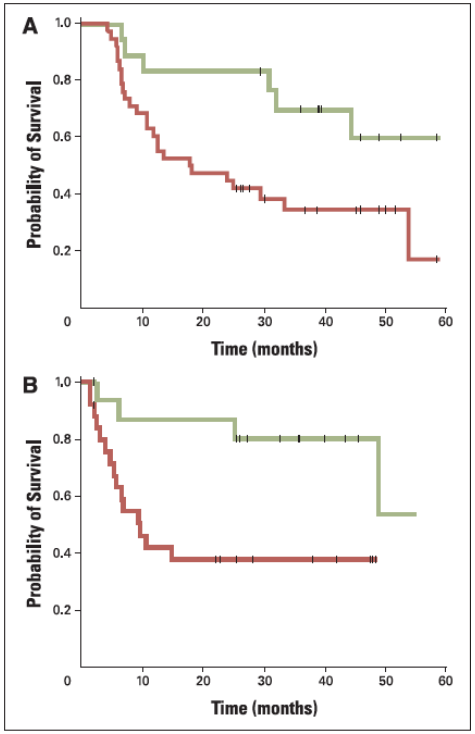


Fig 2. (A) Overall survival (56 patients). Median survival of metabolic responders (18 patients) was not reached; median survival for metabolic nonresponders (38 patients) was 18 months ($P = .01$). (B) Recurrence-free survival after complete tumor resection (41 patients). Median recurrence-free survival for metabolic responders (16 patients) was not reached; median recurrence-free survival for metabolic nonresponders (25 patients) was 10 months ($P = .009$).

Table 3. Accuracy of Early Metabolic Response Evaluation

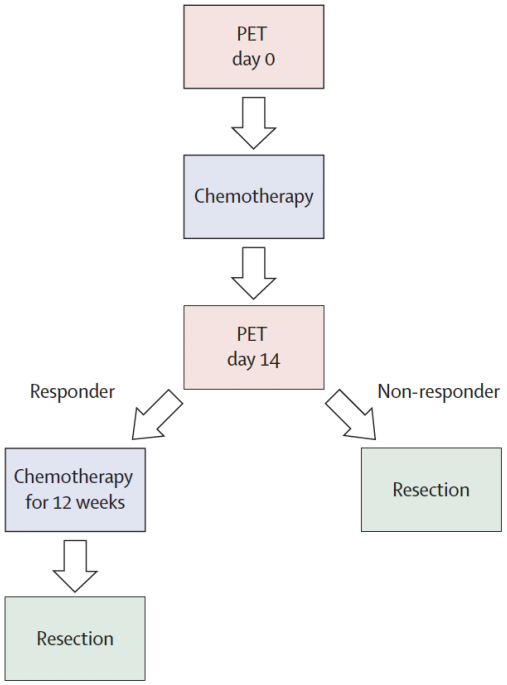
	Histopathologic Response		Clinical Response	
	No.	%	No.	%
Positive predictive value	8/18	44	14/18	78
Sensitivity	8/10	80	14/19	74
Negative predictive value	36/38	95	33/38	87
Specificity	36/46	78	33/37	89
Accuracy	44/56	79	47/56	84

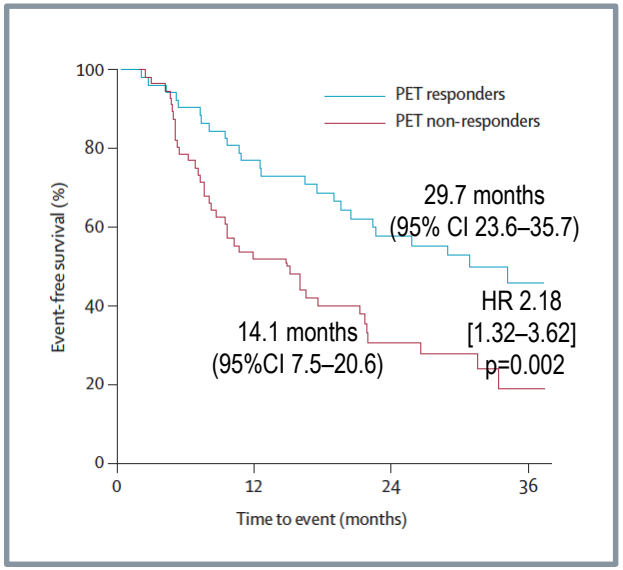
Early (after 1 CT course) FDG-PET/CT-based metabolic response assessment has a high negative predictive value on pathological response

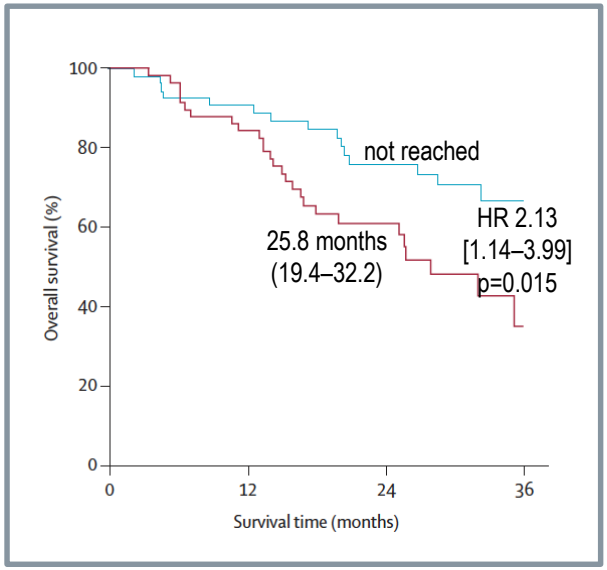
METABOLIC RESPONSE ASSESSMENT (MRA)

In Locally Advanced Solid Tumours – Oesophageal Cancer (2/2)

MUNICON trial





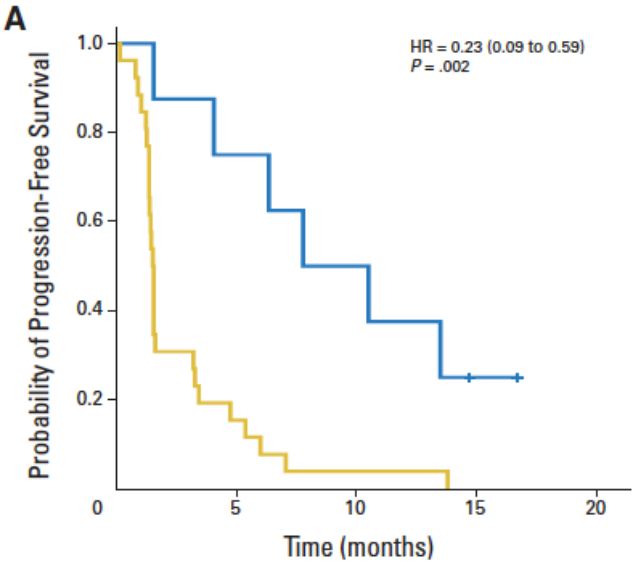


- No histological response in PET non-responders
- Early Assessment of response may induce rapid treatment reorientation (ie stop useless CT and advance curative-intent surgery)

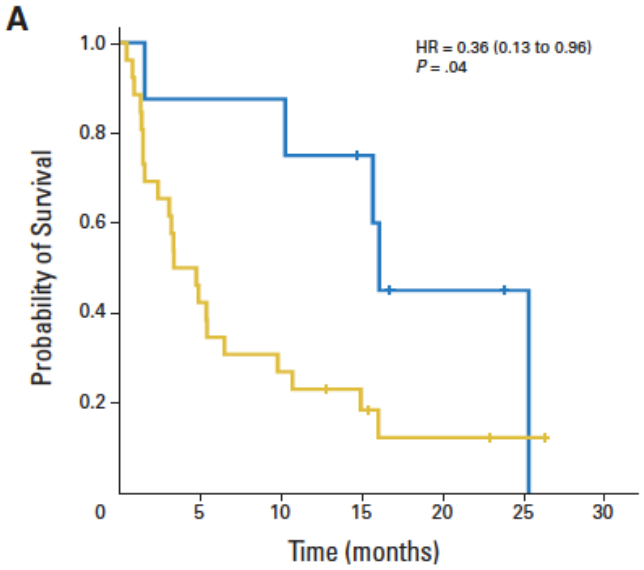
METABOLIC RESPONSE ASSESSMENT (MRA) IN METASTATIC SETTING

FDG-PET metabolic assessment: NSCLC treated with Erlotinib

mPFS according to early (1 week) metabolic response



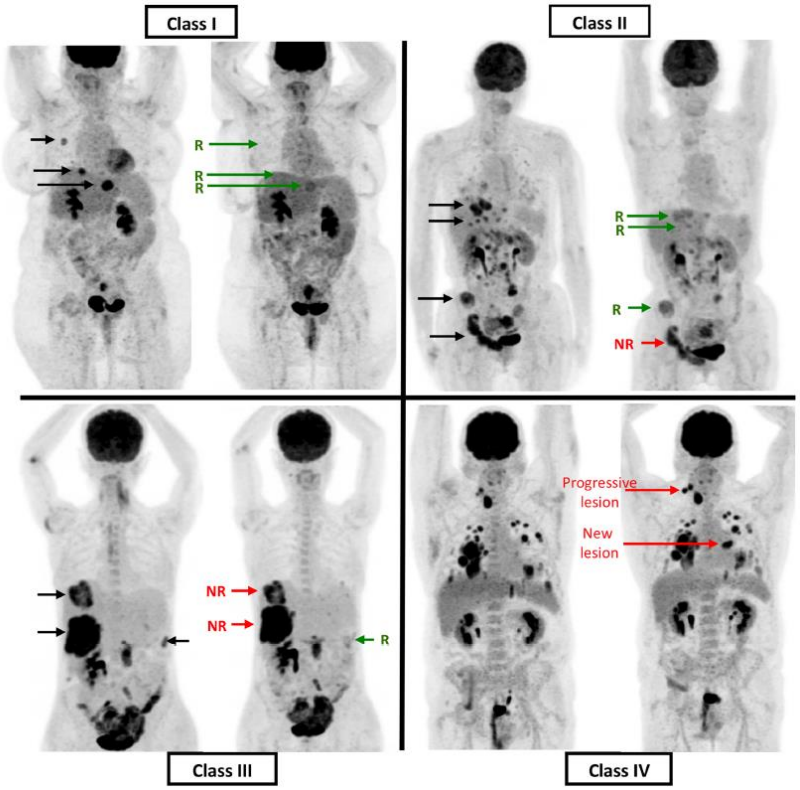
mOS according to early (1 week) metabolic response



Early MRA defines 2 subgroups of patients with significantly different outcomes under treatment

METABOLIC RESPONSE ASSESSMENT (MRA)

In metastatic colorectal cancer



MR Heterogeneity-based classification

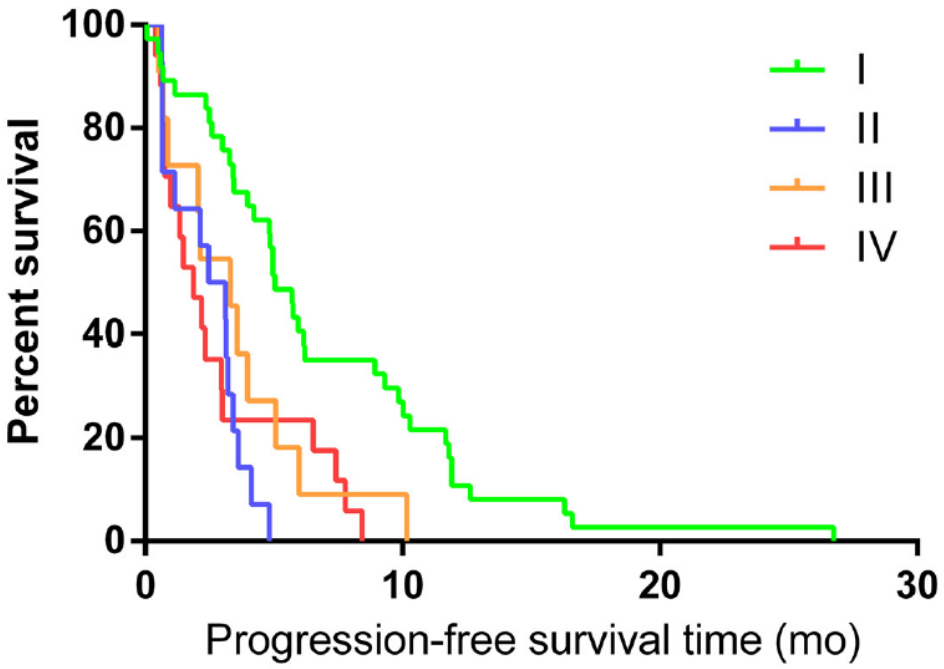
Class I All lesions respond
Class II Most lesions respond
Class III Most lesions do not respond
Class IV No lesion respond, or new or progressive lesion

About 50% of diseases show heterogeneity in response with coexisting responding and non-responding lesions, prompting a descriptive classification

Hendlisz A, *et al.* PLoS One 2015;10(9):e0138341. Available under the terms of the Creative Commons Attribution License https://creativecommons.org/licenses/by/4.0/ . Accessed November 2019. Hendlisz A, *et al.* Ann Oncol 2012.

METABOLIC RESPONSE ASSESSMENT (MRA)

In metastatic colorectal cancer



Patients with homogeneous metabolic response have a significantly improved prognosis as compared with patients with at least one non-responding lesion

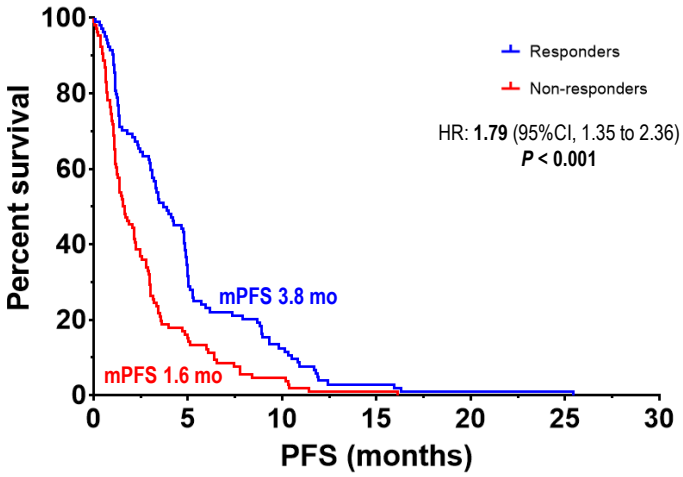
Hendlisz A, *et al.* PLoS One 2015;10(9):e0138341. Available under the terms of the Creative Commons Attribution License https://creativecommons.org/licenses/by/4.0/ . Accessed November 2019. Hendlisz A, *et al* Ann Oncol 2012.

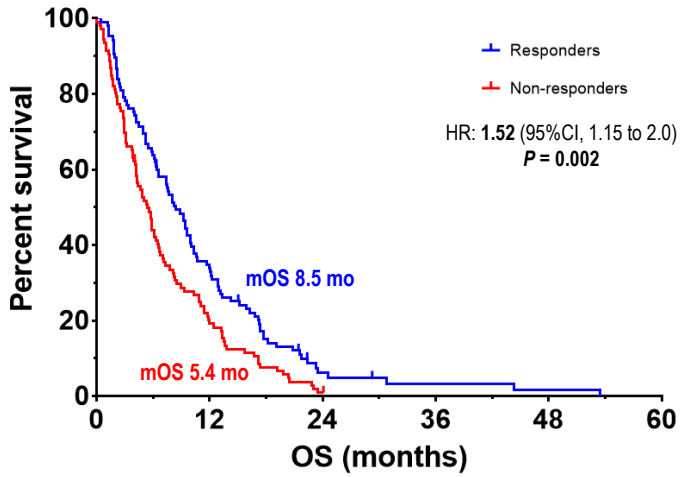
METABOLIC RESPONSE ASSESSMENT (MRA)

In metastatic colorectal cancer

Outcome according to metabolic response (mR) in advanced chemorefractory colorectal cancer

Combined analysis of 2 studies: SoMore (NCT01290926) & RegARd-C (NCT01929616)





Patients with homogeneous metabolic response have a significantly improved prognosis as compared with patients with at least one non-responding lesion

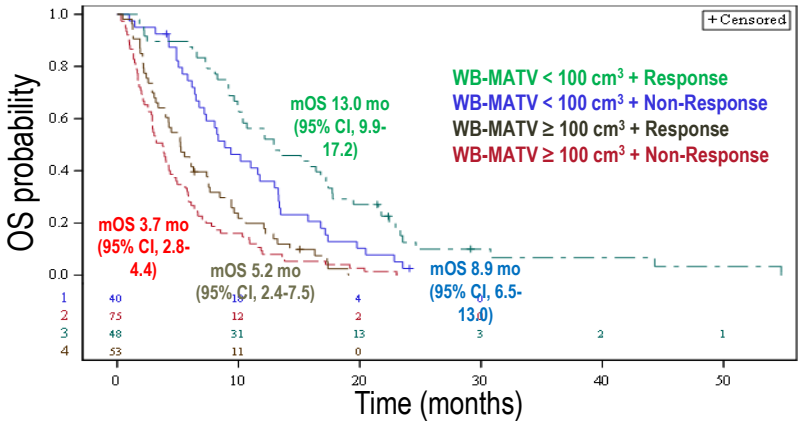
Woff E, *et al.* Eur J Nucl Med Mol Imaging (2019) 46 (Suppl 1): S1–S952. With permission from Professor Patrick Flamen.

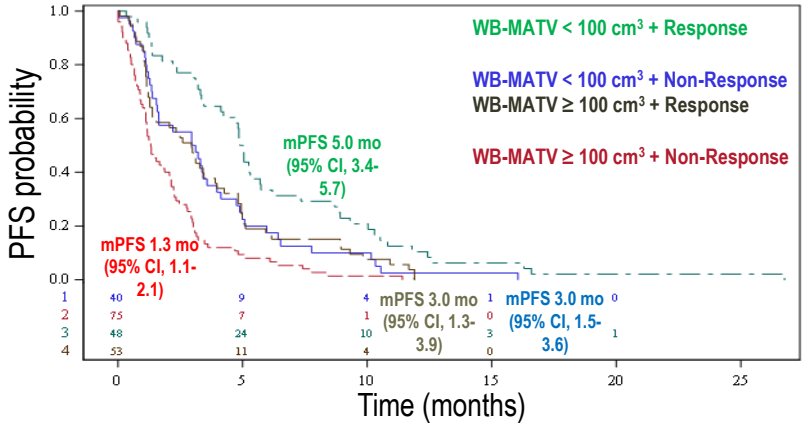
METABOLIC RESPONSE ASSESSMENT

In metastatic setting – metastatic colorectal cancer

Outcome according to metabolic response & baseline MATV

Combined analysis of 2 studies: SoMore (NCT01290926) & RegARd-C (NCT01929616)





Both pre-therapeutic metabolic assessment of tumour burden (MATV)
AND dynamic metabolic assessment of response after 1 treatment course
independently predict the outcome of patients

Woff E, *et al.* Eur J Nucl Med Mol Imaging (2019) 46 (Suppl 1): S1–S952. With permission from Professor Patrick Flamen..

PERSPECTIVES: MOLECULAR RESPONSE ASSESSMENT

In immunotherapy – Granzyme B PET Scan

Several candidates for immuno-imaging biomarkers:

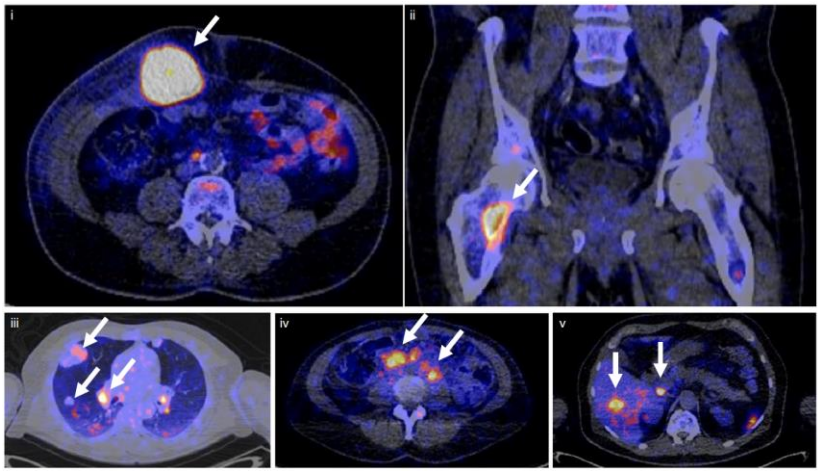
- Granzyme B PET (intratumoural immune activation?)
- Anti-PDL1-PD1 PET (Target of Anti-PDL1-PD1 therapies)
- …

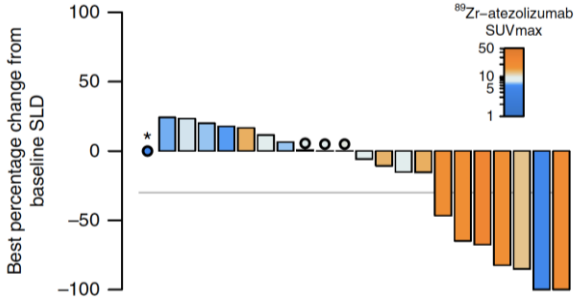
Larimer BM, et al. Clin Cancer Res 2019.

PERSPECTIVES: MOLECULAR DRUG TARGET IMAGING

In immunotherapy – ^{89}Z-atezolizumab PET Scan

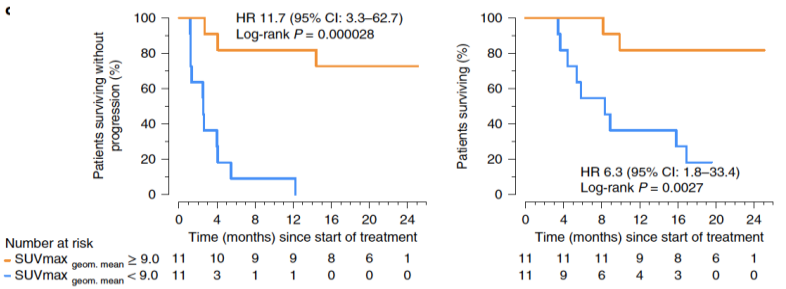
^{89}Z-atezolizumab-PET before atezolizumab therapy



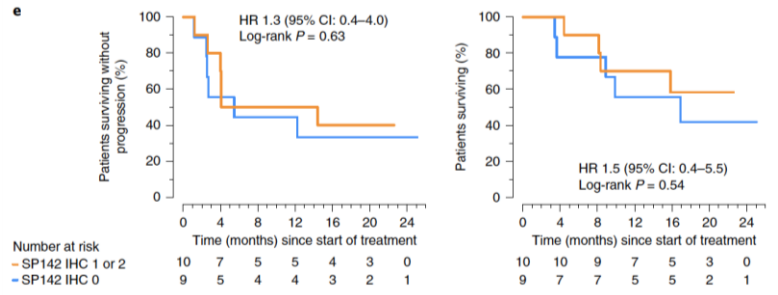


Best RECIST response according to pretherapy ^{89}Z SUV_{max}

mPFS and mOS according to ^{89}Z-atezoPET positivity

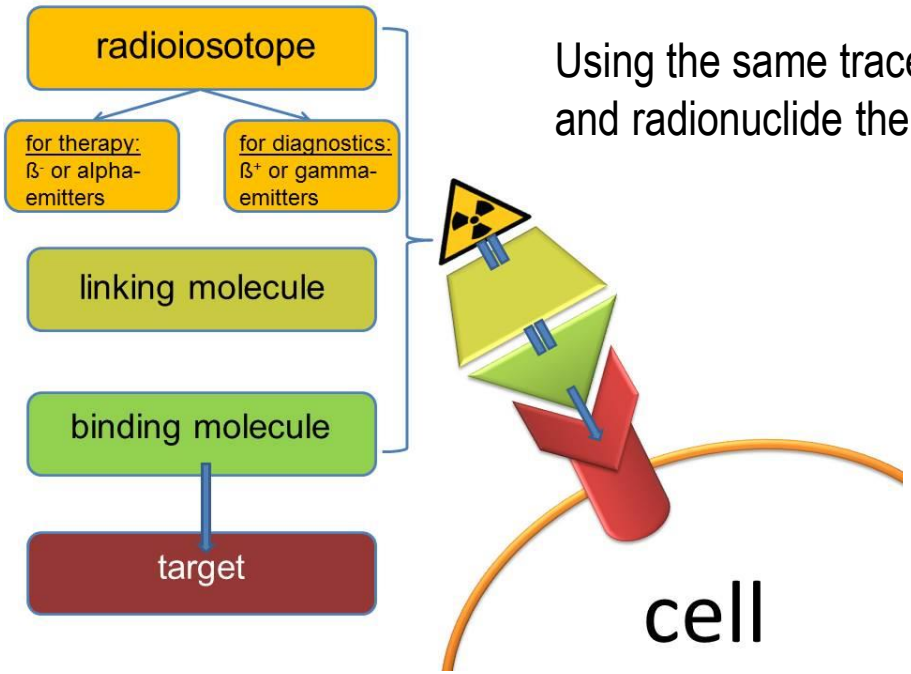


mPFS and mOS according to IHC PD1-PDL1 positivity



Reprinted by permission from Springer Nature: Nature Medicine, [89Zr-atezolizumab imaging as a non-invasive approach to assess clinical response to PD-L1 blockade in cancer. Bensch F, *et al.* COPYRIGHT 2018. Bensch F, *et al.* Nat Med 2019.

PERSPECTIVES: THERANOSTICS IN NUCLEAR MEDICINE



Using the same tracer (vector) for both **Molecular Imaging** and radionuclide therapy (**Molecular Radiotherapy**)

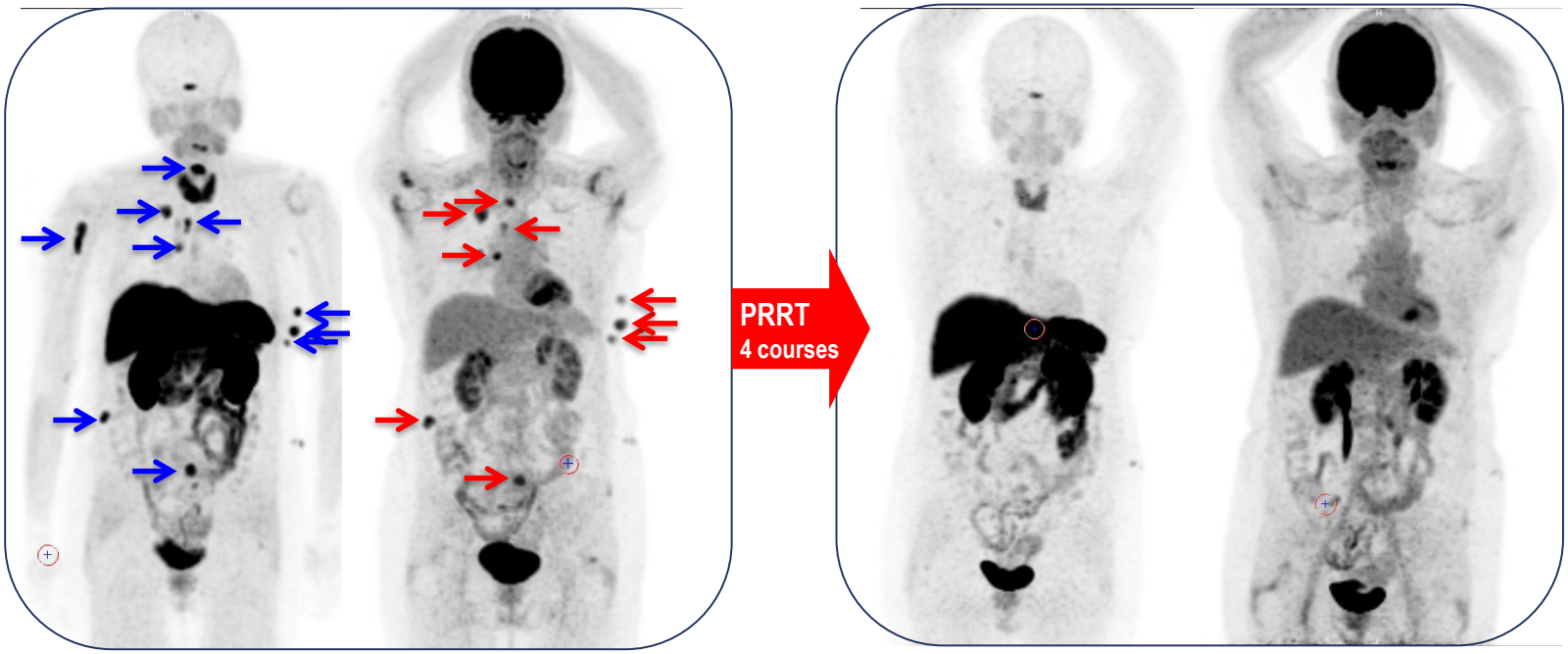
Neuroendocrine tumours
Somatostatine Receptor
Diagnosis: Ga68-DOTA-**octreotate**
Therapy: Lu177-DOTA-**octreotate** **(PRRT)**

Prostate cancer
Prostate Specific Membrane Antigen
Diagnosis: Ga68- **PSMA ligand**
Therapy: Lu177- **PSMA ligand**

PERSPECTIVES: THERANOSTICS

Imaging and treating the same target

Example: PRRT (Peptid Receptor Radionuclide Therapy) for NET's



Baseline Octreo- (left) & FDG- (right) PET/CT
June 2013

Octreo- (left) & FDG- (right) PET/CT post 4 ^{177}Lu-DOTATATE
Sept 2014 (complete remission)

Images Courtesy of Institut Jules Bordet

CONCLUSIONS

Molecular Imaging will deeply impact on management of solid tumours, both as a screening and as a monitoring tool

1. **Screening tool**
   - define disease extension (stage) before curative-intent surgery
   - define disease burden (MATV) as prognostic indicator
   - define disease biology (FDG avidity as a prognostic indicator ie. NET, HCC)
   - define presence of molecular targets (eg. FES-PET), eventually related to theranostics (Octreo-PET, PSMA-PET)

2. **Monitoring tool**
   - assess (FDG-based metabolic response) likelihood to benefit from chemotherapy earlier than RECIST
   - in the near future Molecular Imaging might become able to assess response to immunological agents
     - Granzyme B PET/CT (intratumoural immune activation?)
     - Anti-PDL1-PD1 PET/CT (drug target imaging)

THANK YOU!

DISCLOSURES

- Alain Hendlisz has reported no conflict of interest
- Patrick Flamen has reported no conflict of interest