

Functional imaging in predicting the response to antineoplastic agents

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Anatomic versus Functional Imaging

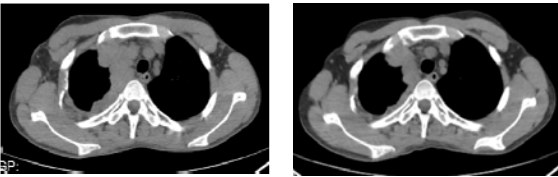
- **Anatomic Imaging**
 - Relies on tumor size, shape, density (i.e. mammography, CT)
 - Measure response by change in size
- **Functional/molecular Imaging**
 - Relies on in vivo tumor biology: perfusion, metabolism, molecular features (i.e.PET, MRI)
 - Measures response by changes in functional/molecular processes

Anatomic Imaging: Limits

- **Macroscopic changes occur with a delay from molecular changes**
- **Macroscopic findings often non-specific (i.e.LN enlargement)**
- **No data about physiology, biological processes or molecular characteristics**

Methods: RECIST 1.1 = "gold standard"

- Eisenhauer EA, Therasse P, Bogaerts J, et al. New Response Evaluation Criteria in Solid Tumors: Revised RECIST Guideline (Version 1.1). Eur J Cancer 2009.



Limitations of RECIST

- line lengths can fail to account for:

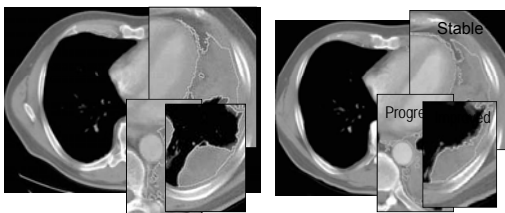
- complex shapes
- changes in non-transaxial extent of disease
- total tumor burden



- assumes uniform contraction or expansion
- inter-rater reliability decreases as disease becomes more complex

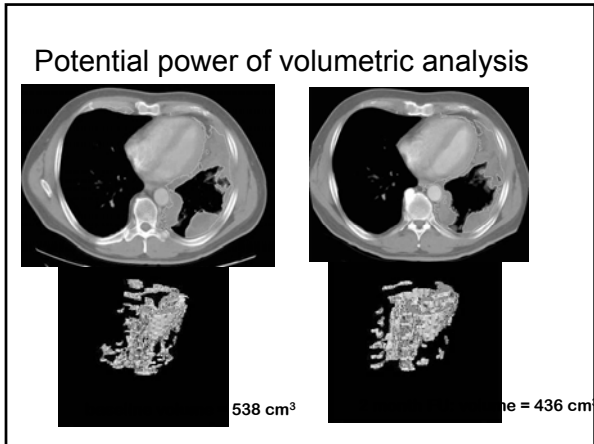
Limitations of RECIST

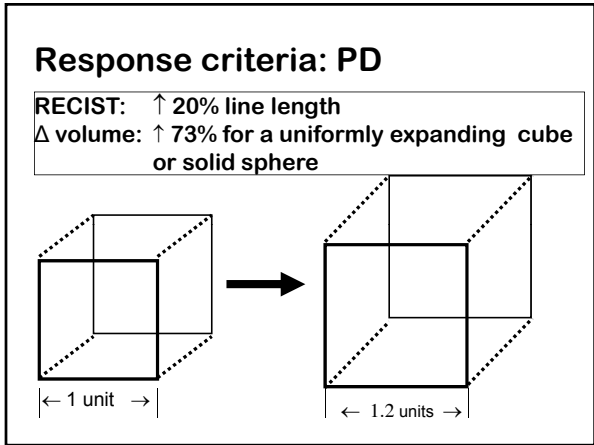
- within subjects variability of response



baseline

after 2 months



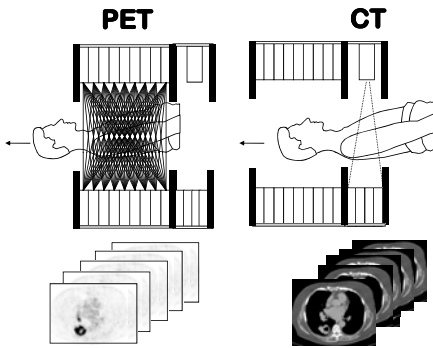


- Functional Imaging Modalities**
- **Magnetic Resonance**
 - Magnetic Resonance Imaging (MRI)
 - Magnetic Resonance Spectroscopy (MRS)
 - **Radionuclide Imaging**
 - Positron Emission Tomography (PET)
 - Single-Photon Emission Computed Tomography (SPECT)
 - **Ultrasound**
 - **Optical Imaging**

Why PET

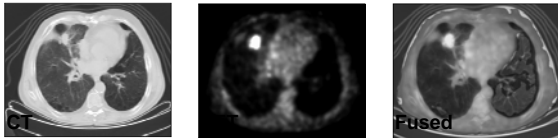
- Improved instrumentation
- Combination of high sensitivity and high spatial resolution
- Exact measure of regional tracer concentration: higher glucose metabolism in tumour cells
- Combination with anatomic detail (PET/CT)

PET/CT System



PET/CT

The PET/CT system produce directly functional PET and anatomical CT data in one session, without moving the patient and with minimal delay between the reconstruction and the fusion of the two images data sets ...



... finally improving the interpretation of PET and CT images

FDG-PET Provides Potential for Early Decisions About Drug Efficacy

- Traditional measures of efficacy may not be appropriate for targeted agents or end points require long trials
 - Tumor shrinkage (RECIST/WHO)
 - Progression-free survival
 - Overall survival
- FDG-PET
 - Decrease in FDG uptake after a few weeks/days predicts response/survival for several cancers
 - Predicts response to some targeted agents

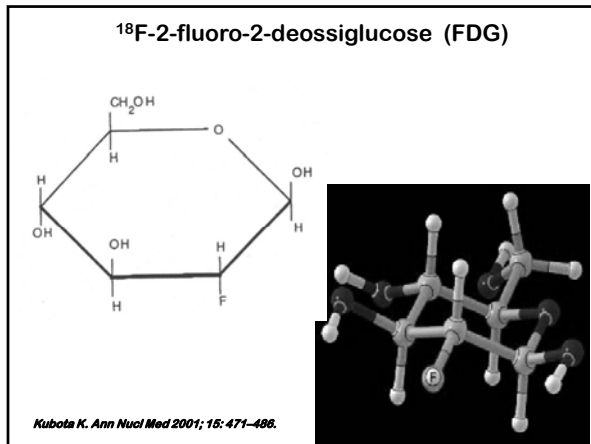
How improve PET

- Better use of existing technology
 - Well-designed clinical studies
 - Appropriate outcome measures
- New probes, new questions
 - Detection – biomarker imaging
 - Assess therapeutic agents
 - Predict aggressiveness and response

Tracers in Oncology

(Radiofarmaceuticals designed to probe specific tumor biology)

- | | |
|-----------------------------|---|
| • Glicidic metabolism | [¹⁸ F]FDG |
| • Pool AA, proteic syntesys | [¹⁸ F]F-DOPA |
| | [¹⁸ F]FET / [¹¹ C]MET |
| • Lipidic metabolism | [¹¹ C o ¹⁸ F]Coline |
| | [¹¹ C o ¹⁸ F]Acetate |
| • Proliferation | [¹⁸ F]FLT |
| | [¹⁸ F]FAZA |
| • Hipoxia | [¹⁸ F]FMISO |
| | [⁶⁴ Cu]ATSM |
| • Apoptosis | [¹⁸ F]Annexin V |
| • Angiogenesis | [¹⁸ F]RGD peptide |



FDG: Semiquantitative Parameters
SUV (standardized uptake value)

$$SUV_{bw} \text{ (g/mL)} = \frac{\text{activity concentration (Bq/mL)}}{\text{injected dose [Bq] / body weight [kg]}}$$

Or SUV adjusted for body surface (cm²/mL), lean mass (g/mL), glycemia at the time of injection...

SUV_{max}
 SUV_{mean}

Glucose metabolism can be also measured using:
 Glucose flux constants → MR_{glu}

PET/SUV a a prognostic factor - The literature

Breast Cancer

- *Avril et al. JNM 2001*: SUV adjusted for partial-volume & glycemia is NOT a good prognostic factor
- *Buck et al EJNMMI 2002*: relationship between SUV & Ki-67
- *Inoue et al. J Cancer Res Clin Oncol 2004*: baseline FDG-PET (SUVmax) before resection is a better prognostic factor in comparison with TNM staging

Cervix Cancer

- *Xue et al. Gynecol Oncol 2006*: in a population of pts who underwent radiotherapy, those with higher SUV had poor prognosis and need a more aggressive treatment

Oesophageal Adenocarcinoma

- *Rizk et al. Ann Thorac Surg 2006*: SUVmax is a good prognostic factor in terms of OS

Soft Tissue Sarcoma

- *Schwarzbach et al. Ann Surg 2005*: preoperative SUVmax is a good prognostic factor in terms of OS and PFS

Role of SUVmax as prognostic and/or predictive factor

Author	Stage	SUV correlation	Cut-Off SUVmax
Ahuja, Cancer 1998	I-IV	OS	10
Vansteenkiste, JCO 1999	I-IIIb	OS	7
Jeong, Nucl Med Comm 2002	I-IV	OS	7
Downey, JCO 2004	pT1-4, N0-2, M0	OS	9
Sasaki, JCO 2005	I,II,IIIa,IIIb	OS	5
Sachs, Clin Lung Cancer 2005	I-IV	Relapse	-
Borst, Eur J Cancer 2005	IIIb, IV	Response, OS	-
Hellwig, EJNMMI 2006	-	Relapses	11
Eschmann, EJNMMI 2006	IIIa, IIIb	Relapse	12

PET & Predictive Value in Locally Advanced Disease

References	Metabolic Response	Sensitivity	Sensibility
Choi NC, 2002	No complete pathologic response → MR _{glu} > 0,130 μmol/min/g Complete pathologic response → MR _{glu} < 0,050 μmol/min/g	86%	81%
Yamamoto Y, 2006	Metabolic response → ΔSUV ≤ 4,5 after therapy	88%	89%
Cerfolio RJ, 2004	Metabolic response → >80% SUVmax reduction after therapy	90%	100%
Pottgen C, 2006	Metabolic response → ΔSUV ≤ 3,3 after therapy	80%	80%
Ryu JS, 2002	Metabolic response → ΔSUV ≤ 3,0 after therapy	88%	67%
Hellwig D, 2004	Metabolic response → ΔSUV ≤ 2,5 after therapy	81%	64%
Cerfolio RJ, 2003	Residual cancer: residual FDG uptake in the primary tumor, Metabolic complete response: no residual FDG uptake in primary tumor	97%	76%

FDG-PET in ONCOLOGY
Treatments changes after performing PET

Tumour	Use of PET	N	Change
Lung	Staging	1867	37%
Colon	Ri- Staging	1387	32%
Colon	Staging	236	36%
Oesophagus	Staging	545	20%
Melanoma	Staging	283	26%
Linfoma	Staging	407	21%
Linfoma	Ri-staging	158	10%
Breast	Staging	111	24%
Breast	Ri-staging	23	40%
Head-Neck	Staging	30	33%

Gambir SS, et al. JNM 2001; 42: 18-93S

FDG-PET: early evaluation of response in patients with advanced NSCLC

- N=57 pts (55 evaluable for response) with stage IIIB and IV NSCLC treated with platinum regimen
- Metabolic response defined as decrease in tumour [¹⁸F]-FDG SUV > 20%
- PR in 20/28 PET responders (71%)
- PD in 26/27 PET non-responders (96%)

Weber et al. J Clin Oncol, 2003

Patients Characteristics

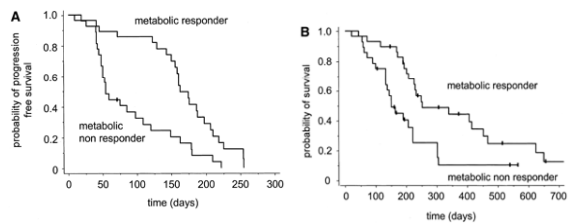
Table 1. Patient Characteristics and Best Overall Response to Chemotherapy

	All Patients (n = 57)		Patients With Dynamic Score (n = 32)	
	No. of Patients	%	No. of Patients	%
Age, years	60 ± 9		59 ± 9	
Sex				
Female	12	21	5	16
Male	45	79	27	84
Tumor stage				
IIIB	9	16	8	25
IV	48	84	24	75
Histopathology				
Adenocarcinoma	31	54	17	53
Squamous cell carcinoma	18	32	10	31
large cell carcinoma	6	11	5	16
Adenosquamous carcinoma	2	4	0	0
Tumor response*	N = 55		N = 32	
Complete response	0	0	0	0
Partial response	21	38	12	38
Stable disease	17	31	12	38
Progressive disease	17	31	8	25

*Two patients died prior to assessment of response.

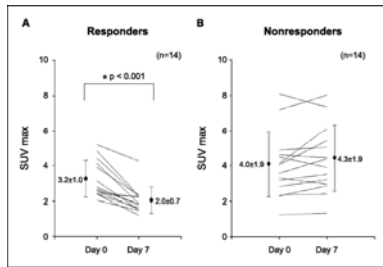
Weber et al. J Clin Oncol, 2003

FDG-PET: early evaluation of response in patients with NSCLC



Weber et al. J Clin Oncol, 2003

Experience with FLT-PET in EGFR-treated patients



FLT-PET response in patients responding to gefitinib after 7 days of therapy

Sohn et al., *Clinical Cancer Research* 14:7423-7429, 2008

Early Prediction of Response to Gefitinib

- 5 pts NSCLC stage IIIB and IV treated with gefitinib 250mg orally/once daily
- Analysis of EGFR mutations in exons 19 & 21
- Response evaluated with RECIST criteria: baseline CT within 14 days prior to the treatment and every 4 wks, then every 8 wks after 4 months
- FDG-PET within 14 days prior to the treatment and on day 2 and at 4 wks

Sunaga N et al, *Lung Cancer* 2008

Patients Characteristics

Table 1 Patient characteristics

Patient no.	Age	Gender	Smoking status ^a	Histology	Stage	EGFR mutation	CT response	PFS (m)	OS (m)
1	56	F	0	Ad	IIIB	delE746-A750	PR	14.9	19.7
2	56	F	35	Ad	IV	delL747-P753	PR	4.5	6.3
3	80	F	0	Ad	IIIB	L858R	SD	12.9	16.9
4	59	F	0	Ad	IV	L858R	SD	12.5	21.0
5	78	F	40	Sq	IV	None	PD	ND	2.7

F, Female; Ad, adenocarcinoma; Sq, squamous cell carcinoma; PFS, progression-free survival; OS, overall survival; ND, not determined.

^a Back years.

^b EGFR mutations in exon 19 or 21.

^c CT response was evaluated according to the RECIST criteria.

^d Patients 2-4 had died while Patients 1 and 5 were alive at the data cutoff point (end of March 2007).

• After 4 wks pts with SD or PR experienced a further decrease in SUVmax

• Patients with SD had a longer PFS

• Correlation between TC and PET response, but detected earlier with PET

Table 2 Changes in FDG uptake in target lesions before and after gefitinib treatment

Patient no.	Target lesion	%SUVmax (%)		
		Before	2 days	4 weeks
1	Primary	5.18	2.45(48)	1.23(24)
2a	Primary	9.59	8.39(87)	2.74(29)
2b	Adrenal	9.64	5.79(60)	1.51(15)
2c	Bone	9.50	4.61(49)	1.70(18)
3a	Primary	3.22	1.87(58)	1.62(50)
3b	Spine	3.16	1.92(61)	1.07(33)
4a	Primary	5.13	2.42(47)	1.45(28)
4b	Bone ¹	3.77	4.33(79)	3.19(55)
4c	Spine ²	4.49	3.71(81)	2.81(64)
5a	Primary	3.77	6.68(177)	7.31(194)
5b	lymph ¹	3.24	4.63(142)	10.27(317)
5c	lymph ²	3.99	7.69(191)	10.41(264)

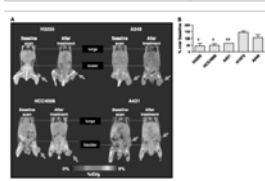
¹ SUVmax¹ was defined as the ratio of the SUV max level at 2 days or 4 weeks after treatment to the level before treatment.

² If SUV uptake was not detected, the value of SUVmax was determined as 1 m.

Sunaga N et al, *Lung Cancer* 2008

Monitoring tumor glucose utilization by PET to predict response to EGFRis

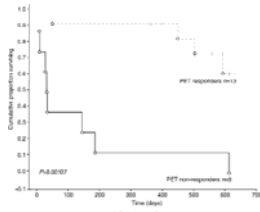
- In gefitinib-sensitive cell lines, there was a dramatic decrease in FDG uptake 2 hours after treatment
- Micro PET studies showed an up to 55% decrease of tumor FDG uptake in sensitive xenografts within 48 hours
- Gefitinib-resistant cells exhibited no measurable changes in FDG uptake, either in cell culture or in vivo



Su et al, Clin Cancer Res 2006

Predictive Role of PET in GIST

- 18F-FDG PET is superior to CT in predicting early response to therapy



Gayed J Nucl Med 2004, Stroobants EJC 2003

Predictive Role of PET in NHL & HL

- Higher levels of SUV are typically observed in more aggressive NHL compared to lower grade NHL
- Detection of an especially FDG-avid lesion in the setting of documented low-grade NHL should raise the possibility of histological transformation to a higher grade lymphoma
- The prognostic significance of early PET response can identify patients at higher risk of treatment failure
- Both early and late PET responses correlated well with event-free survival and overall survival

MacManus Cancer Imaging 2007

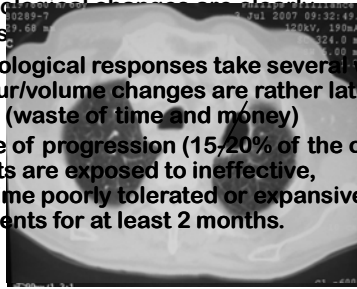
Pilot Study of Early Repeated 18F-FDG PET During Cycle 1 Predicts Objective Response to Chemotherapy in Advanced Non-Small Cell Lung Cancer

U. Ricardi*, S. Novello, E. Pelosi**, M. Gaj Levrà, G. Selvaggi, M. Longo, E. Cappelletto, B. Crida, SG Rapetti, GV Scagliotti

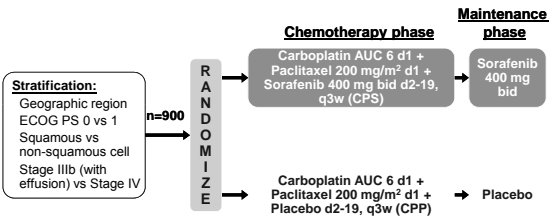
University of Turin, Thoracic Oncology Unit, *Division of Radiation Oncology & **IRMET Nuclear Medicine Service, Turin - Italy

Rationale of the study

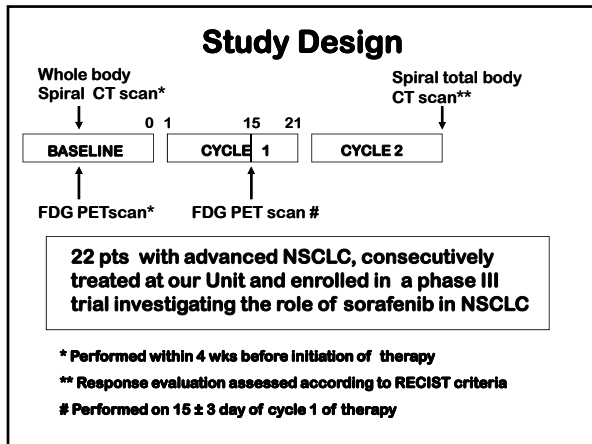
- For molecular targeted therapies tumor response criteria based only on morphological changes are unsatisfactory
- Morphological responses take several weeks to occur/volume changes are rather late events (waste of time and money)
- In case of progression (15-20% of the cases) patients are exposed to ineffective, sometime poorly tolerated or expansive treatments for at least 2 months.



Design of Clinical Study



Scagliotti GV et al. Proc. ESMO/IASLC 2008



Patients' Characteristics

Median Age (range)	62 (45 – 70)
Males	18 (81.8 %)
ECOG PS 0,1	16 (73%), 6 (27%)
Never Smokers	1 (4.5%)
Adenocarcinoma	10 (46%)
Squamous Cell	4 (18%)
Large Cell	2 (9%)
NSCLC, NOS	6 (27%)
Stage IV (no brain mts)	20 (91%)
Stage IIIB (1 wet, 1 supracl. LN)	2 (9%)

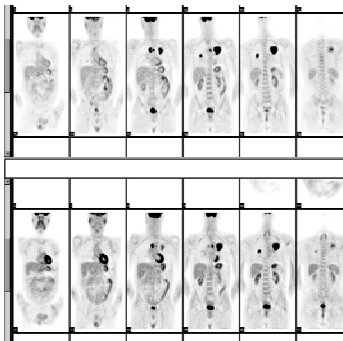
- ### PET/CT Protocol
- All patients signed a dedicated informed consent to participate in the study
 - At the time of tracer injection all patients had glucose blood level under 160 mg/dl
 - Whole scan was acquired 60 minutes after i.v. injection of FDG (dose range 222-370 MBq)
 - CT scan (voltage 140 kV, tube current 60 mA/s) from proximal femur to the base of skull
 - At the end of CT scan, bed position was moved to PET field of view (FOV)
 - PET data acquired in 3D mode from pelvis to neck
 - FOV: 50 cm, image matrix size: 128x128. All viewing co-registered images performed with a dedicated software (Advantage 4.2, GE Healthcare, Chalfont St. Giles, UK)
 - $SUV = \text{activity (MBq/ml)} \times \text{body weight (g)} / \text{injected dose (MBq)}$

Response Criteria with PET

- **Progressive Metabolic Disease** : increase in [¹⁸F]-FDG tumor SUV > 25% within the tumor region defined at baseline, visible increase in the extent of tumor uptake (>20% in the longest dimension) or appearance of "new uptake"
- **Stable Metabolic Disease** : increase in tumor [¹⁸F]-FDG SUV < 25% or a decrease < 15% and no visible increase in extent of tumor uptake (>20% in the longest dimension)
- **Partial Metabolic Response**: reduction of a minimum of 15-25% in tumor [¹⁸F]-FDG SUV after one cycle of chemotherapy and > 25% after more than one treatment cycle. Reduction in the extent of tumor uptake is not a requirement for partial response.
- **Complete Metabolic Response**: complete resolution of uptake within tumor volume becoming indistinguishable from surrounding normal tissue

Young H et al. , EJC 1999

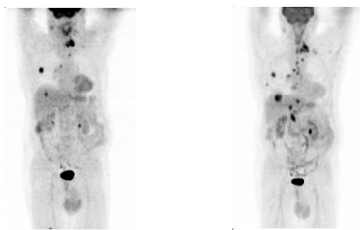
Stable Disease with FDG-PET



Baseline
PET

Repeated
PET

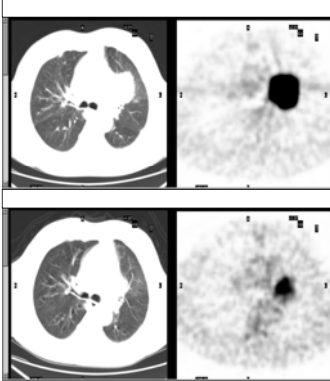
Progressive Disease at the FDG-PET



Baseline PET

Repeated PET

Partial Response at the FDG-PET



Baseline
PET

Repeated
PET

Agreement Between Metabolic and Morphological Tumor Response

Patient ID	TC Overall Response*	PET Early Response
04	PR	PR
06	SD	SD
08	SD	SD
09	SD	SD
13	PR	PR
14	PR	PR
16	PR	PR
17	SD	SD
18	PR	PR
19	PR	PR
20	SD	SD
22	SD	SD

* Best response at TC achieved after 2 cycles of therapy in all patients

Disagreement Between Metabolic and Morphological Tumor Response

Patient ID	TC Overall Response*	PET Early Response
01	PD	PR
02	PD	PR
03	SD	PD
05	PR	SD
07	SD	PD
10	SD	PR
11	SD	PR
12	PD	SD
15	SD	PR
21	**	SD

* Best response at TC achieved after 2 cycles of therapy in all patients

** One patient died because of heart attack after the first cycle

Correlation of FDG-PET and CT Response

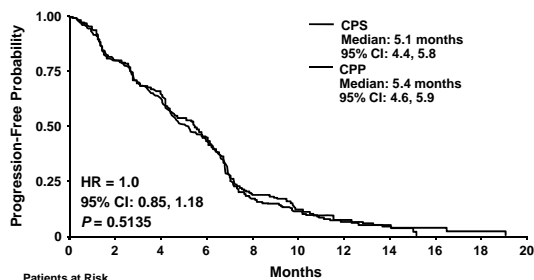
- Patients were dichotomized between responders and non-responders based on the overall assessment of FDG-PET changes in all visible lesions as evaluated in baseline FDG-PET and repeated FDG-PET.
- Morphological changes detected at spiral CT scans performed at the end of cycle 2 were compared with early FDG-PET changes.
- Fisher's exact Test

Results

	CT Responders	CT non Responders	Mean ΔSUV (range)
PET responders	55% (6/11)	45% (5/11)	-40% (-9,9 / -72,5)
PET non responders	10% (1/10)	90% (9/10)	-9% (-65.5 / +17,3)

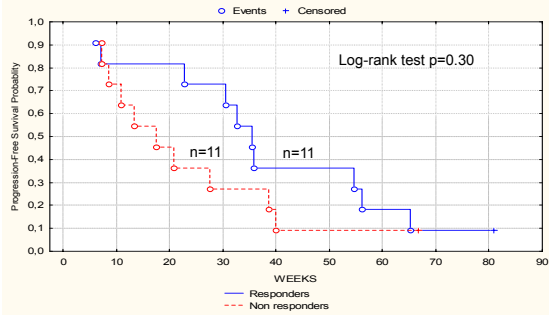
Fisher exact test, p=0.04

ESCAPE Progression-Free Survival (Intent-to-Treat Population)

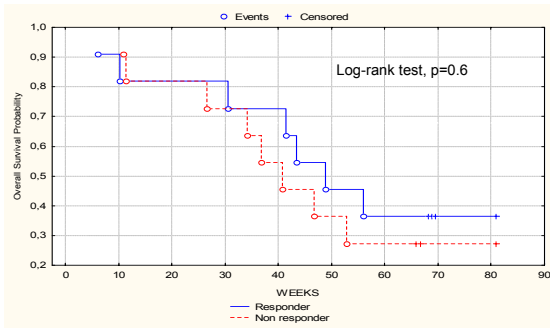


Scagliotti GV et al. Proc. ESMO/IASLC 2008

K-M Progression-Free Survival Curves According to PET Response



K-M Overall Survival Curves According to PET Response



SUV Values and Survival Outcomes in the Control Arm

Patient ID	SUV_baseline	ΔSUV (%)	PFS (week)	OS (week)
1	12,7	50,4	7,1	10,3
3	14,3	6,3	8,6	40,7
6	12	0,0	40,0	80,9
7	9,8	-17,3	17,4	36,9
8	9,2	0,0	7,3	26,6
9	3,3	0,0	66,7	66,7
10	30	40,0	22,7	48,9
11	11,1	9,9	56,1	69,6
15	9	46,7	30,6	30,6
16	7,5	24,0	32,7	56,0
17	10,1	-13,9	13,4	34,1
20	16,5	9,1	27,6	52,9
22	33,3	29,4	20,9	65,9

Median ΔSUV (%) 14,2 ± 22,08

MRI and Neoangiogenesis

• **The ability in detection of vasculature profile is due to the contrast:**

MRI contrast can be divided in:

- MW → low molecular weight agents <1 kDa → quick distribution in extracellular fluid (DCE technique). Validated in pre-clinical studies as appropriate biomarker for monitoring the effect of anti-angiogenetic drugs

- IMW (10-30 kDa) → intermediate → prolonged intravascular retention

- MMCM (>30kDa) → macromolecular → measurement of tumour macromolecular hyperpermeability

• Tumor angiogenesis can also be analysed using intrinsic susceptibility weighted or blood oxygenation level dependent (**BOLD**)

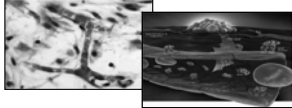
Padhani AR, The British Journal of Radiology, 2003

Which is the correct timing of DCE-MRI?

Most of available data come from experimental xenograft data (phase I), which have tested DCE-MRI at different timing (*Galbraith SM, J Clin Oncol, 2003*)



Changes in microvessel permeability can occur as early as 90min after dose (*Pham CD, Cancer Invest, 1998*)



Early response could be evaluate immediately after the first dose of anti-VEGF drugs



We need good pre-clinical data to found the correct timing to perform DCE-MRI in humans

Willet CG, Nat Med, 2004

The use of perfusion weighted imagine (PWI) to evaluate the response to anti-angiogenetic therapy in patients (pts) with non small cell lung cancer (NSCLC) and brain metastases (mts).

S Novello, M Longo, M Giaj Levra, D Sardo*, E Capelletto, S Rapetti, B Crida, C Fava*, GV Scagliotti, L Rizzo*

University of Turin, Thoracic Oncology Unit, *Division of Radiology, Turin - Italy

Background

- Brain is one of the commonest metastatic site in NSCLC. Few data are available from clinical trials because of the fact that in the majority of the cases pts with cerebral mts are excluded.
- SU011248 (Sunitinib) is a multiple TKI inhibitor which activity has been demonstrated in solid tumours.
- Magnetic Resonance Imagine (MRI) has an higher accuracy in the study of brain mts in comparison with brain CT scan, permitting also the assessment of angiogenesis process through perfusional detection.

Aim of the Study

- The aim of this pivotal trial is the evaluation of perfusion MRI as a potential imaging marker of efficacy in pts with NSCLC and brain mts, treated with an anti-angiogenic drug.

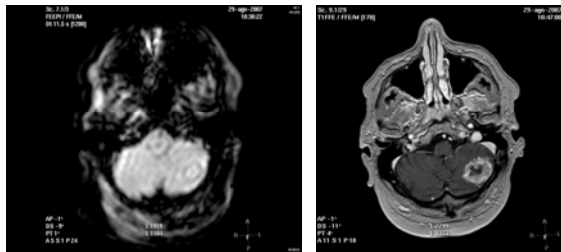
Patients and Methods

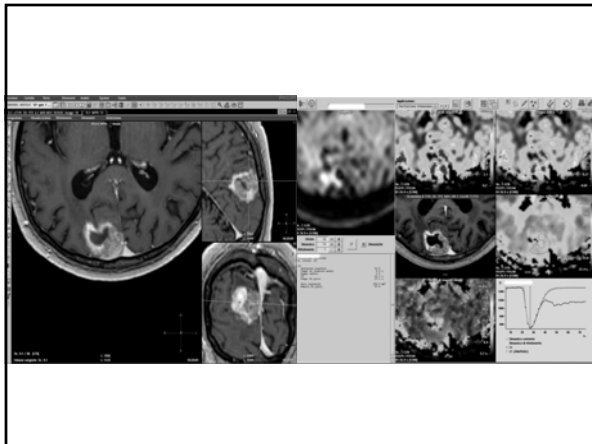
- From June to November 2007, seven pts with NSCLC and brain mts, previously treated with whole brain radiation therapy (WBRT) and 1 prior platinum based chemotherapy, were sequentially studied within a clinical trial evaluating the efficacy profile of SUO 11248 (37,5 mg/daily in 28 days cycle).
- These pts underwent a cerebral perfusion MRI after WBRT, before starting treatment, every 28 days for the first 2 cycles and every 56 days thereafter.
- The total number of MRI evaluations ranges, for each pts, from a minimal of 3 to a maximum of 4.
- We made a morphological and perfusional evaluation for every lesion of each pts, until radiological and/or clinical progression (according to RECIST criteria), from a minimal surface of 9 pixel to maximum neo-angiogenesis.

MRI Technique

- Hyperconductive magnet working at 1,5 Tesla-Philips Achieva.
- Paramagnetic contrast material: Gadobutrol, 2 injection (pre-bolus 0,05 ml/kg-next bolus 0,15 ml/kg).
- Reading software of PWI by View Forum Extended MR workspace.

MR-PWI : Perfusion Weighted Imaging



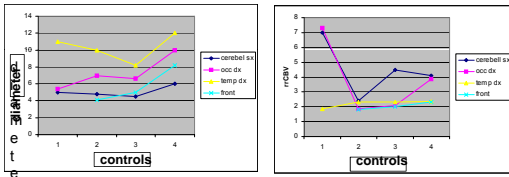


Results

	Studied lesions (N)	Sincronous PD ¹	Previous PD ²
Case 1	21	7/21	14/21
Case 2	3	0/3	3/3
Case 3	4	2/4	2/4
Case 4	2	0/2	2/2
Case 5	2	0/2	2/2
Case 6	3	2/3	1/3
Case 7	6	3/6	3/6
Total	41	14/41	27/41

1- Clinical/radiological PD concomitant with PWI changes,
 2- PWI changes prior to clinical-radiological changes

Case n 7



Comparison between change of dimensional and perfusional response to anti-angiogenic drugs

Conclusions

- We noticed that changes of angiogenesis (measured with PWI) precede the clinical or radiological progression in more than 50% of described brain lesions
- These very preliminary data suggest that perfusion value MRI could be a valid method for the evaluation of brain mts, anticipating progression of the disease, in pts treated with Antiangiogenic Drug

Conclusions

- A wide variety of functional imaging techniques are currently under active investigation.
- These will help to characterize biomarkers of disease and new endpoints for assessment of tumor response.
- Prospective trials are strongly needed to confirm this potentiality.
