Il ruolo dell'imaging molecolare nell'era della immunoterapia

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Issues

- Needs and priorities
- Current guidelines
- Literature evidences
- Potential reccomendations
- The future is……

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Needs

- Is there any response to immunotherapy?
- How can differentiate between pseudoprogression and hyperprogression?
- May I predict the response to immunotherapy, by selecting appropriate patients?
- May I anticipate the development of immune related side effects?

Priorities

- Selection of patients who may benefit from immunotherapy
- An early prediction of response to immunotherapy (indirect on costs)
- Data about follow-up after stopping immunotherapy
- Standardization of the criteria interpretation

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Current guidelines – ESMO and AIOM

Lung cancer

- No specific recommendation are present
- Probably RECIST 1.1. is recommended

Tumour burden: devalues the importance of each target lesion in favour of the whole 'quantity' of disease.

Confirmation: any response, other than stable disease, requires to be confirmed by a consecutive assessment at least 4 weeks after first documentation.

New lesions: do not necessarily represent a PD. They must be included into the whole tumour burden and their significance is subordinate to the following confirmation.

No data about FDG PET/CT

Melanoma

- For the evaluation of response to Ipilimumab, the IrRC (immune-related response criteria) are suggested.

	irRC
New, measurable lesions (i.e., ≥5 × 5 mm)	Incorporated into tumor burden
New, nonmeasurable lesions (i.e., <5 × 5 mm)	Do not define progression (but preclude irCR)
Non-index lesions	Contribute to defining irCR (complete disappearance required)
CR	Disappearance of all lesions in two consecutive observations not less than 4 wk apart
PR	≥50% decrease in tumor burden compared with baseline in two observations at least 4 wk apart
SD	50% decrease in tumor burden compared with baseline cannot be established nor 25% increase compared with nadir
PD	At least 25% increase in tumor burden compared with nadir (at any single time point) in two consecutive observations at least 4 wk apart

Issues

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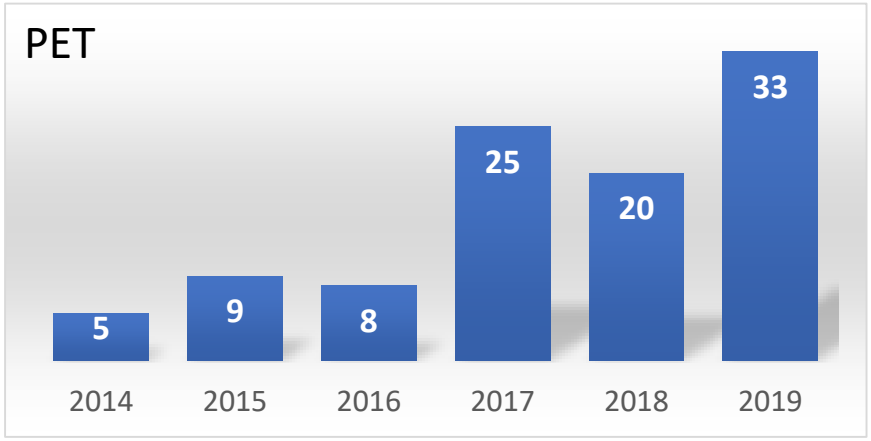
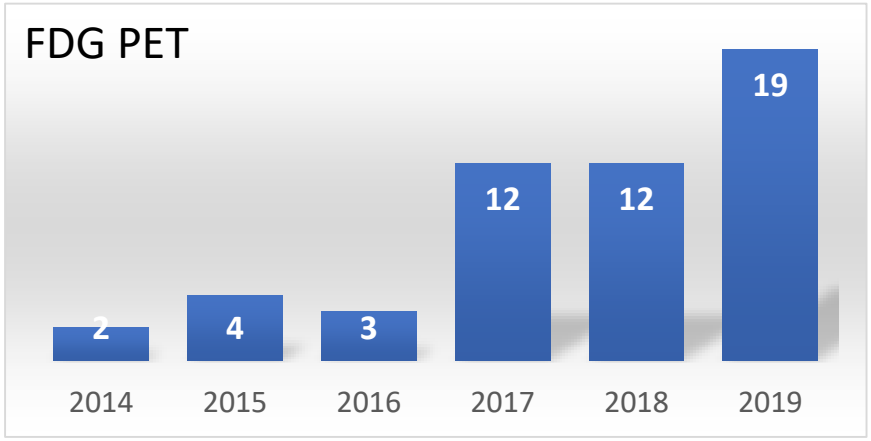
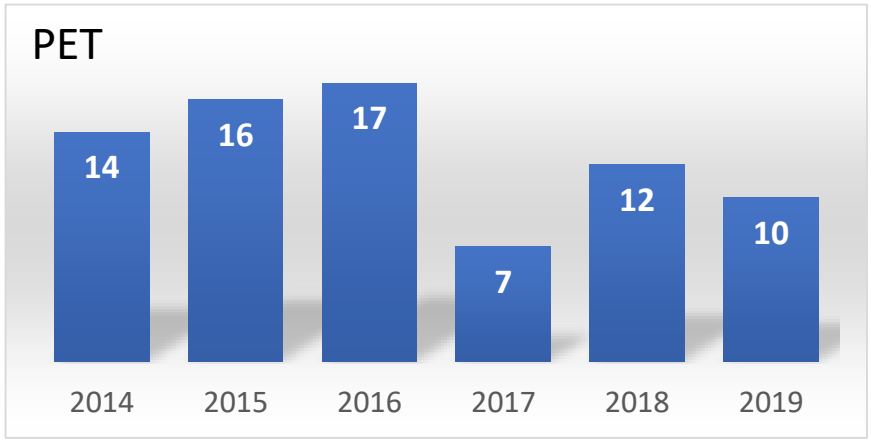
Pubmed evidences

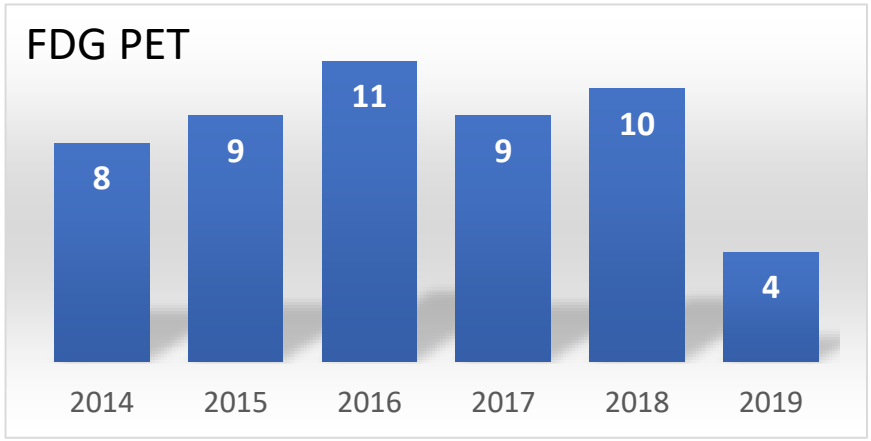
Immunotherapy and melanoma





Immunotherapy and lung cancer





Summary of evidences - Melanoma

Author (year)	Study design	N of pts	Treatment	Results
Sachpekidis et al (2015)	Prospective	22	Ipilimumab	Early response to ICIs
Kong et al (2016)	Prospective	27	20 pembrolizumab 7 nivolumab	Residual disease at CT but + at PET (43%)
Breki et al (2016)	Prospective	31	Ipilimumab	Reclassification after PERCIST analysis
Cho et al (2017)	Prospective	20	16 Ipilimumab 1 nivolumab 3 BMS-936559	RECIST 1.1 and PERCIST give a 100% PPV for the response
Annor et al (2018)	Prospective	41	Ipilimumab	A specific cut-off for FDG uptake was defined for the evaluation of response to therapy
Sachpekidis et al (2018)	Prospective	41	Ipilimumab	PERCIMT is a more sensitive predictor of response to therapy
Sachpekidis et al (2019)	Prospective	41	Ipilimumab	Spleen and sarcoid-like lymphadenopathy are weakly correlated with the response to ICIs
Sanli et al (2019)	Retrospective	34	Ipilimumab	Tumor heterogeneity is associated with a poor response to ICIs
Saben et al (2019)	Retrospective	55	Ipilimumab	Low tumor burden (by metabolic analysis) correlates with a better prognosis
Ito et al (2019)	Retrospective	142	Ipilimumab	wMTV is a predictor of response and OS to ICIs
Ito et al (2019)	Retrospective	60	Ipilimumab	PERCIST criteria are correlated with OS

Summary of evidences – Lung cancer

Author (year)	Study design	N of pts	Treatment	Results
Kaira et al (2018)	Prospective	24	Nivolumab	TLG is able to predict the response to ICIs
Grizzi et al (2018)	Prospective	27	23 Nivolumab 4 Pembrolizumab	SUVmax < 17.1 is associated with a fast progression during ICIs therapy
FIR trial (2018)	Prospective	114	Nivolumab	PET/CT is able to early predict the response to ICIs (particularly in patients with a PD at CT)
Evangelista et al (2019)	Retrospective	32	Nivolumab	Whole semiquantitative analysis area associated with a poor response to therapy
Humbert et al (2019)	Prospective	62	Pembrolizumab Nivolumab	Serial FDG PET can identify patients with a potential response to ICIs and that should be continously treated with ICIs
Goldfarb et al (2019)	Prospective	28	Nivolumab	New criteria for the evaluation of response to ICIs (iPERCIST)
Castello et al (2020)	Prospective	35	Pembrolizumab Nivolumab	FDG PET (MTV and TLG) and high CTC have a prognostic impact on the response to ICIs
Polverari et al (2020)	Retrospective	57	Nivolumab	FDG PET can have an important prognostic role in prediction of response to ICIs

Literature evidences – FDG PET

The prediction of response to immunotherapy → Is it possible to predict who will respond to ICIs and the OS?

Early evaluation of response to immunotherapy →

- Interpretation
- Timing
- Standardization

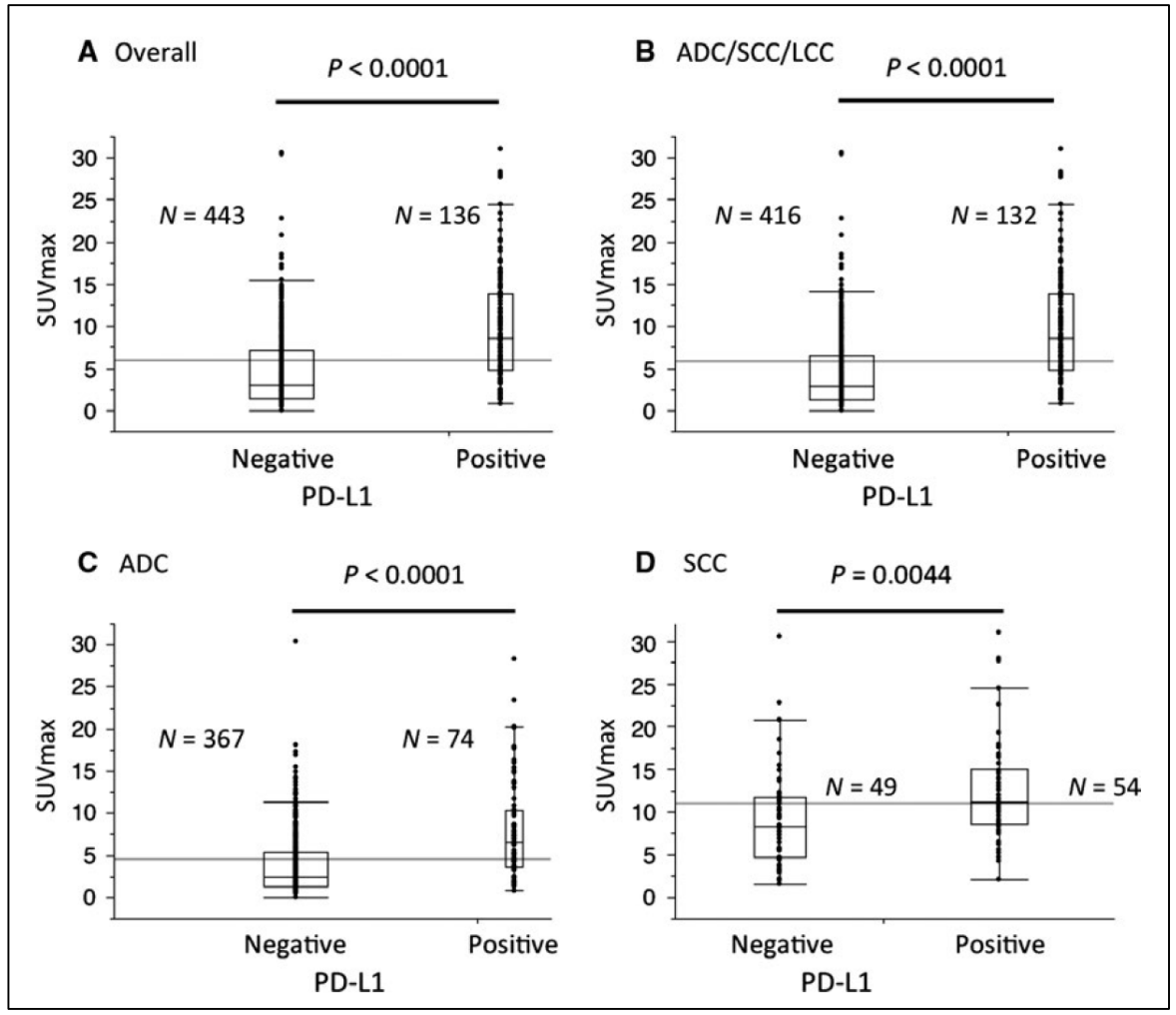
Literature evidences – FDG PET

The prediction of response to immunotherapy

Is it possible to predict who will respond to ICIs and the OS?

PD-L1 expression and FDG PET

Semiquantitative features



Histology	*N*	SUVmax according to PD-L1 expression, mean value (range)		
		Negative	Positive	*P* value
Overall[1]	579	4.69 (0–30.6)	9.89 (0.8–31.05)	<0.0001
ADC	441	3.84 (0–30.4)	7.81 (0.8–28.3)	<0.0001
SCC	103	9.18 (1.5–30.6)	12.60 (2.1–31.05)	0.0044
LCC	4	-	12.76 (4.81–21.4)	-
SCLC	16	7.40 (2.42–14.7)	3.4	0.3225
LCNEC	15	8.88 (2.8–14.57)	10.91 (6.1–14.54)	0.4491

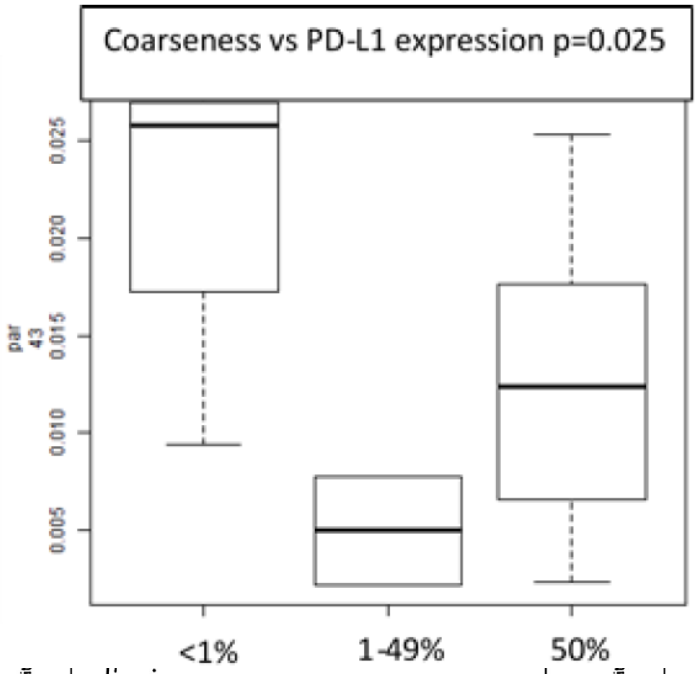
- **Glucose metabolism was generally higher in patients with PD-L1 protein expression** than those without PD-L1.
- Smoking, the presence of pleural invasion, and **high SUVmax** in PET/CT were **predictors of PD-L1 protein expression** in patients with lung cancer, especially NSCLC.

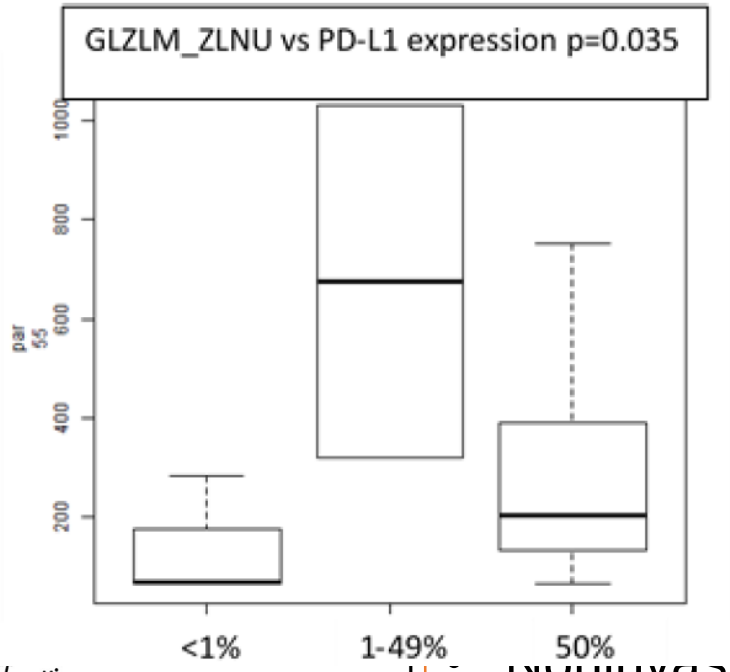
Cancer Medicine 2017; 6:2552

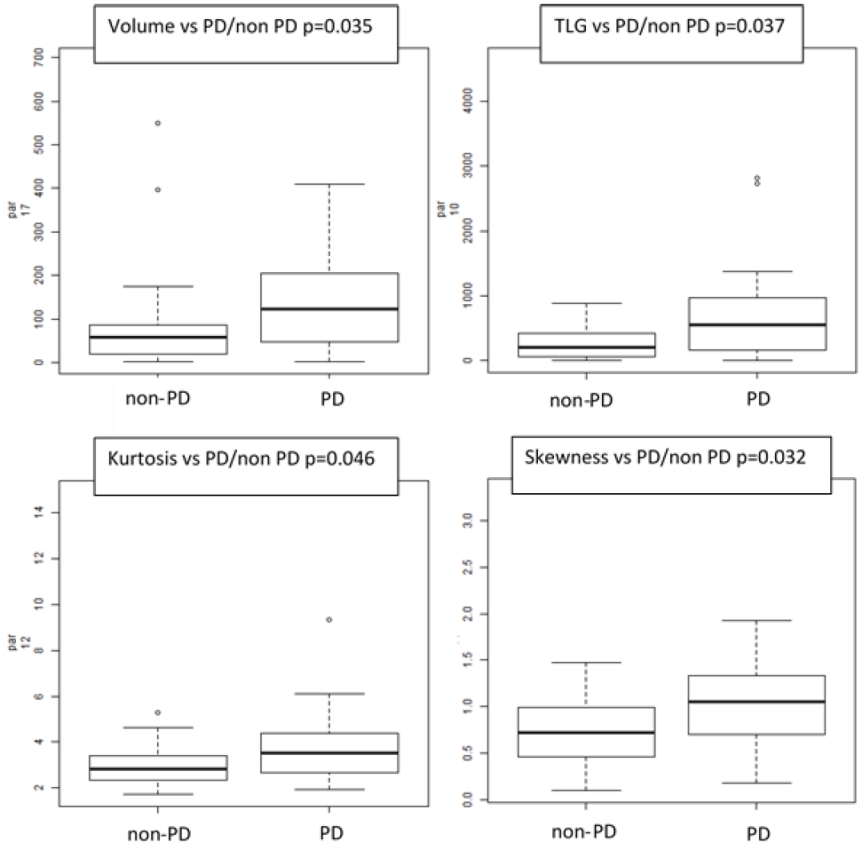
Assessing PD-L1 Expression Level by Radiomic Features From PET/CT in Nonsmall Cell Lung Cancer Patients: An Initial Result

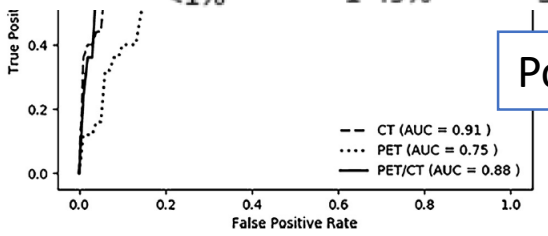
Mengmeng Jiang, MD, Dazhen Sun, MA, Yinglong Guo, MM, Yixian Guo, MD, Jie Xiao, MD, Lisheng Wang, PhD, Xiuzhong Yao, MD, PhD

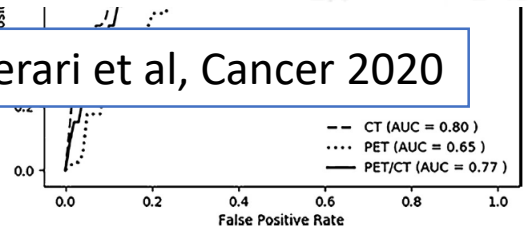
Radiomic features









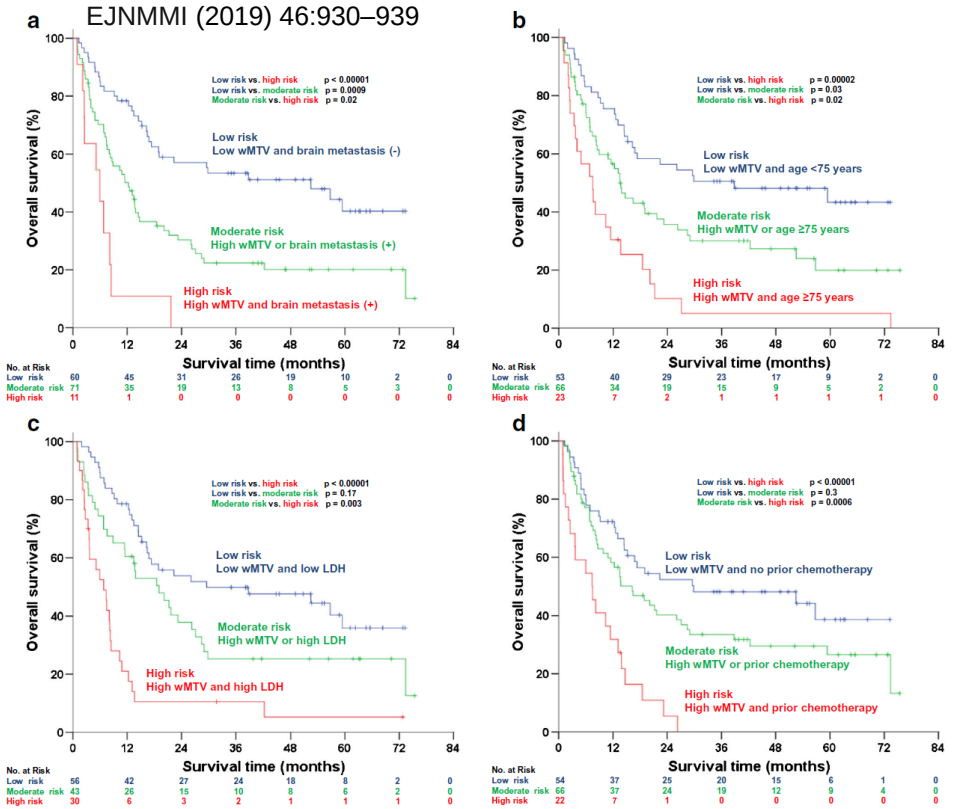


Polverari et al, Cancer 2020

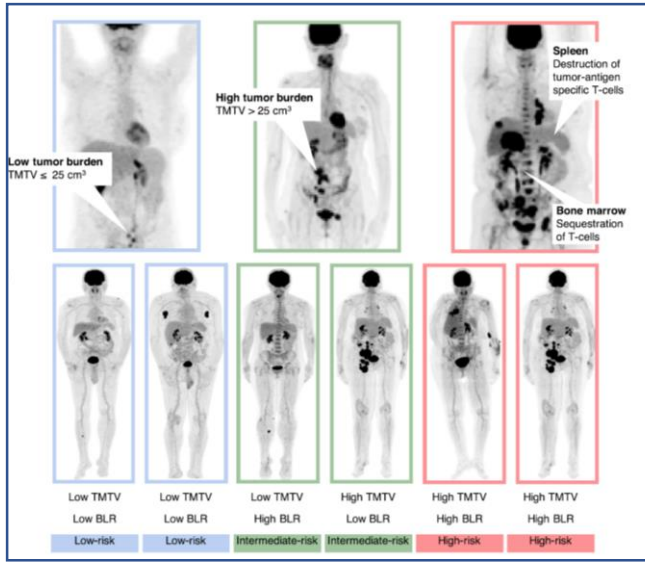
Noninvasi
future of g
expressed NSCLC patients and deserves further investigation.

Prediction of response-1

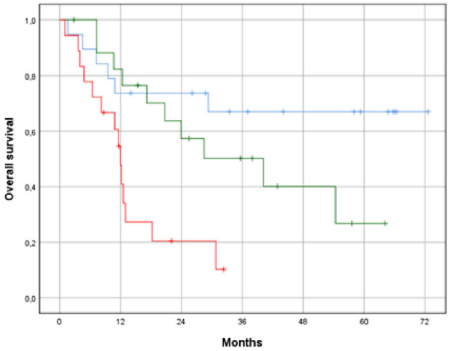
EJNMMI (2019) 46:930–939



Tumor burden in patients with advanced melanoma as quantified by 18F-FDG PET/CT is a strong independent prognostic factor for OS after immunotherapy with ipilimumab.



BLR= bone marrow to liver ratio
TMTV=total metabolic tumor



EJNMMI (2019) 46:2298–2310

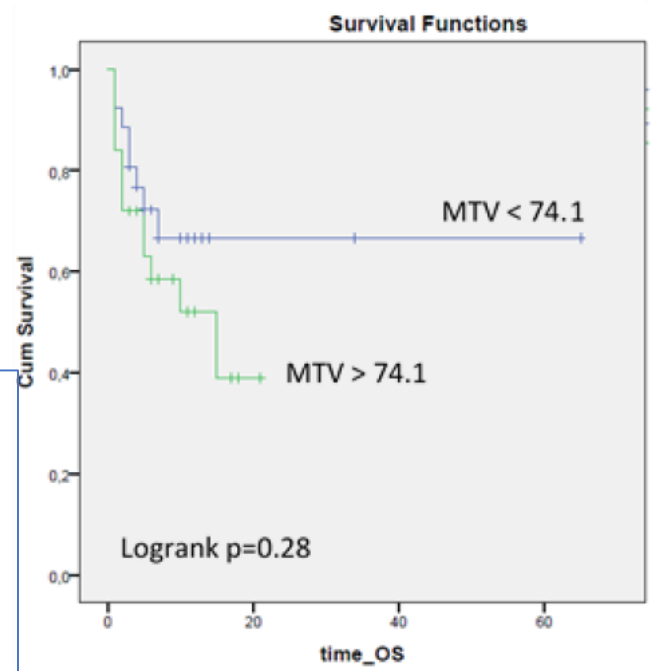
AJR 2019; 212:1318–1326

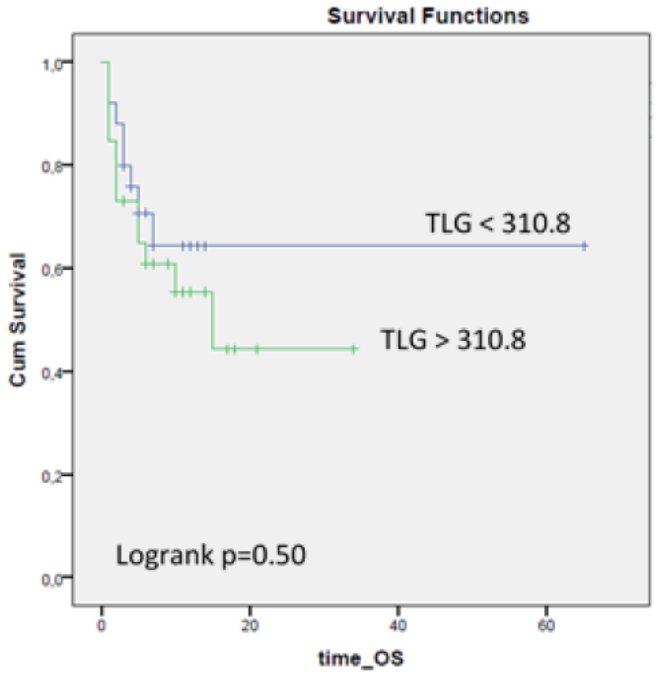
Biomarker	Disease Progression Status				Survival Status			
	Patients With Progression (n = 19; 55.9%)		Patients Without Progression (n = 15; 44.1%)		Patients Who Died (n = 12; 35.3%)		Patients Who Survived (n = 22; 64.7%)	
	Median	Mean ± SD	Median	Mean ± SD	Median	Mean ± SD	Median	Mean ± SD
SUV_{max}	7.73	9.04 ± 5.38	7.13	10.48 ± 8.01	9.88	12.09 ± 8.22	7.03	8.36 ± 5.28
Peak SUV	5.58	7.18 ± 4.86	6.5	8.63 ± 6.97	8.16	10.15 ± 7.02	5.51	6.55 ± 4.78
MTV (mL)	6.1	60.11 ± 142.46	46.03	109.64 ± 152.59	56.47	136.67 ± 160.15	2.84	52.12 ± 133.49
TLG (g)	14.06	349.53 ± 870.95	102.79	789.53 ± 1172.71	316.28	985.97 ± 1240.9	12.14	302.38 ± 815.43
TH index	6433.18	5978.36 ± 1147.73	5461.19	5667.84 ± 1389.53	5245.52	5158.08 ± 808.54	6658.94	6214.06 ± 1303.86

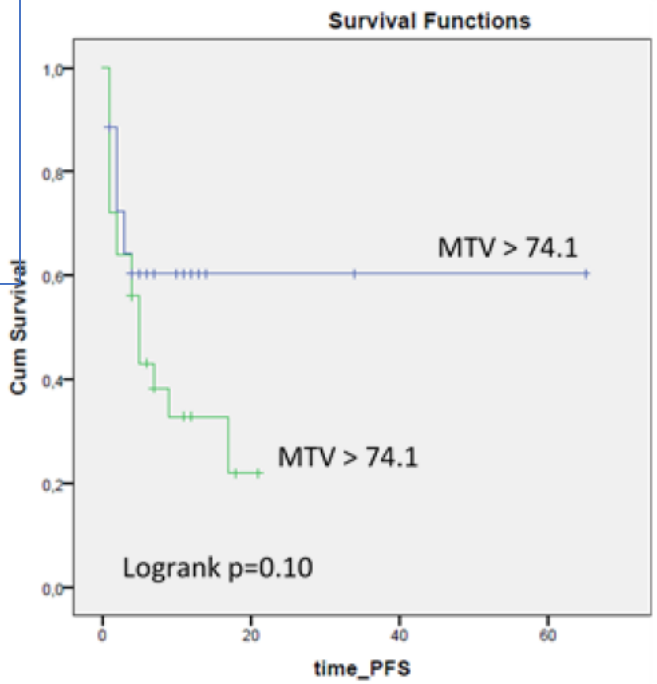
The TH index of FDG-avid lesions was found to be significantly associated with the OS of patients with metastatic or recurrent melanoma treated with immune modulation therapy.

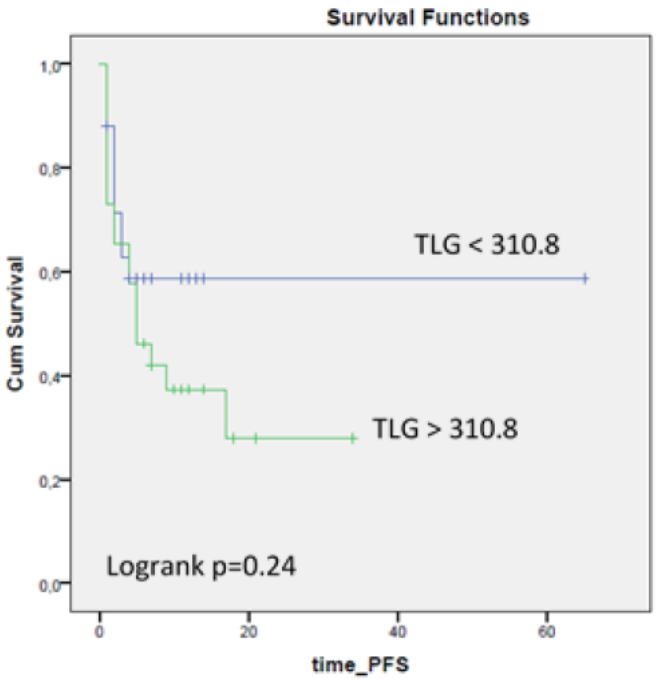
TH index=AUC value of a cumulative SUV volume histogram obtained by plotting the percentage of volume greater than the percentage of SUV_{max} with a lower AUC value corresponding to higher degrees of TH.

Polverari et al. Cancers 2020

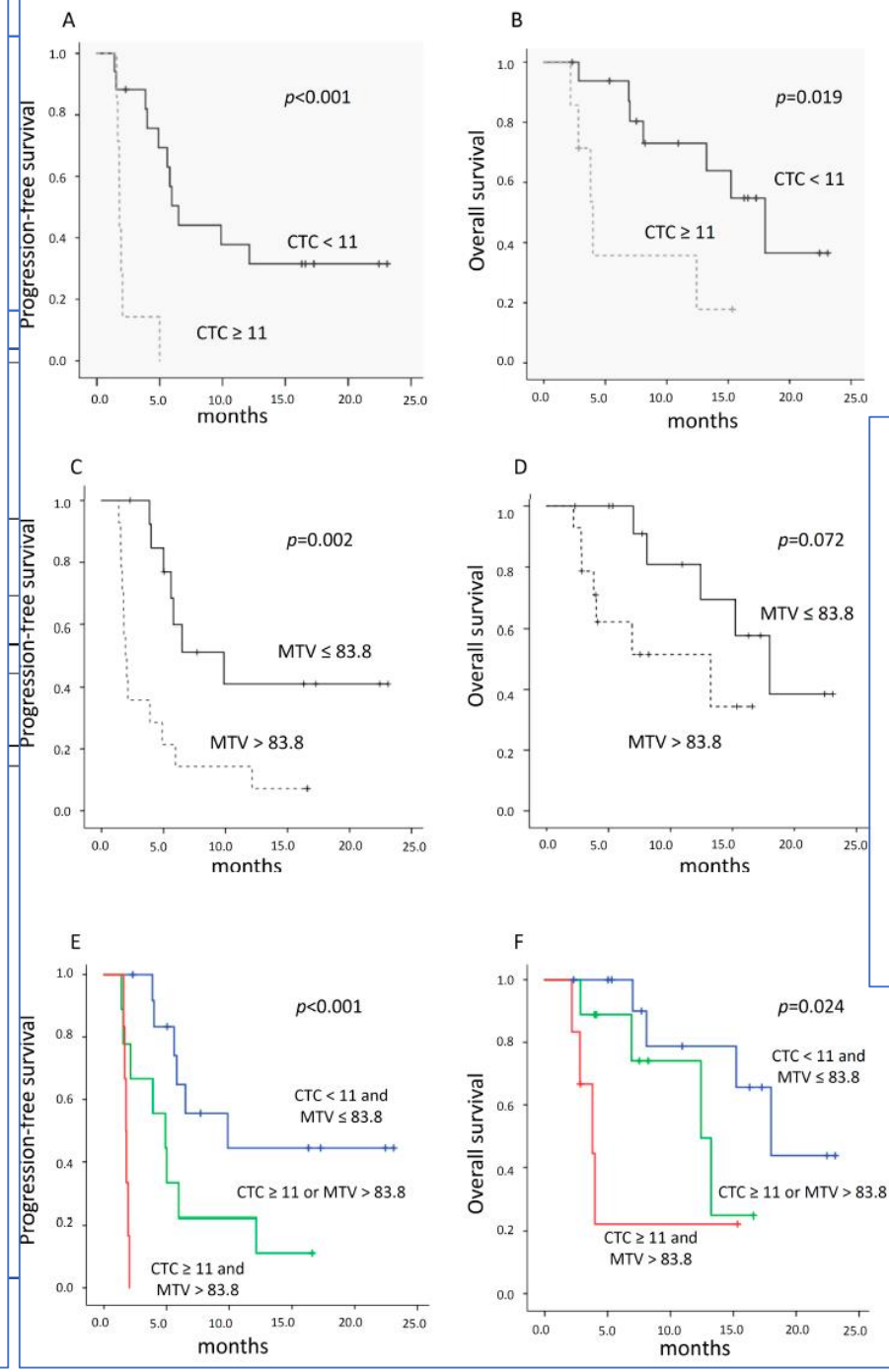








Castello et al. Cancers 2020



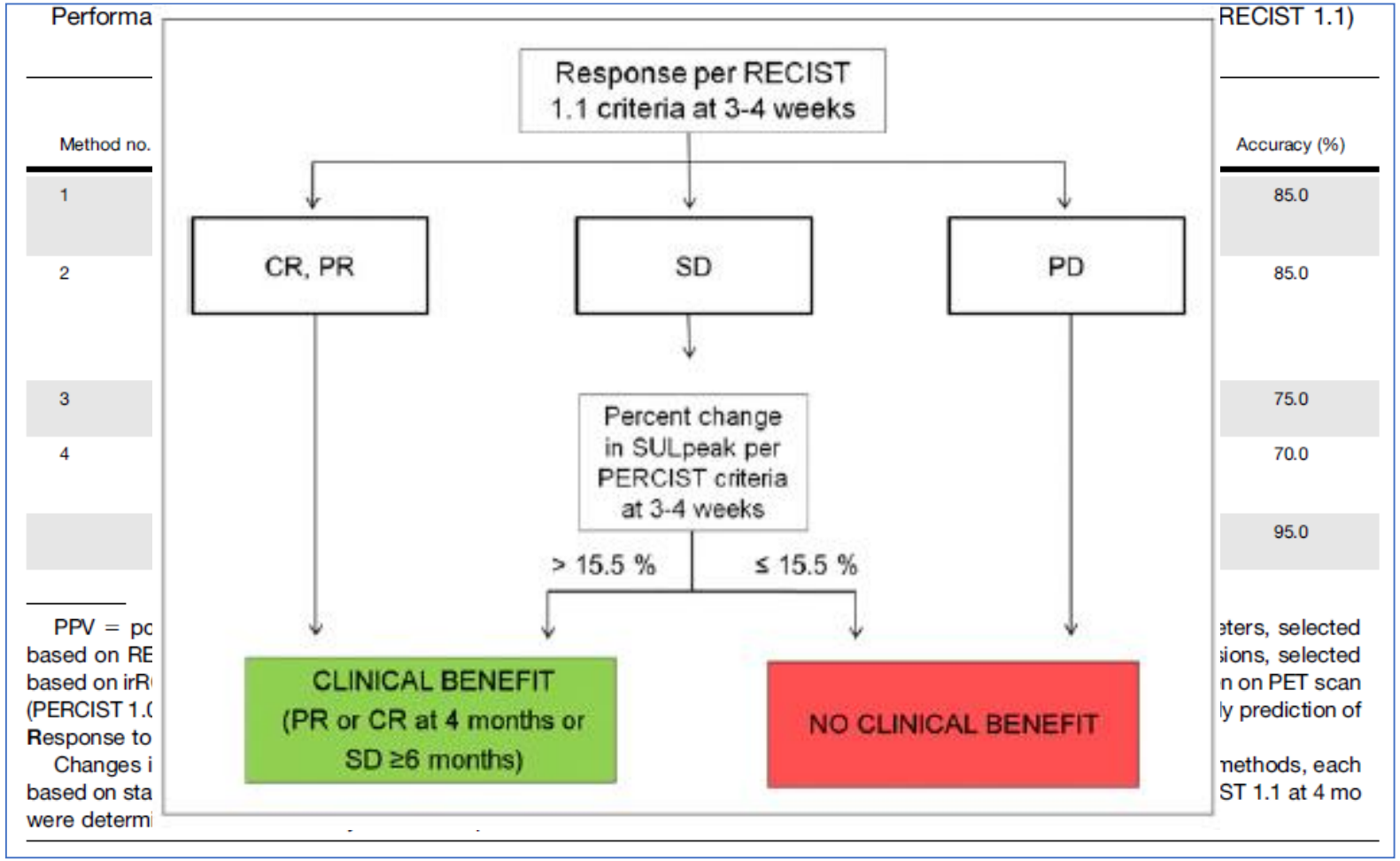
Literature evidences – FDG PET

Early evaluation of response to immunotherapy

- Interpretation
- Timing
- Standardization

Evaluation of response to immunotherapy-1

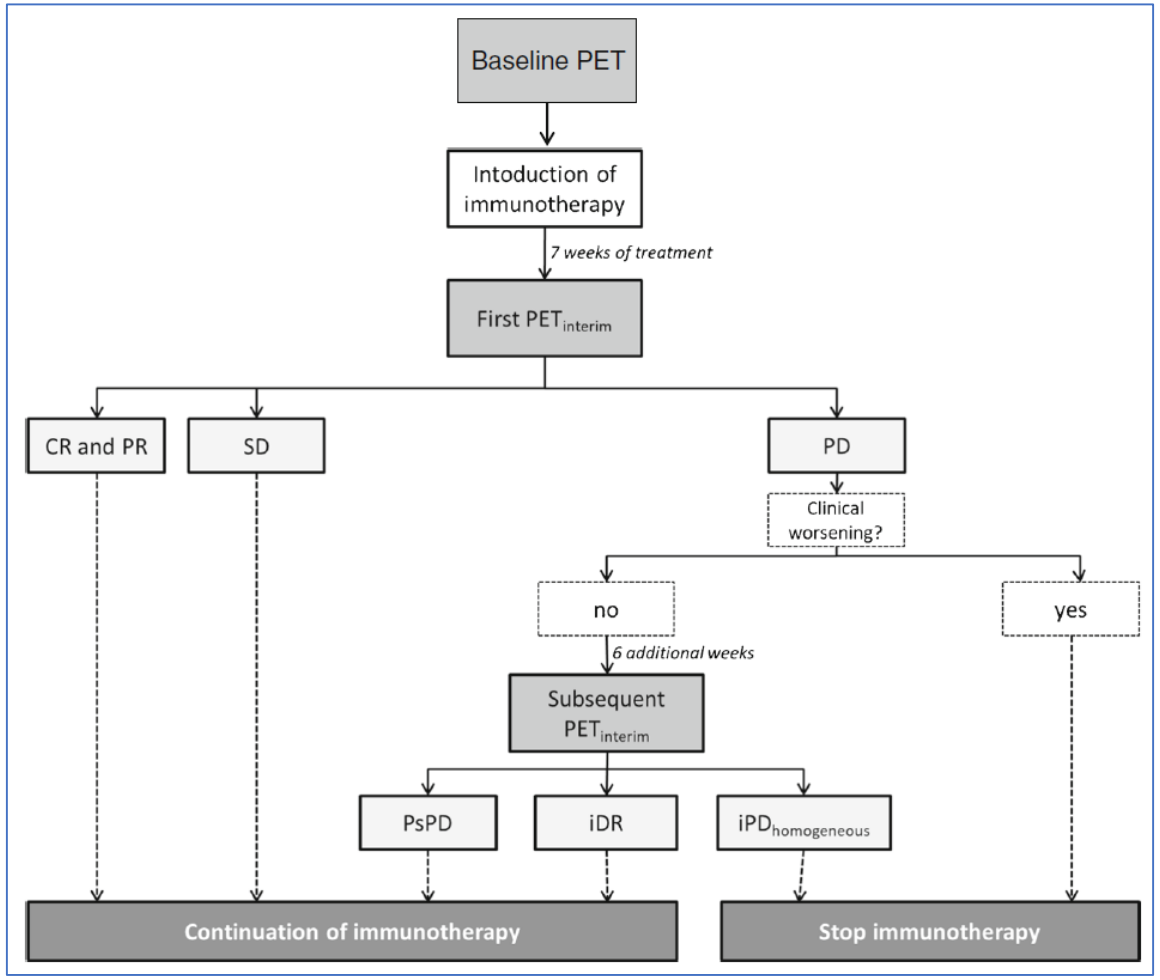
- 20 patients with melanoma
- Ipilumab or nivolumab
- Scan intervals: before (SCAN-1), days 21–28 (SCAN-2), 4 mo (SCAN-3)



J Nucl Med 2017; 58:1421–1428

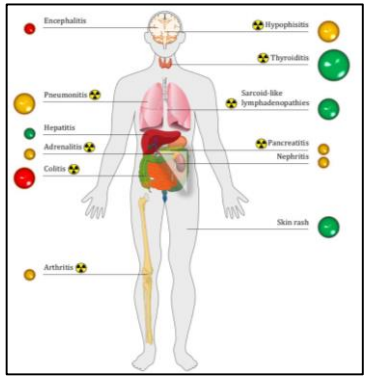
Evaluation of response to immunotherapy-2

- 62 patients with lung cancer
- Pembrolizumab or nivolumab
- Scan intervals: before (SCAN-1), 7-weeks (SCAN-2), 6 additional weeks (SCAN-3)

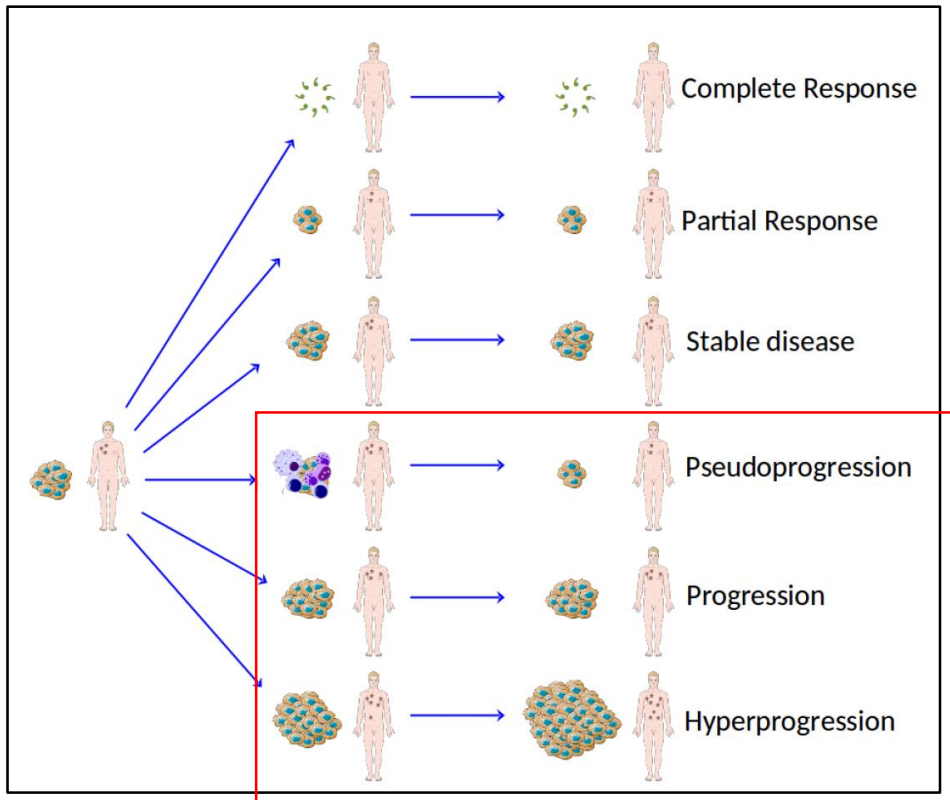


EJNMMI 2019; October 2019

Limitations of FDG PET/CT: pitfalls



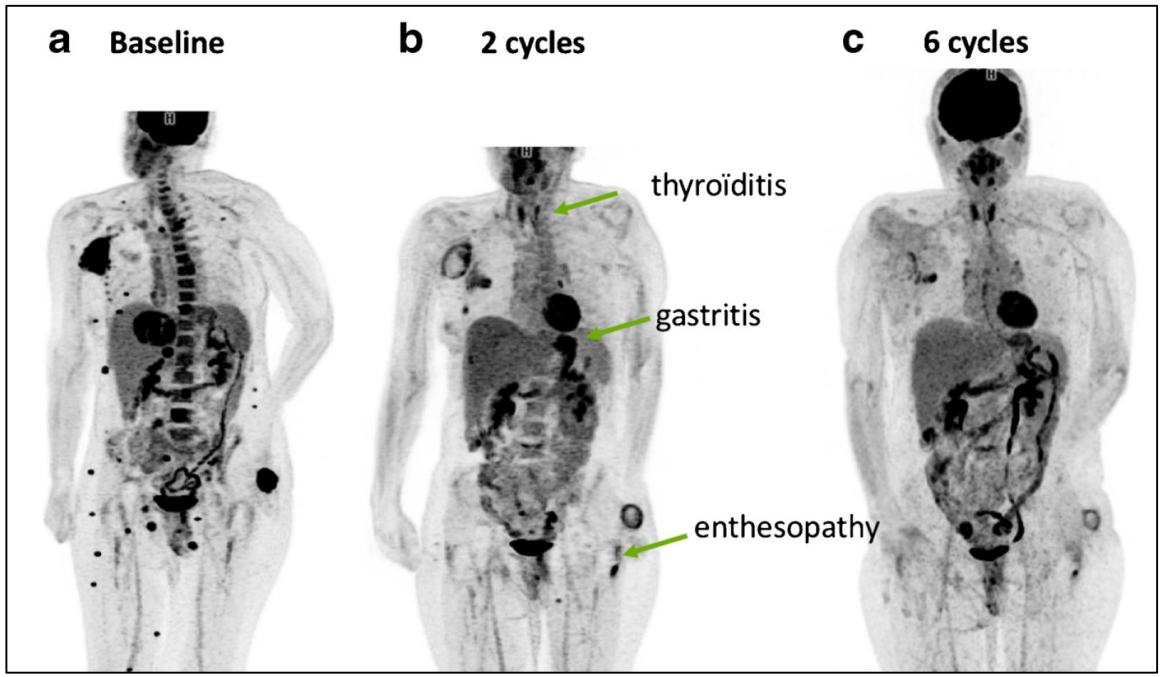
Evolution of disease



Cancers 2020; in press

FDG is not specific for the inflammed and the cancer cells

Immune-related side effects



Eur J Nucl Med Mol Imaging. 2019;46:238-250

The response to therapy: old *vs* immuno-criteria

Eur J Nucl Med Mol Imaging. 2019;46:238-250

Response	EORTC[a]	PERCIST[b]	PECRIT[c]		PERCIMT[d]	
Complete response (CR)	Complete resolution of FDG uptake	Disappearance of all metabolically active tumours	RECIST 1.1 (disappearance of all target lesions; reduction in short axis of target lymph nodes to	Clinical benefit	Complete resolution of all preexisting ^{18}F-FDG-avid lesions; no new ^{18}F-FDG-avid lesions	Clinical benefit
Partial response (PR)					of	Clinical benefit
Stable disease (SD)						Clinical benefit
Progressive disease (PD)	Increase in tumour FDG uptake of >25%; increase in maximum tumour of >20%; new metastases	Increase in SULpeak of >30% or the appearance of a new metabolically active lesion	RECIST 1.1 (increase in target lesion diameter sum of >20% and at least 5 mm or new lesions)	No clinical benefit	Four or more new lesions of <1 cm in functional diameter or three or more new lesions of >1.0 cm in functional diameter or two or more new lesions of more than 1.5 cm in functional diameter	No clinical benefit

imPERCIST5	iPERCIST
The appearance of a single lesion cannot be considered a true PMD. Melanoma n= 60 pts	Two new categories replacing the PMD category: unconfirmed progressive metabolic disease (UPMD) and confirmed progressive metabolic disease (CPMD). Lung cancer n=28 pts
Ito, JNM 2019; 60: 35-341	EJNMMI 2019; 9:8

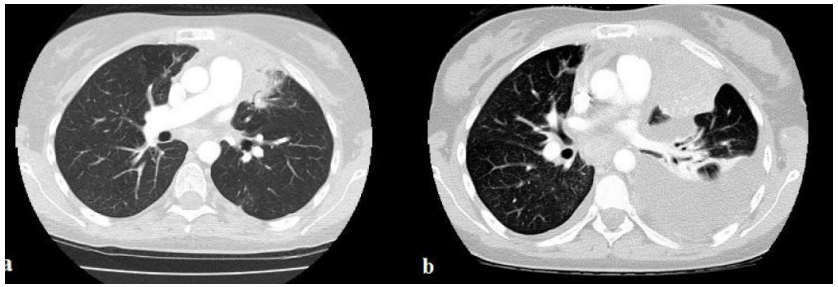
Lymphoma model: Lymphoma Response to Immunomodulatory Therapy Criteria (LYRIC)

LYRIC is an adapted Lugano classification for the evaluation of lymphoma after immune-based treatment.

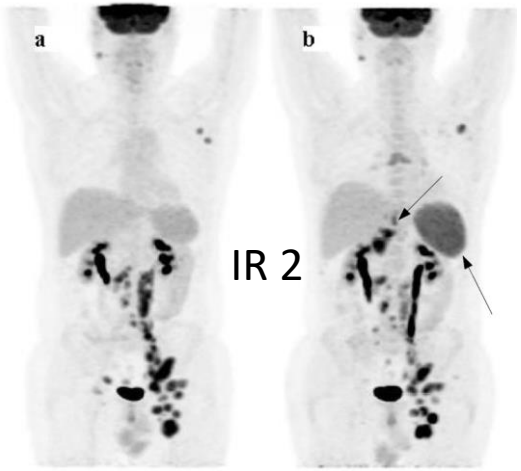
Indeterminate response (IR)

- **IR(1):** ≥ 50% increase in overall tumor burden (sum of the product of the perpendicular diameters (SPD) of up to six target measurable nodes and extranodal sites) occurred in the first 12 weeks of therapy and without clinical deterioration
- **IR(2):** new lesions or ≥ 50% increase of existing lesion(s) without a ≥ 50% increase of overall tumor burden at any time during treatment.
- **IR(3):** increased FDG uptake of one or more lesions without any increase in size or number of those lesions.

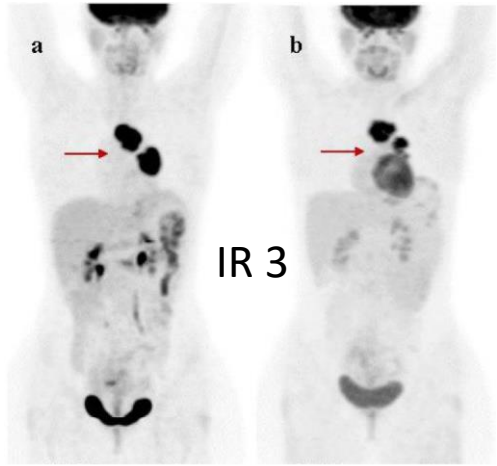
In case of IR: biopsy or “wait and watch”



IR 1



IR 2



IR 3

Issues

- Needs and priorities
- Current guidelines
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- Potential reccomendations
- The future is……

When to use FDG PET/CT ?

	Melanoma		Lung cancer	
	Ready?	Further evidences?	Ready?	Further evidences?
Prediction of response	Probably yes (n= >250 pts)	Sure	Not yet (n= 59 pts)	Sure
Assessment of response	Not yet (n= >300 pts)	Sure	Not yet (n= >200 pts)	Sure
Standardized criteria	Not yet (n= >300* pts)	Sure	Not yet (n= > 200* pts)	Sure

*variable criteria

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Other than FDG -alternative tracers

clinical evidence

J Nucl Med 2019; in press

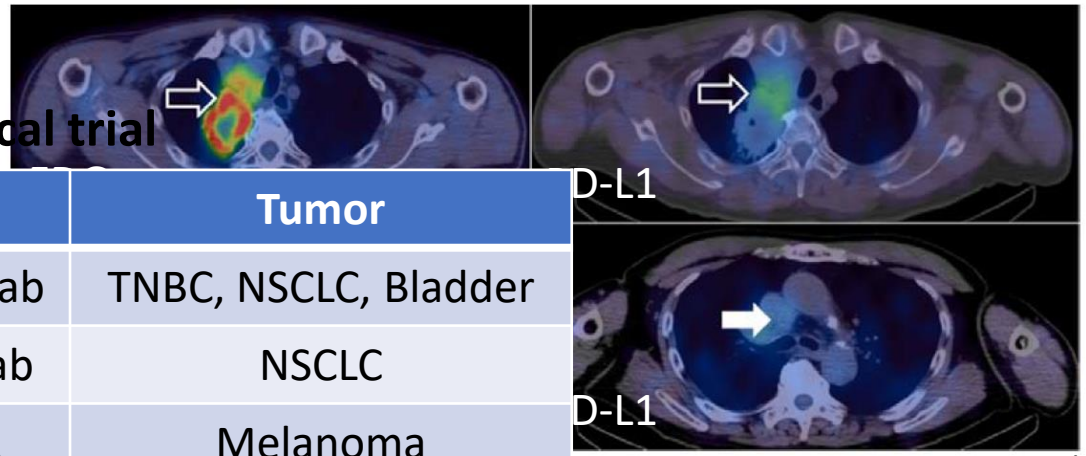
Table 1: Patient Characteristics

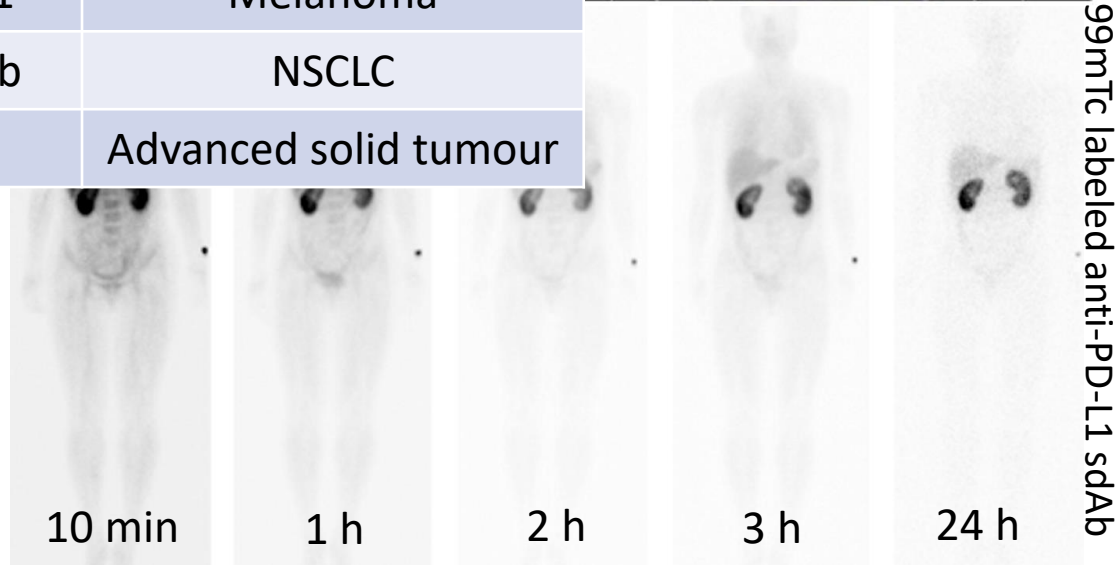
Dose Group	Patient No.	Age	Gender	Tumor Type	Tumor Size (CT axial dimensions)	PD-L1 IHC (%)	ECOG Score
100 µg Group 1 3.8-8.4 MBq/kg- 1.2-2.1 µg/kg	1	49	Male	Adenocarcinoma	37*27mm	NA	1
	2	75	Male	Squamous Cell Carcinoma	44*48mm	20	
	3	75	Male				
400 µg Group 2 9.1-10.4 MBq/kg- 5.6-6.1 µg/kg	4	65	Male				
	5	57	Male				
	6	65	Male				
100 µg Group 1 3.8-8.4 MBq/kg- 1.2-2.1 µg/kg	7	75	Fema				
	8	52	Fema				
	9	36	Female	Adenocarcinoma	45*35mm	1	1
	10	46	Female	Adenocarcinoma	42*35mm	50	0
	11	51	Male	Squamous Cell Carcinoma	47*35mm	2	0
	12	72	Male	Adenocarcinoma	46*53mm	NA	1
	13	55	Male	Squamous Cell Carcinoma	71*78mm	85	0
	14	69	Male	Squamous Cell Carcinoma	20*28mm	10	0
	15	71	Female	Squamous Cell Carcinoma	78*95mm	NA	1
	16	60	Male	Adenocarcinoma	93*75mm	2	0

*NA= not available

Ongoing clinical trial

Number	RF	Tumor
NCT02453984	89Zr-Atezolizumab	TNBC, NSCLC, Bladder
2015-005765-23	89Zr-Durvalumab	NSCLC
NCT03520634	18F-anti-PD-l1	Melanoma
NCT03514719	89Zr-avelumab	NSCLC
NCT03638804	89Zr-KN035	Advanced solid tumour





99mTc labeled anti-PD-L1 sdAb

Thanks for the kind attention!

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