

# Harnessing Imaging Tools to Guide Immunotherapy Trials: FDG PET/CT

Richard L. Wahl, M.D.



Washington University in St. Louis School of Medicine

MIR Mallinckrodt Institute of Radiology

### Disclosures

- RW-Scientific Advisory board and consultant: Clarity Pharmaceuticals
- Consulting: Jubilant Draximage, BMS
- Research contracts: Actinium Pharmaceuticals, BMS, Siemens

# **Literature Review**

- Pub Med: Immunotherapy 345,192 refs
- Immunotherapy + Cancer: 116,795 refs
- Immunotherapy + Imaging: 9297 refs
- Immunotherapy and Positron Emission Tomography: 1155 refs

# Immunotherapy and Imaging Literature is Growing Rapidly



### **Infections and FDG**

FDG for infections/inflammation

Intense uptake in most pyogenic infections
Intense uptake in active inflammatory arthritis
Intense uptake in sarcoidosis

FDG has been used to label WBC's as well with somewhat different targeting capabilities



Eur J Nucl Med (1998) 25:1238–1243

# Immunotherapies

- Immunization: COVID 19 vaccine
- Passive Immunity: Monoclonal antibodies to a variety of targets: CD20, EGFR, IGF-1
- Radioimmunotherapy: anti CD20 and other targets
- Antibody Drug Conjugates: Brentuximab in HD
- CART T cells and other attack cells
- Bi specific antibodies (anti tumor and anti CD3)
- Immune Checkpoint Inhibitors (antibody and small molecule)

# Challenges in Assessing Immunotherapies with FDG PET/CT

- Immune Response in tumor can be confused with tumor progression (pseudo progression)
- Immune response in normal tissues can appear to suggest new tumor or tumor progression (eg. Sarcoid-like reactions)
- Caution is in order



<sup>18</sup>F-fluorodeoxyglucose PET/CT findings in a systemic inflammatory response syndrome after COVID-19 vaccine <sup>18</sup>Ffluorodeoxyglucose PET/CT shows uptake in the fat stranding posterior to the right deltoid (arrow; upper image) with moderately increased uptake within multiple right axillary lymph nodes (arrow; centre image), and diffusely increased splenic uptake (bracket; lower image).

•. Lancet 2021 Mar 20;397(10279):e9. syndrome after COVID-19 vaccine

<sup>18</sup> F-fluorodeoxyglucose PET/CT findings in a systemic inflammatory response

•Julie Steinberg<sup>1</sup>, Alex Thomas<sup>2</sup>, Amir Iravani<sup>3</sup>

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

Richard L. Wahl<sup>1,2</sup>, Heather Jacene<sup>1</sup>, Yvette Kasamon<sup>2</sup>, and Martin A. Lodge<sup>1</sup>

J Nucl Med 2009 50: 122S-150S

#### **Key Aspects of PERCIST**

- Defined Acceptable Uptake Time for Study 1 and Study 2
- Must have same scanner and software
- Validation with normal tissue background (liver or blood)
- Minimum acceptable tumor lesion metabolic activity and statistical basis
- Specified # of lesions
- Use of SUV lean (SUL)
- Continuous scale

#### **PMR**

Baseline



#### Baseline



9 days after therapy



O Joo, Luber, Brandon S., Jeffrey P. Leal, Hao Wang, Vanessa Bolejack, Scott M. Schuetze, Lawrence H. Schwartz, Lee J. Helman, Denise Reinke, Laurence H. Baker, and Richard L. Wahl Journal of Nuclear Medicine 57, no. 5 (2016): 735-740.





O Joo, Luber, Brandon S., Jeffrey P. Leal, Hao Wang, Vanessa Bolejack, Scott M. Schuetze, Lawrence H. Schwartz, Lee J. Helman, Denise Reinke, Laurence H. Baker, and Richard L. Wahl *Journal of Nuclear Medicine* 57, no. 5 (2016): 735-740.

# Day 0 and Day 15 pCR to trastuzumab + pertuzumab therapy



Connolly, Roisin M et al. Journal of Clinical Oncology 37, no. 9 (2019): 714-722.



Connolly, Roisin M et al. Journal of Clinical Oncology 37, no. 9 (2019): 714-722.

#### **Response to RIT (Bexxar)**



**FIGURE 2.** Percentages of SUV-lean after RIT relative to baseline value (patients 1–8). PET was performed at baseline and at 33–70 d after RIT. NR = no response; PR = partial response; CR = complete response.



**FIGURE 4.** Percentages of SUV-lean after tracer dose and after RIT relative to baseline values (patients 9–14). PET was performed at baseline, at 6–7 d after tracer dose, and at 5–7 d after RIT. CR = complete response; PR = partial response.

Metabolic Response of Non-Hodgkin's Lymphoma to <sup>131</sup>I-Anti-B1 Radioimmunotherapy: Evaluation with FDG PET THE JOURNAL OF NUCLEAR MEDICINE • Vol. 41 • No. 6 • June 2000

Tatsuo Torizuka, Kenneth R. Zasadny, Paul V. Kison, Stephen G. Rommelfanger, Mark S. Kaminski, and Richard L. Wahl

#### **CAR-T cells**



Schematic of the treatment of a patient with chimeric antigen receptor (CAR) T cells. (1) Isolation of peripheral T cells from patient via apheresis. (2) Transfection of T cells with a lentivirus containing genes for CAR directed against the tumor target antigen: binding of virus to T-cell membrane, fusion of virus with cell membrane, reverse transcription, DNA integration, and transcription/protein expression of CAR genes, and insertion of CAR into cell membrane. (3) Adoptive transfer of autologous CAR-T cells via infusion with or without prior lymphodepleting conditioning. (4) Patient monitoring for treatment response, and for persistence of CAR-T cells. Professional illustration by A. Y. Chen.



#### After CAR-T Cells

# "Immune-related" response patterns to ipilimumab in melanoma



Ribas A et al., Clin Cancer Res 2009

Slide courtesy of S. Topalian

#### Response assessed using FDG PET/CT



FDG PET/CT images of a responding patient who received 4 cycles of combination ipi+nivo followed by 43 cycles of single agent nivo. A left internal iliac lymph node metastasis is highlighted with a baseline  $SUL_{MAX}$  of 18.5, which reduced to 2.3 on follow-up imaging at 3 months.



#### Prediction of Response to Immune Checkpoint Inhibitor Therapy Using Early-Time-Point <sup>18</sup>F-FDG PET/CT Imaging in Patients with Advanced Melanoma

Steve Y. Cho<sup>\*1,2</sup>, Evan J. Lipson<sup>\*1</sup>, Hyung-Jun Im<sup>\*2,3</sup>, Steven P. Rowe<sup>1</sup>, Esther Mena Gonzalez<sup>1</sup>, Amanda Blackford<sup>1</sup>, Alin Chirindel<sup>1</sup>, Drew M. Pardoll<sup>1</sup>, Suzanne L. Topalian<sup>1</sup>, and Richard L. Wahl<sup>1,4</sup>

J Nucl Med 2017; 58:1421-1428 DOI: 10.2967/jnumed.116.188839

### Progressive Disease Case – Patient #3



# Partial Response Case – Patient #2



### **Partial Response Case – Patient #4**

Baseline



4 weeks of therapy



4 months of therapy





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The Journal of Nuclear Medicine • Vol. 61 • No. 7 • July 2020

### FDG as Marker of Response to ICB





FIGURE 4. Kaplan-Meier estimates of OS for responders and nonresponders (left) and survival rates by response category (right). (A and B) PERCIST5. (C and D) PERCIST1. (E and F) imPERCIST5.



Kimiteru Ito et al. J Nucl Med 2018;59:279



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TABLE 1           Immune-Modified <sup>18</sup> F-FDG PET Response Criteria—PECRIT, PERCIMT, and imPERCIST							
Parameter	PECRIT (15)	PERCIMT (17)	imPERCIST 5 (18)				
Tumor type	Melanoma	Melanoma	Melanoma				
ICI	Anti-CTLA-4	Anti-CTLA-4	Anti-CTLA-4				
n	20	41	60				
Timing	3–4 wk	3 mo	3 mo				
Standard of reference	Clinical benefit: PR or CR at 4 mo or SD $\ge$ 6 mo per RECIST 1.1 (45)	Clinical benefit: composite of clinical follow-up, <sup>18</sup> F-FDG PET/ CT, brain MRI, and LDH	Follow-up and overall survival				
Definition of response	CR or PR: per RECIST 1.1	CR: resolution of all lesions on PE, <sup>18</sup> F-FDG PET/CT, and brain MRI; decrease or no increase in LDH; no new lesion	CR, PR, or SD: per PERCIST in 5 lesions				
		PR: decrease in size or resolution of lesions on PE, <sup>18</sup> F-FDG PET/CT, and brain MRI; decrease or no increase in LDH; no new lesion					
	SD: per RECIST 1.1 and >15.5% increase in SUL <sub>peak</sub> per PERCIST (46)	SD: neither CR/PR nor PD					
Definition of progression	Per RECIST 1.1	No clinical benefit and new lesions on <sup>18</sup> F-FDG PET/CT as follows	Change in sum of $SUL_{peak}$ in 5 lesions $> 30\%$				
		For lesions $< 1 \text{ cm}$ require $\ge 4 \text{ new}$ lesions					
		For lesions 1–1.5 cm require $\ge 3$ new lesions	New lesions can be incorporated				
		For lesions $>$ 1.5 cm require $\ge$ 2 new lesions					
Emphasis and advantages	Combining anatomic and metabolic criteria	Incorporation of clinical benefit in criteria	New lesions are incorporated to sum of metabolic activity of lesions and not immediately considered PD				
	Early response assessment	Number and metabolic size of new lesions on <sup>18</sup> E-EDG PET/CT					

PECRIT = PET/CT Criteria for Early Prediction of Response to ICI Therapy; PERCIMT = PET Response Evaluation Criteria for Immunotherapy; imPERCIST = Immunotherapy-Modified PERCIST; LYRIC = Lymphoma Response to Immunotherapy Criteria; iPERCIST = Immune PERCIST; HL = Hodgkin lymphoma; PR = partial response; CR = complete response; SD = stable disease; LDH = lactate dehydrogenase; PE = physical examination; CMR = complete metabolic response; PMR = partial metabolic response; SMD = stable metabolic disease; PD = progressive disease; SUL<sub>peak</sub> = lean body mass-corrected SUV<sub>peak</sub>; PMD = progressive metabolic disease; UPMD = unconfirmed PMD; IR = indeterminate response; SPD = sum of product of diameters; CPMD = confirmed progressive metabolic disease; PPD = product of perpendicular diameters.

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TABLE 2           Immune-Modified <sup>18</sup> F-FDG PET Response Criteria—LYRIC and iPERCIST							
Parameter	LYRIC (19,20)	iPERCIST (22)					
Tumor type	HL	NSCLC					
ICI	Anti-PD-1	Anti-PD-1					
n	16	28					
Timing	3 mo	2 mo					
Standard of reference	Multidisciplinary experts' consensus based on clinical and imaging results	Clinical benefit and confirmatory <sup>18</sup> F- FDG PET/CT or CT 4 wk later					
Definition of response	CR or PR: per Lugano (21)	CMR, PMR, or SMD: per PERCIST					
Definition of progression	Per Lugano with following exceptions	PMD as per PERCIST is considered UPMD					
	IR1: ≥50% increase in SPD in first 12 wk						
	IR2a: <50% increase in SPD with new lesions	UPMD needs to be confirmed by second <sup>18</sup> F-FDG PET/CT at 4–8 wk later to be classified as CPMD					
	IR2b: <50% increase in SPD with ≥50% increase in PPD of lesion or set of lesions at any time during treatment						
	IR3: increase in <sup>18</sup> F-FDG uptake without concomitant increase in lesion size meeting criteria for PD						
Emphasis and advantages	Introduction of concept of IR categories until biopsy or subsequent imaging confirms either pseudoprogression or true progression	Introduction of concept of UPMD with clinical stability					
		Allowing treatment continuation					

PECRIT = PET/CT Criteria for Early Prediction of Response to ICI Therapy; PERCIMT = PET Response Evaluation Criteria for Immunotherapy; imPERCIST = Immunotherapy-Modified PERCIST; LYRIC = Lymphoma Response to Immunotherapy Criteria; iPERCIST = Immune PERCIST; HL = Hodgkin lymphoma; PR = partial response; CR = complete response; SD = stable disease; LDH = lactate de-hydrogenase; PE = physical examination; CMR = complete metabolic response; PMR = partial metabolic response; SMD = stable metabolic disease; PD = progressive disease; SUL<sub>peak</sub> = lean body mass-corrected SUV<sub>peak</sub>; PMD = progressive metabolic disease; UPMD = unconfirmed PMD; IR = indeterminate response; SPD = sum of product of diameters; CPMD = confirmed progressive metabolic disease; PPD = product of perpendicular diameters.

IMAGING IMMUNE ENVIRONMENT: <sup>18</sup>F-FDG • Iravani and Hicks The JOURNAL OF NUCLEAR MEDICINE • Vol. 61 • No. 7 • July 2020

Refinement of the Lugano classification response criteria for lymphoma in the era of immunomodulatory therapy (LYRIC)

Cheson et al. Blood 2016 128;2489-2496

### Indeterminate Response

#### Definition

PD at follow up

1 Increased SPD ≥ 50%, first 12 w No "clinical deterioration" Further increase 10% and 5 mm

- New lesions at any time or increase
   Increase 50% nadir
   50% any 1 lesion, but not overall PD
   value
- 3 Increase FDG uptake only

Increase in size

### LYRIC Summary

- By time
- New lesions in total tumor volume
- Stable is good
- Treat beyond PD if clinically stable

#### Table 1 Available and/or proposed response criteria for use with FDG PET

From: FDG PET/CT for assessing tumour response to immunotherapy

Response	EORTC <sup>a</sup>	PERCIST	PECRIT <sup>C</sup>			PERCIMT <sup>d</sup>	
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 <1 cm; no new lesions)		Clinical benefit	Complete resolution of all preexisting <sup>18</sup> F- FDG-avid lesions; no new <sup>18</sup> F-FDG-avid lesions	Clinical benefit
Partial response (PR)	Minimum reduction of ±15– 25% in tumour SUV after one cycle of chemotherapy, and >25% after more than one treatment cycle	Decline in SULpeak by 0.8 unit (>30%) between the most intense lesion before treatment and the most intense lesion after treatment	RECIST 1.1 (decrease in target lesion diameter sum >30%)		Clinical benefit	Complete resolution of some preexisting <sup>18</sup> F-FDG-avid lesions. No new, <sup>18</sup> F-FDG avid lesions.	Clinical benefit
Stable disease (SD)	increase in SUV of less than 25% or a decrease of less than 15%	Does not meet other criteria	Does not meet other criteria	Change in SULpeak of the hottest lesion of >15%	Clinical benefit	Neither PD nor PR/CR	Clinical benefit
				Change in SULpeak of the hottest lesion of ≤15%	No 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

# Evaluation of <sup>18</sup>F-FDG-PET/CT for Response Assessment in Patients with Advanced Melanoma Treated with Immune Checkpoint Inhibitors

Dominique Fuser M.D., Leonel Hernandez-Aya M.D., Joyce C. Mhlanga M.D., John P. Crandall, Lauren Ash, Richard L. Wahl M.D., Delphine L. Chen M.D.

**RSNA 2018** 





Washington University in St. Louis School of Medicine

#### MIR Mallinckrodt Institute of Radiology

#### Conclusion

- PET metrics at approximately 3 months after starting immunotherapy may differentiate responders from nonresponders
- Pseudoprogression was not definitely seen in this cohort
  - Sub-analyses ongoing
- Cutoffs suggested by our data will need to be tested prospectively

#### **KSNA**°



Figure 11a Immune-related sarcoid-like reaction in a patient with oligometastatic melanoma to a right axillary lymph node after undergoing radiation therapy to the right axilla and recombinant cytokine therapy with interferon- $\alpha$ . (a) Left: MIPmaximum intensity projection PET image obtained 2 months after treatment shows FDGfluorodeoxyglucose uptake in the paratracheal mediastinal and bilateral hilar nodes in the chest (arrow), as well as in the spleen (\*). Top right: Fused axial PET/CT image of the lung apices shows inflammatory FDGfluorodeoxyglucose uptake within radiation pneumonitis changes of the right lung apex. Bottom right: Fused PET/CT image of the upper abdomen shows multifocal areas of intense FDGfluorodeoxyglucose uptake in the spleen. (b) Corresponding images obtained 5 months after treatment show complete resolution of FDGfluorodeoxyglucose uptake in the mediastinal and hilar nodes, and spleen. In addition, the right apical radiation pneumonitis has resolved. Physiologic FDGfluorodeoxyglucose uptake is seen in the fundal wall of the stomach on the MIPmaximum intensity projection PET (left) and fused axial PET/CT (right) images.







Figure 11b Immune-related sarcoid-like reaction in a patient with oligometastatic melanoma to a right axillary lymph node after undergoing radiation therapy to the right axilla and recombinant cytokine therapy with interferon- $\alpha$ . (a) Left: MIPmaximum intensity projection PET image obtained 2 months after treatment shows FDGfluorodeoxyglucose uptake in the paratracheal mediastinal and bilateral hilar nodes in the chest (arrow), as well as in the spleen (\*). Top right: Fused axial PET/CT image of the lung apices shows inflammatory FDGfluorodeoxyglucose uptake within radiation pneumonitis changes of the right lung apex. Bottom right: Fused PET/CT image of the upper abdomen shows multifocal areas of intense FDGfluorodeoxyglucose uptake in the spleen. (b) Corresponding images obtained 5 months after treatment show complete resolution of FDGfluorodeoxyglucose uptake in the mediastinal and hilar nodes, and spleen. In addition, the right apical radiation pneumonitis has resolved. Physiologic FDGfluorodeoxyglucose uptake is seen in the fundal wall of the stomach on the MIPmaximum intensity projection PET (left) and fused axial PET/CT (right) images.







Figure 5c Autoimmune colitis in a patient with metastatic melanoma who presented to the emergency department with abdominal pain approximately 1 month after receiving the third dose of ipilimumab therapy. (a, b) Coronal reformatted (a) and axial (b) CT images of the abdomen show wall thickening of a segment of the descending colon (arrow) with associated inflammatory stranding in the pericolonic fat, a finding compatible with colitis. A diagnosis of diverticulitis was made, and the patient underwent antibiotic therapy. Unfortunately, the patient did not improve and presented a few weeks later with rectal bleeding resulting from colonic perforation. A diagnosis of autoimmune colitis was then made, and corticosteroid therapy was begun. (c) MIPmaximum intensity projection PET (left), fused axial PET/CT (top right), and localization CT (bottom right) images of the abdomen from a FDGfluorodeoxyglucose PET/CT study performed 1 month after initiation of corticosteroid therapy show persistent descending colonic wall thickening with intense inflammatory FDGfluorodeoxyglucose uptake and surrounding inflammatory pericolonic fat stranding. Infliximab therapy was begun. (d) Follow-up PET/CT image (top right) shows near-complete resolution of the colitis; MIPmaximum intensity projection PET image (left) shows FDGfluorodeoxyglucose uptake in the left lower abdomen, a finding that corresponds to physiologic bowel activity near the colostomy site; and localization CT image (bottom right) shows a marked decrease in colonic wall thickening and pericolonic fat stranding.





Figure 8a Autoimmune pancreatitis in a patient who was asymptomatic and presented for follow-up imaging 3 months after completion of ipilimumab therapy. (a) MIPmaximum intensity projection PET (left) and fused axial PET/CT (top right) images show intense FDGfluorodeoxyglucose uptake in the pancreas. Localization CT image obtained at the level of the pancreas (bottom right) shows a mildly enlarged pancreas with no peripancreatic inflammatory changes and rounded pancreatic contours that can be described as having the "sausage" appearance of autoimmune pancreatitis. (b) Follow-up T2-weighted fat-saturated (top) and contrast-enhanced T1-weighted fatsaturated (bottom) MR images obtained at the level of the pancreas to evaluate for pancreatic metastases show no focal pancre atic lesions suspicious for metastatic disease. (c) Follow-up MIPmaximum intensity projection PET image (left) obtained 1 month later shows no abnormal FDGfluorodeoxyglucose uptake in the pancreas. PET/CT image (top right) shows resolution of FDGfluorodeoxyglucose uptake in the pancreas. Localization CT image of the pancreas (bottom right) shows interval decrease in the size of the pancreas.

Kwak JJ. Published Online: March 12, 2015 https://doi.org/10.1148/rg.352140121

#### **RadioGraphics**





Figure 8c Autoimmune pancreatitis in a patient who was asymptomatic and presented for follow-up imaging 3 months after completion of ipilimumab therapy. (a) MIPmaximum intensity projection PET (left) and fused axial PET/CT (top right) images show intense FDGfluorodeoxyglucose uptake in the pancreas. Localization CT image obtained at the level of the pancreas (bottom right) shows a mildly enlarged pancreas with no peripancreatic inflammatory changes and rounded pancreatic contours that can be described as having the "sausage" appearance of autoimmune pancreatitis. (b) Follow-up T2-weighted fat-saturated (top) and contrast-enhanced T1-weighted fatsaturated (bottom) MR images obtained at the level of the pancreas to evaluate for pancreatic metastases show no focal pancre atic lesions suspicious for metastatic disease. (c) Follow-up MIPmaximum intensity projection PET image (left) obtained 1 month later shows no abnormal FDGfluorodeoxyglucose uptake in the pancreas. PET/CT image (top right) shows resolution of FDGfluorodeoxyglucose uptake in the pancreas. Localization CT image of the pancreas (bottom right) shows interval decrease in the size of the pancreas.

Kwak JJ. Published Online: March 12, 2015 https://doi.org/10.1148/rg.352140121

#### **RadioGraphics**







**RSNA**°



Figure 10 Immune-mediated arthritis in a patient with metastatic melanoma who underwent ipilimumab therapy. MIPmaximum intensity projection PET image shows a diffuse pattern of periarticular FDGfluorodeoxyglucose uptake (arrowheads) compatible with immune-mediated arthritis and evidence of superimposed degenerative osteoarthritis in the medial compartments of the bilateral knees (arrow).



#### False Positive FDG PET

- Case Report
- Inflammatory Reaction Secondary to Immune Checkpoint Inhibitor Therapy Mimicking a Post-Operative Brain Abscess
- Author links open overlay panel<u>Ankur</u> <u>R.PatelM.D.<sup>1</sup>ScottConnorsM.D.<sup>1</sup>ZabiWardakM.D.<sup>2</sup>JamesBru</u> <u>garolasM.D., Ph.D.<sup>3</sup>Toral R.PatelM.D.<sup>1</sup></u>
- <u>https://doi.org/10.1016/j.wneu.2019.06.024</u>

# PET Imaging of Value in Checkpoint Inhibitor Imaging

- Pseudo-progression more common, it seems, with CTLA4 blockade and early assessments intra therapy
- Do not make decisions too quickly on progression—3 months post Rx may be OK
- Extensive progression is still bad
- Uncertain how to best assess early response
- Evolving literature, but not all early "progression" is true progression
- Recall basics of FDG PET



### Auto-PERCIST™

Software for the Semi-Automated Assessment of 18F-FDG PET Imaging Studies using the PERCIST v1.0 Criteria

Richard L. Wahl, MD Mallinckrodt Institute of Radiology Washington University School of Medicine

Jeffrey Leal Department of Radiology Sidney Kimmel Comprehensive Cancer Center Johns Hopkins School of Medicine

# Successful detection at both thresholds



#### AUTO-PERCIST™



### Thanks to many:

- Jeff Leal
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- John Crandall