

AWARD NUMBER: W81XWH-15-1-0171

TITLE:

Exploring Mechanisms and Predictors of Treatment Response to Improve Outcome of Standard Chemotherapy in Non-Small Cell Lung Cancer

PRINCIPAL INVESTIGATOR:

Anthony F. Shields, MD, PhD

CONTRACTING ORGANIZATION:

Wayne State University
Detroit, MI

REPORT DATE:

December 2019

TYPE OF REPORT:

Final Report

PREPARED FOR: U.S. Army Medical Research and Development Command
Fort Detrick, Maryland 21702-5012

DISTRIBUTION STATEMENT: Approved for Public Release;
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REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

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1. REPORT DATE December 2019	2. REPORT TYPE Final	3. DATES COVERED 30Sep2015-29Sep2019
4. TITLE AND SUBTITLE Exploring Mechanisms and Predictors of Treatment Response to Improve Outcome of Standard Chemotherapy in Non-Small Cell Lung Cancer		5a. CONTRACT NUMBER
		5b. GRANT NUMBER W81XWH-15-1-0171
		5c. PROGRAM ELEMENT NUMBER
6. AUTHOR(S) Anthony F. Shields, MD, PhD E-Mail: shieldsa@karmanos.org	5d. PROJECT NUMBER	
	5e. TASK NUMBER	
	5f. WORK UNIT NUMBER	
7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES) Wayne State University 5057 Woodward 13th floor Detroit, MI 48202		8. PERFORMING ORGANIZATION REPORT NUMBER
9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES) U.S. Army Medical Research and Development Command Fort Detrick, Maryland 21702-5012		10. SPONSOR/MONITOR'S ACRONYM(S)
		11. SPONSOR/MONITOR'S REPORT NUMBER(S)
12. DISTRIBUTION / AVAILABILITY STATEMENT Approved for Public Release; Distribution Unlimited		
13. SUPPLEMENTARY NOTES		

14. ABSTRACT

Abstract;

Relevance: Non-small cell lung cancer (NSCLC) constitutes 85 percent of all lung cancers with systemic chemotherapy as the major treatment option. This cancer affects all major cross sections of the population in the US including military service members, veterans, their families, and other military beneficiaries. The standard front-line and maintenance therapies for non-squamous NSCLC rely heavily on pemetrexed (PEM) but the response to PEM is highly variable. Our preliminary data indicate that the dexamethasone (Dex), given to prevent PEM toxicity, may interfere with such treatment, mediated by the glucocorticoid receptor (GR) present in many tumors.

Furthermore, work in our laboratories has shown that extended Dex treatment induces irreversible cell cycle blockade and senescence, which itself may be therapeutic. Also, induction of cellular senescence may contribute to tumor sensitivity to the treatments, by mobilizing immune response against the tumors. We have assessed if this is a significant clinical issue using the experimental tracer, 3'-fluoro-3'-deoxy-thymidine (FLT) (IND #105034), for positron emission tomography (PET), which we developed. FLT-PET will be used to determine if Dex, by interfering with proliferation in GR-positive tumors could make them resistant to PEM and help induce senescence.

Background: PEM targets thymidylate synthase (TS) and other synthetic enzymes in folate metabolism, thus inhibiting DNA synthesis. Dex, which acts through the GR, is typically administered on the days prior to, during and following PEM chemotherapy mainly to alleviate PEM-induced severe skin rash. Our studies of a panel of NSCLC cell line models have shown that Dex frequently arrests cells in the early G1 phase of the cell cycle. We have found in cell lines the effect of Dex leads to decreased FLT retention. This was confirmed by PET imaging in our first pilot patient, who demonstrated a marked decline of FLT retention after Dex treatment. As a result of pre-treatment with Dex, the cytotoxicity of PEM is abrogated in cell lines with high GR. We have also reported progressive, irreversible loss of clonogenic growth, whose time of onset was dependent on GR level and Dex dose, was due to transcriptional activation of p27^{Kip1} by Dex (M. Patki, Scientific Reports, 2018 PMID 30375484). The *in vitro* observations were reflected by growth suppression and p27^{Kip1} induction in GR-overexpressing tumor xenografts compared with isogenic low-GR tumors. Additional data indicates that specific chemokines secreted by the senescent tumor cells attract and activate immune cells. Therefore, Dex treatment could improve outcome of surgery and pemetrexed chemotherapy and sensitize tumors to immunotherapy.

Hypotheses: In many NSCLC patients, the antimetabolite-based modality of PEM-based chemotherapy that includes Dex could be futile or minimally effective because of the ability of Dex to cause reversible tumor cell cycle arrest in G1 phase. We have tested the hypothesis that Dex can block proliferation in patients using FLT-PET imaging and that this may be associated with loss of the pharmacodynamic response to PEM and tumor senescence.

Aims: We have applied FLT-PET imaging as a functional approach to assess the immediate effect of Dex on NSCLC and also assess the effect of prolonged Dex treatment as a means of inducing tumor senescence. Patients with advanced, chemotherapy naïve non-squamous NSCLC patients were imaged at baseline and after the start of Dex to determine whether Dex produces S-phase suppression. One cohort stopped Dex at day 3 and was imaged 1-2 weeks after the last dose to assess recovery of proliferative capacity. A second cohort continues Dex for 14 days to determine if longer term treatment leads to senescence, as measured by repeat FLT-PET 6-8 days after the two week treatment.

Clinical Impact: These FLT-PET imaging studies with Dex provide results predicting response in a minority of advanced NSCLC patients to Dex. In patients on treatment for advanced disease, Dex may abrogate the effect of chemotherapy and/or stimulate immunotherapy. In patients refractory to many treatments, Dex alone may provide some antiproliferative benefit, but this will require the development of a simple molecular marker to select such patients and further trials

15. SUBJECT TERMS

Non-small cell lung cancer (NSCLC), dexamethasone (Dex), 3'-fluoro-3'-deoxy-thymidine (FLT), positron emission tomography (PET), glucocorticoid receptor (GR), pemetrexed (PEM)

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT Unclassified	18. NUMBER OF PAGES 17	19a. NAME OF RESPONSIBLE PERSON USAMRMC
a. REPORT Unclassified	b. ABSTRACT Unclassified	c. THIS PAGE Unclassified			19b. TELEPHONE NUMBER <i>(include area code)</i>

Standard Form 298 (Rev. 8-98)
Prescribed by ANSI Std. Z39.18

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1. Introduction

We have previously shown that Dex co-administered to lung adenocarcinoma patients with pemetrexed chemotherapy, protects against pemetrexed cytotoxicity by inducing reversible G1 arrest, reflected by the effect of Dex on FLT-PET images of in mice with implanted GR positive cell lines and patient tumors. In cells with GR expression corresponding to higher clinical tumor levels, Dex-induced growth arrest was followed by marked cell expansion. We have also reported progressive, irreversible loss of clonogenic growth, whose time of onset was dependent on GR level and Dex dose, was due to transcriptional activation of p27^{Kip1} by Dex (M. Patki, Scientific Reports, 2018 PMID 30375484). The *in vitro* observations were reflected by growth suppression and P27Kip1 induction in GR-overexpressing tumor xenografts compared with isogenic low-GR tumors.

Extended Dex treatment induces irreversible cell cycle blockade and a senescence phenotype through chronic activation of the p27Kip1 gene in GR overexpressing lung tumor cell populations. Additional data from the co-PI's lab indicates that specific chemokines secreted by the senescent tumor cells attract and activate immune cells. Therefore, Dex treatment could improve outcome of surgery and pemetrexed chemotherapy and sensitize tumors to immunotherapy.

2. Keywords

Non-small cell lung cancer (NSCLC), dexamethasone (Dex), 3'-fluoro-3'-deoxy-thymidine (FLT), positron emission tomography (PET), glucocorticoid receptor (GR), pemetrexed (PEM)

3. Accomplishments

We have imaged five patients with two different Dex treatment/imaging schedules (schemas in Appendix). All were imaged at baseline and on day 3 of Dex 4 mg bid. Of the 5 patients 4 had a change in maximum standardized uptake value (SUVmax) within the range of reproducibility of FLT uptake (+/-10%). Actually, one patient with two quantifiable lesions the one in the chest changed by -9.28%, while the adrenal lesion changed by +9.24%. One patient had a change of -34.3%, but as noted below this was not sustained when Dex was stopped after 14 days and the patients was reimaged (change from baseline only -5.36%)

The first three patients had Dex stopped and were imaged again 6-9 days after completing Dex. While none had significant declines in FLT activity while on Dex at day 3, one patient had a decrease from baseline of 23.8% and 37.1% of the two measured lesions (this image was delayed for technical reasons until 17 days after stopping Dex).

Two patients had Dex 4 mg bid continued for 14 days and then Dex was stopped. They were then imaged again 6 days after completing the drug. As previously noted, one patient had a marked decline in SUVmax of 34.3% on day 3, but activity returned to near baseline after Dex was stopped on day 14 and reimaged 6 days later (-5.36%). The other patient had stable FLT activity on day 3 (-8.29%) but it changed by +22.6% compared to baseline 6 days after stopping Dex.

In summary, we found variable uptake of FLT in patients during Dex (day 3) of treatment, but only one of five had a marked decline. Furthermore, declines in FLT activity after completing 3 or 14 days of Dex was only seen in one patient.

F-18 FLT (DEX)

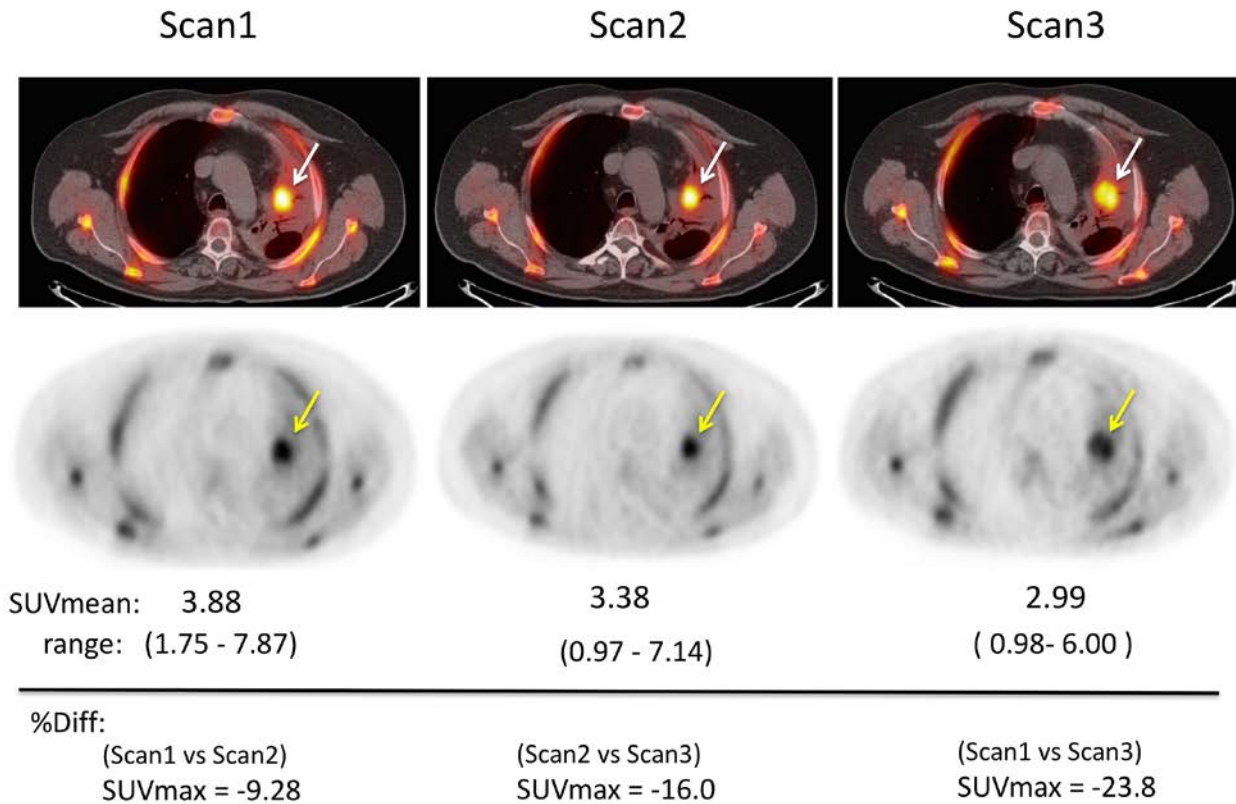


Figure 1. Images and quantitation for lung lesion in patient 2. The patient was scanned at baseline (scan 1), one day 3 of Dex 4 mg bid, and then 17 days after stopping Dex. Further images and results above and in Appendix.

4. Impact

Fluorothymidine-positron emission tomography (FLT-PET) imaging is a functional approach to assess the affect of dexamethasone (Dex) on non-small cell lung cancers (NSCLC). It demonstrates that Dex can decrease tumor proliferation in a minority of patients in this pilot study. Dex treatment 4 mg bid has been shown to improve symptoms in patients with advanced lung cancer, but the impact of this change is quite variable and a good predictive marker is need to help select patients likely to benefit from Dex treatment. This might be integrated with new genomic testing, now including full transcriptome at KCI, which could be used to assess GR levels and other markers.

5.Changes/Problems

One notable issue is the change in the treatment paradigm for lung cancer over the last few of years. Our initial protocol was designed with the standard use of chemotherapy, most commonly pemetrexed and a platinum, in mind. We continue to expand the use of targeted therapies, but more importantly, immunotherapy has become the standard of care, even for first-line treatment of NSCLC. One often combines anti-PD-1 immunotherapy with the chemotherapy, which has been shown to improve outcomes in randomized trials. Hence, our initial plan to combine Dex with chemotherapy alone was no longer current. We altered to plan to study more prolonged therapy with Dex. Preliminary results have demonstrated that this may lead to senescence and may provide a complementary approach to both chemotherapy and immunotherapy.

We still have had problems in recruitment and our colleagues downtown and in the community identified two patients interested and apparently eligible for the study in the last two months. We then found that

they had diabetes and hence were not eligible to get Dex. We believe that patients with advanced lung cancer and well-controlled diabetes have little risk from Dex. We amended that protocol to allow hemoglobin A1c levels of <8% to expand the pool of patients including those who will receive prolonged Dex on the separate study.

6. Products

Nothing to Report

7. Participants & Other Collaborating Organizations

Name: Anthony F. Shields MD PhD
Project Role: MPI
Research Identifier: ORCID ID 0000-0002-9122-1014
Nearest person month worked: 4.80
Contribution to Project: PI

Name: Manohar Ratnam PhD
Project Role: MPI
Research Identifier: N/A
Nearest person month worked: 1.92
Contribution to Project: PI

Name: Shirish Gadgeel, MD
Project Role: Co-Investigator
Research Identifier: N/A
Nearest person month worked: 0.96
Contribution to Project: PI

Name: Lance Heilbrun, PhD
Project Role: Co-Investigator
Research Identifier: N/A
Nearest person month worked: 1.44
Contribution to Project: Biostatistician

Name: Larry Matherly, Ph.D.
Project Role: Co-Investigator
Research Identifier: N/A
Nearest person month worked: 1.92
Contribution to Project: PI

Name: F. Huang
Project Role: research assistant
Research Identifier: N/A
Nearest person month worked: 4.80
Contribution to Project: Image analysis

Name: Jawana Lawhorn-Crews BS MS
Project Role: research assistant
Research Identifier: N/A
Nearest person month worked: 19.68
Contribution to Project: Image analysis

Change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period

Grants: A.F. Shields

NCI UG1CA233163 L Flaherty and A Shields (PIs) 3/5/2019-2/28/2025

NCI National Clinical Trials Network – Network Lead Academic Participating Site

The relationship between WSU/KCI and the NCTN has been built on the foundational premise that multidisciplinary clinical research provides the best treatment option for patients with cancer. Our goal over the next few years is to extend that level of commitment and participation through the McLaren community cancer research network within the State of Michigan.

NCI 5P30-CA22453-23 Bepler, Gerold (PI) 08/08/97 -11/30/20

Cancer Center Support Grant

Dr. Shields serves as Associate Center Director for Clinical Sciences. The major goals are for research infrastructure of the comprehensive cancer center grant. Roles: Senior Leadership and past Program Leader

NCI U01 CA199240 AG Schwartz and T Albrecht (PIs) 2/27/2017 -1/31/2022

Detroit Research on Cancer Survivors (Detroit ROCS)

The overall goal is to better understand major factors affecting cancer progression, recurrence, mortality and quality of life in Africa American cancer survivors. Role: Co-Investigator

Grants: M. Ratnam

W81XWH-17-1-0243 Ratnam (PI) 06/30/2017 -06/29/2020

ELK-1 Targeted Molecules as a New Paradigm for Prostate Cancer Treatment

Testing the hypothesis that small molecules may be used to disrupt the ELK1-AR interaction and selectively suppress growth signaling by AR in PC/CRPC cells.

Other organizations were involved as partners:

Nothing to Report

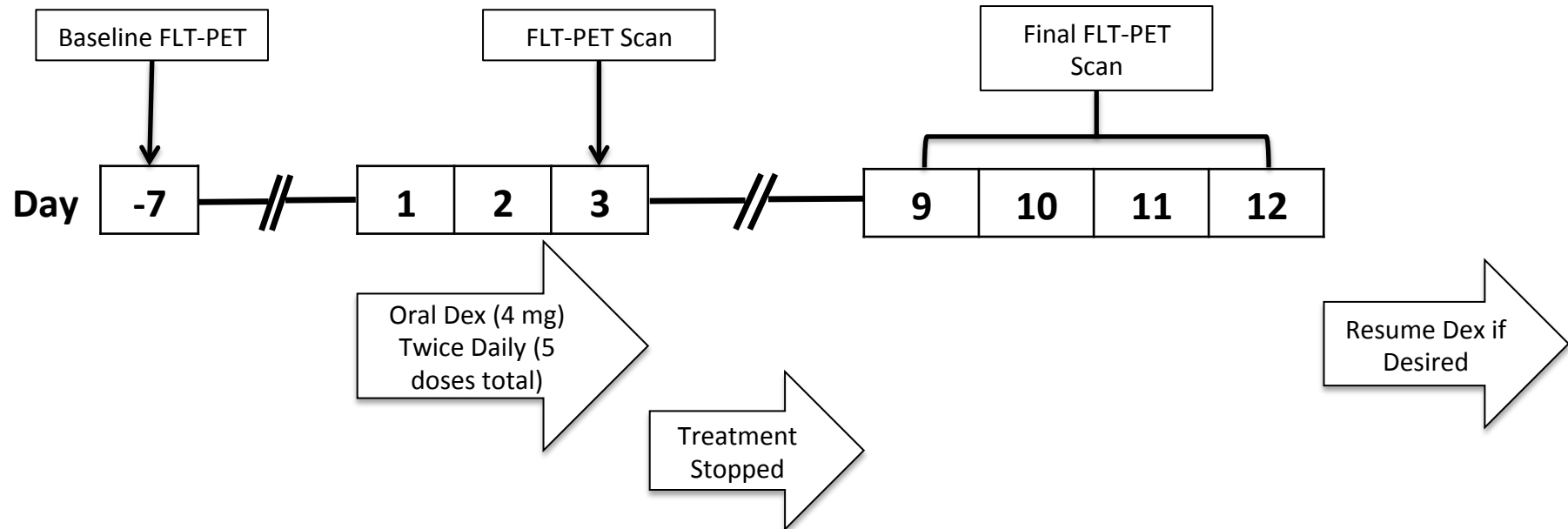
8. Special Reporting Requirements

Nothing to Report

9. Appendices

Treatment scheme and images with quantitation:

Treatment Plan #1



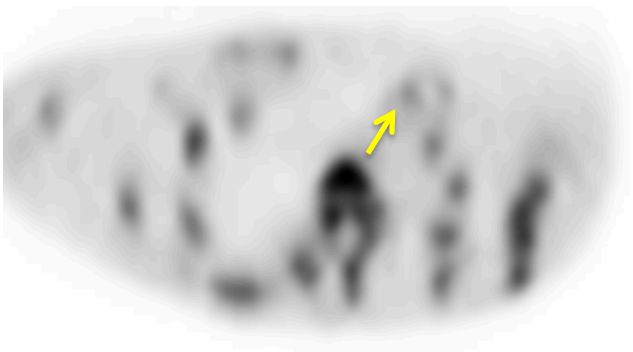
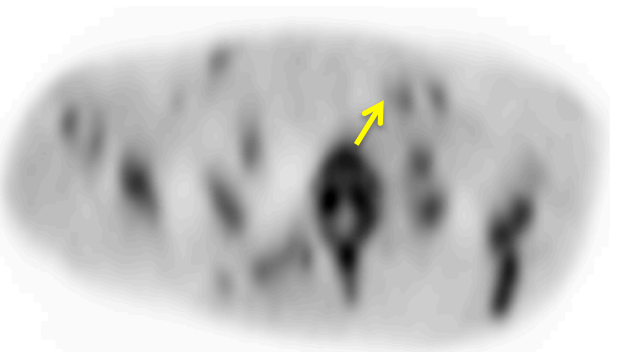
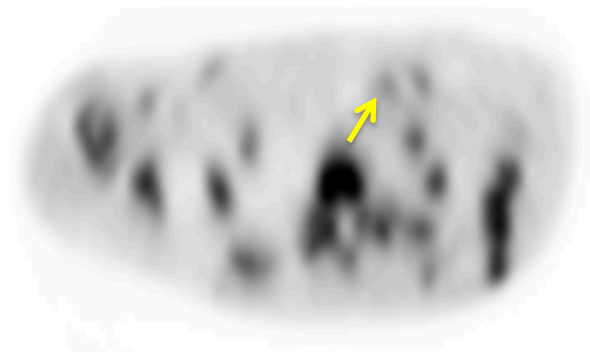
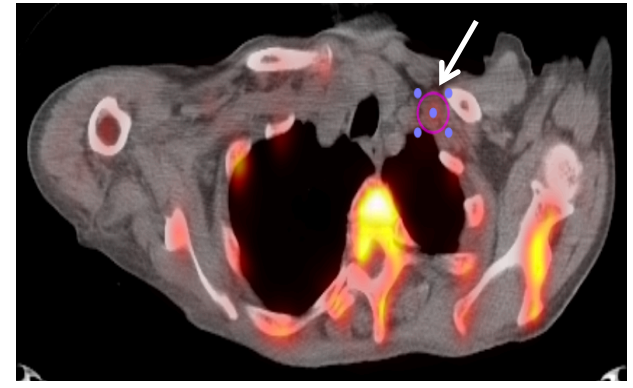
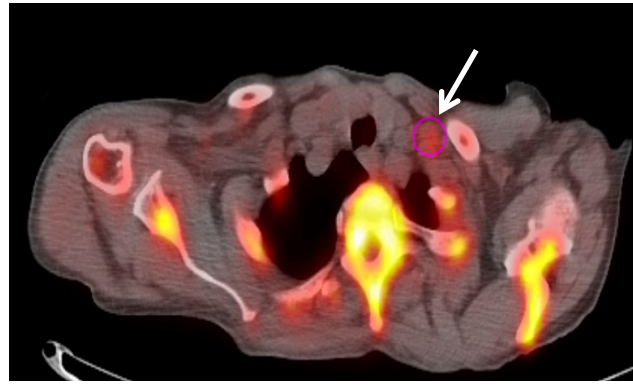
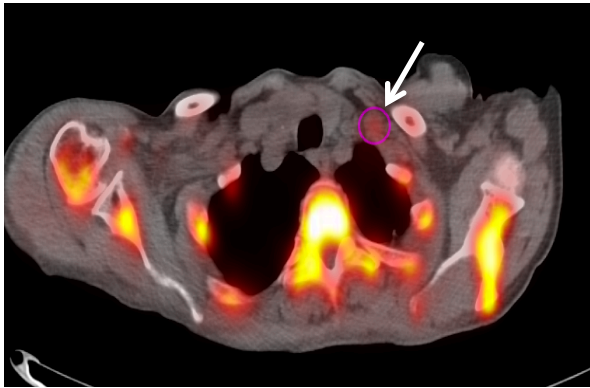
- Scan 1: Baseline FLT-PET imaging within 7 days before Dex treatment.
- Scan 2: After the 5th dose of Dexamethasone
- Scan 3: Final scan 6-9 days after the last dose of Dex.
- Dex (4 mg bid) may be resumed if agreed to by the patient and MD.

FLT- PET/ CT : Dex - Patient #1

Scan 1

Scan 2

Scan 3



SUVmean: 1.22
range: (0.87 – 1.79)

1.27
(0.85 – 1.85)

1.21
(0.76-1.74)

%Diff:

(Scan1 vs Scan2)
SUVmax = 3.35

(Scan2 vs Scan3)
SUVmax = -5.95

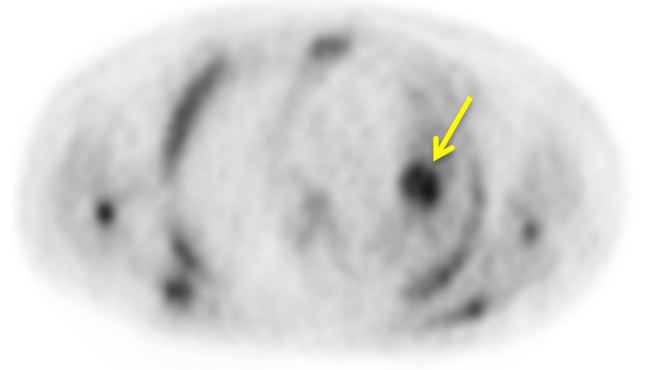
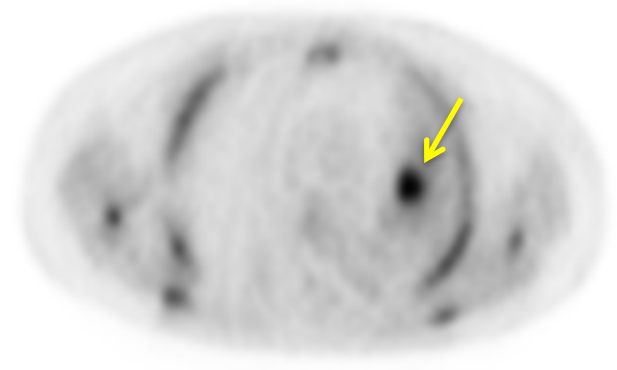
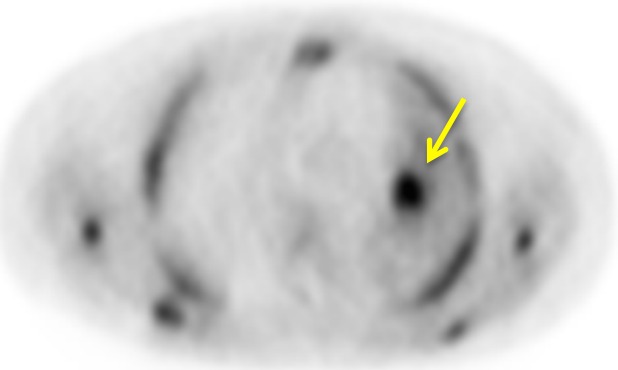
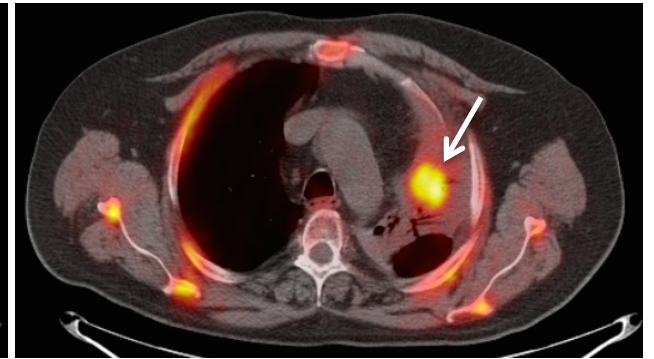
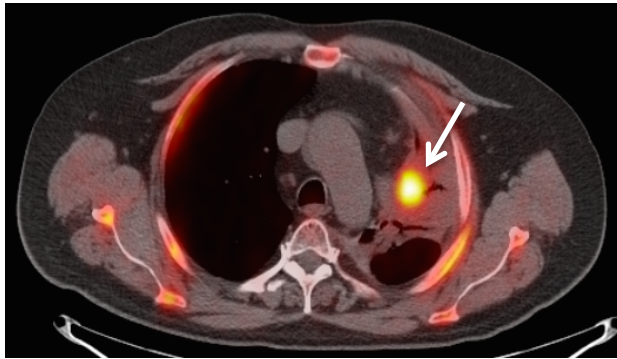
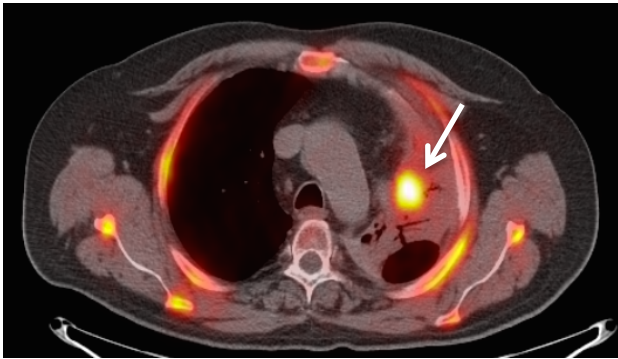
(Scan1 vs Scan3)
SUVmax = -2.79

F-18 FLT (DEX) Patient #2 -Tumor 1

Scan1

Scan2

Scan3



SUVmean: 3.88
range: (1.75 - 7.87)

3.38
(0.97 - 7.14)

2.99
(0.98- 6.00)

%Diff:

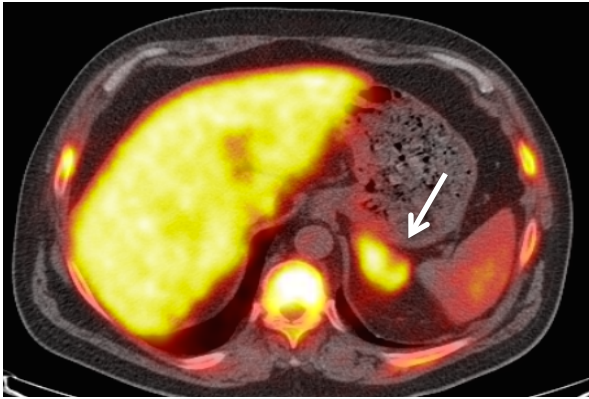
(Scan1 vs Scan2)
SUVmax = -9.28

(Scan2 vs Scan3)
SUVmax = -16.0

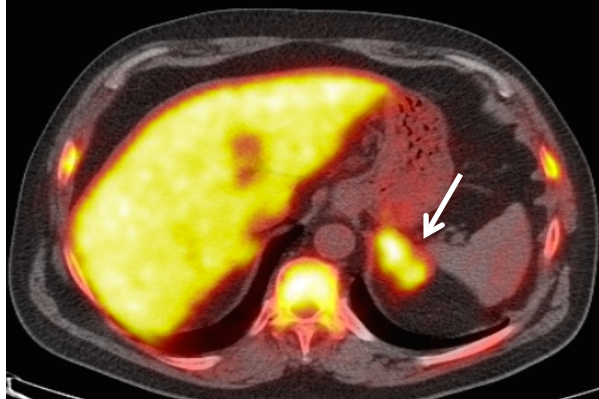
(Scan1 vs Scan3)
SUVmax = -23.8

F-18 FLT (DEX) Patient #2 - Tumor 2

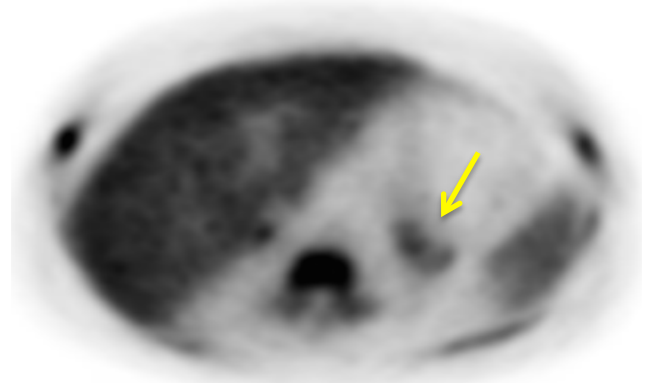
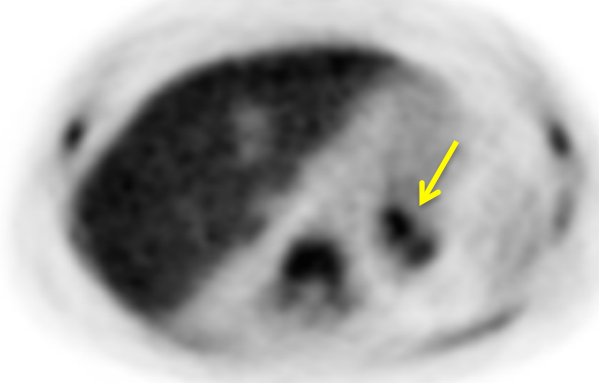
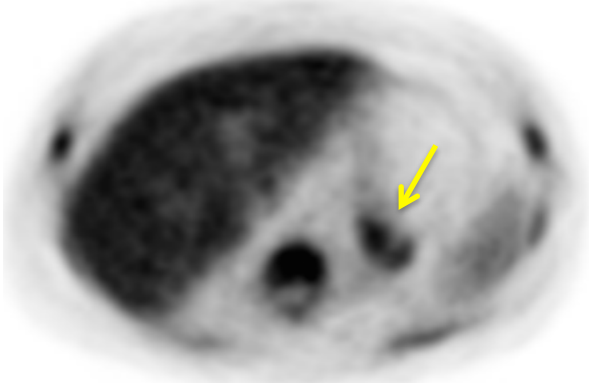
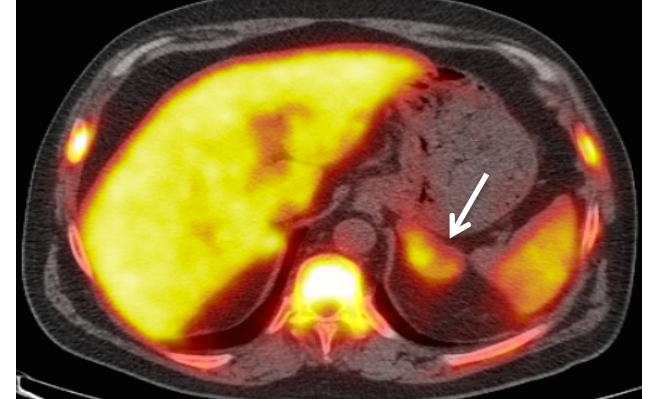
Scan1



Scan2



Scan3



SUVmean: 4.61
range: (1.81 - 6.77)

4.55
(2.09 - 7.40)

2.91
(1.51 - 4.26)

%Diff:

(Scan1 vs Scan2)
SUVmax = 9.24

(Scan2 vs Scan3)
SUVmax = -42.4

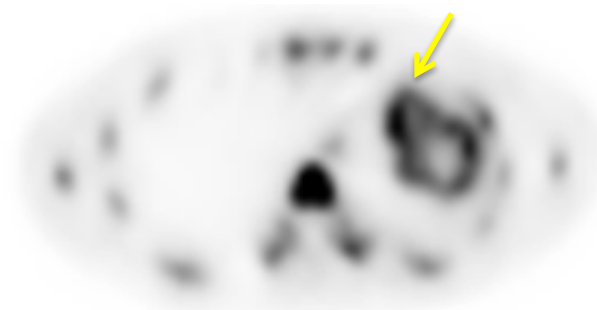
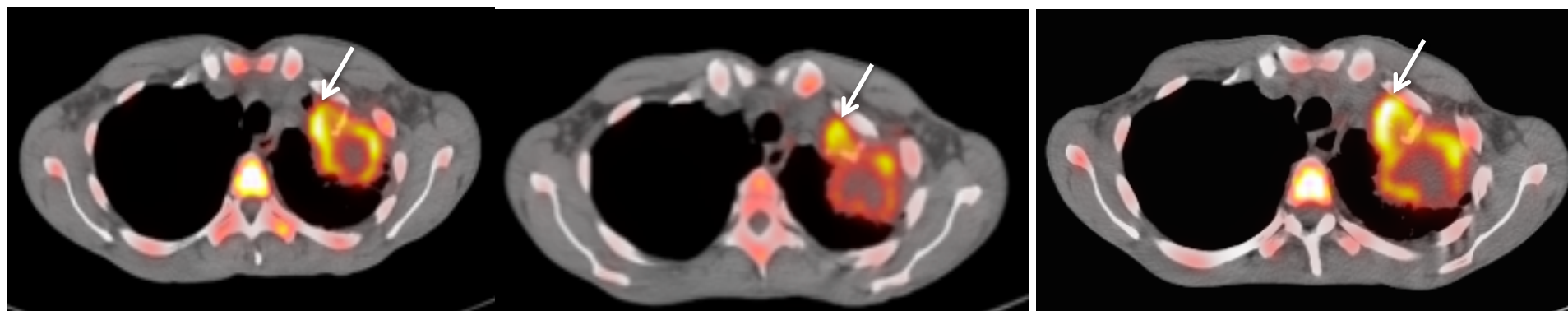
(Scan1 vs Scan3)
SUVmax = -37.1

F-18 FLT (DEX) Patient #3

Scan1

Scan2

Scan3



SUVmean: 5.63
range: (2.05 – 6.14)

5.51
(1.60 – 5.75)

6.72
(2.13 - 6.85)

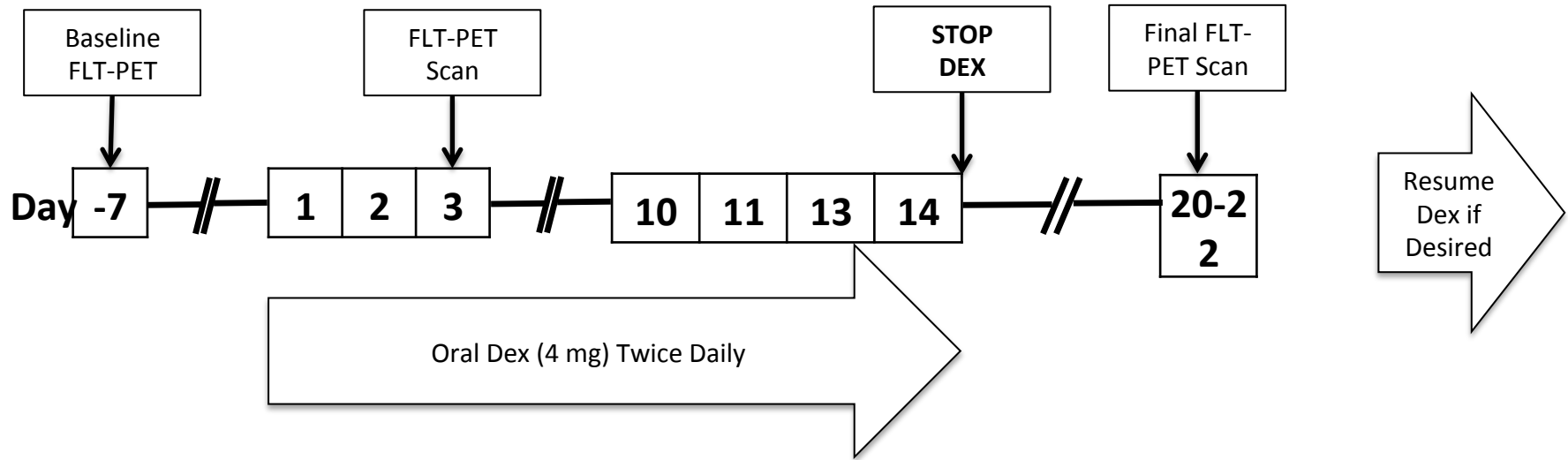
%Diff:

(Scan1 vs Scan2)
SUVmax = -6.35

(Scan2 vs Scan3)
SUVmax = 19.1

(Scan1 vs Scan3)
SUVmax = 11.6

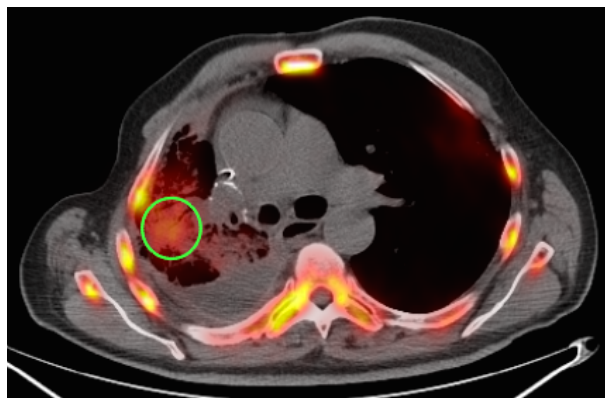
Treatment Plan #2



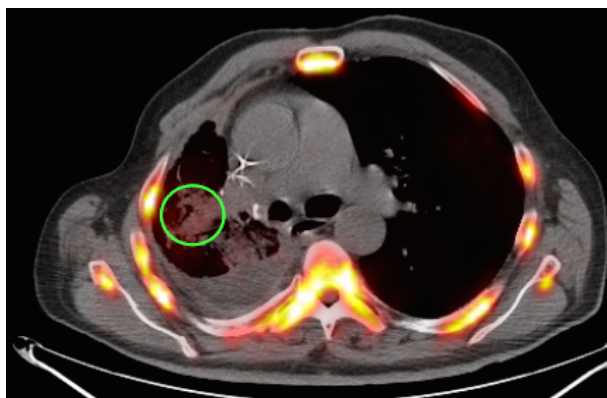
- Scan 1: Baseline FLT-PET imaging within 7 days before Dex treatment
- Scan 2: After the 5th dose of Dex on Day 3
- Continue Dex for total of 14 days
- Stop Dex
- Scan 3: Final scan 6-8 days after the last dose of Dex
- Dex (4 mg bid) may be resumed if agreed to by the patient and MD

F-18 FLT (DEX) Patient # 4

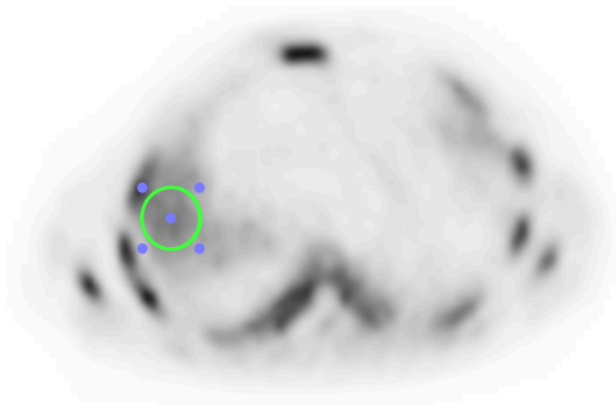
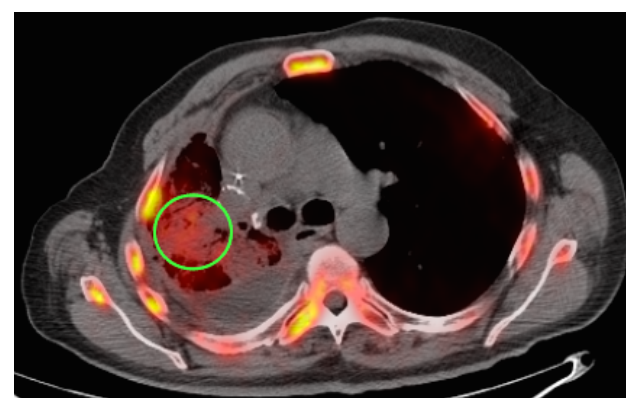
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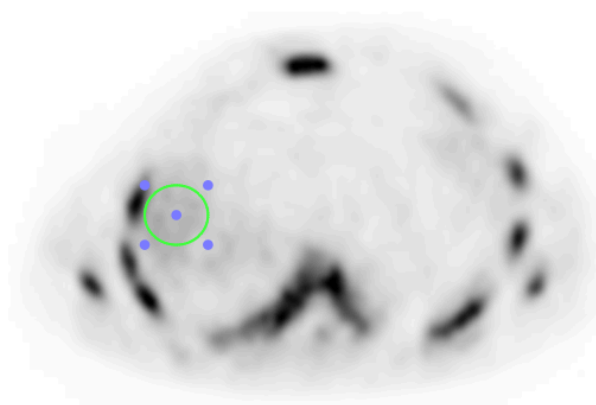
Scan 2



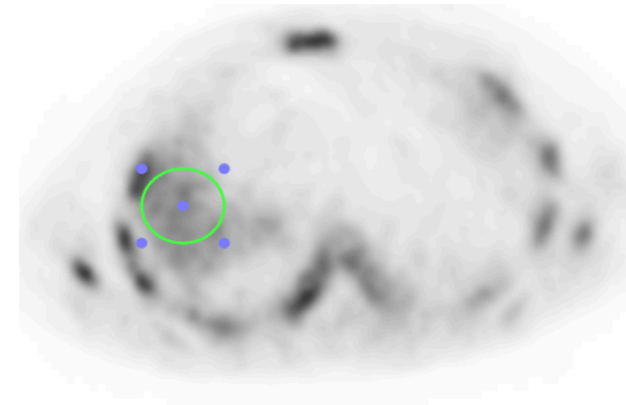
Scan 3



SUV mean: 2.25
range: (1.50 - 2.80)



1.41
(0.91 - 1.84)



2.03
(0.95 - 2.65)

%Diff:

(Scan1 vs Scan2)
SUVmax = -34.3

(Scan2 vs Scan3)
SUVmax = 44.0

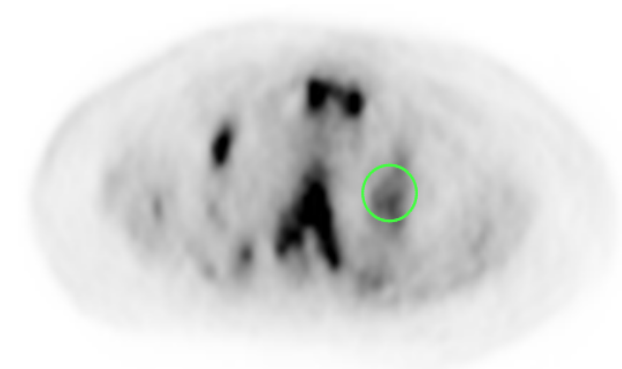
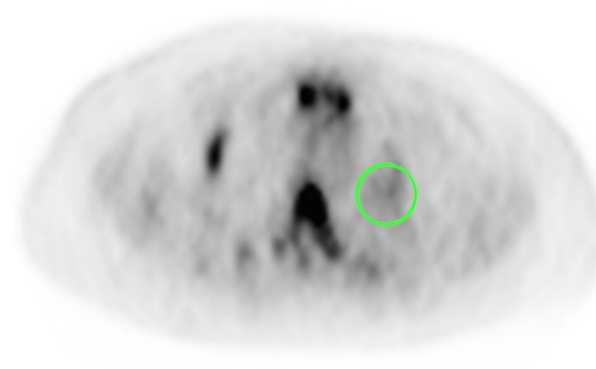
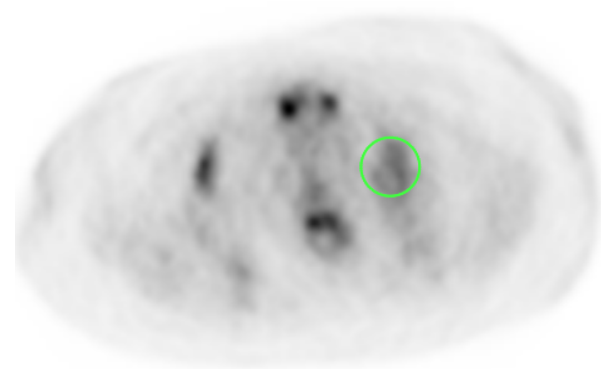
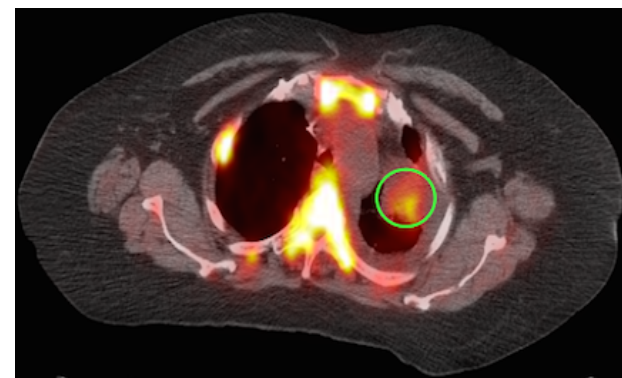
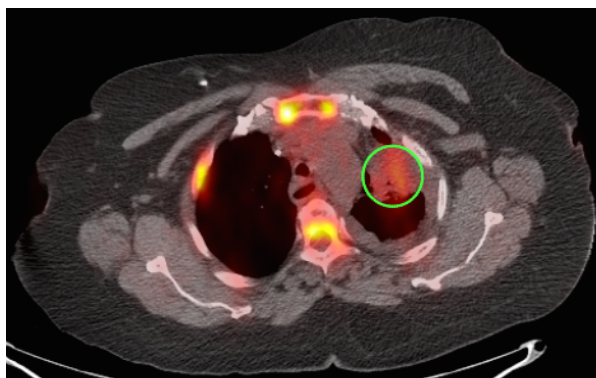
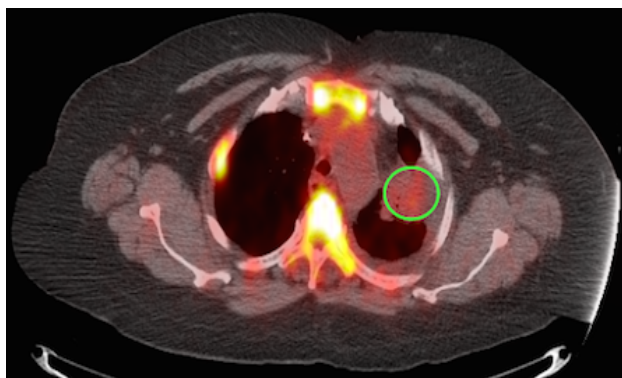
(Scan1 vs Scan3)
SUVmax = -5.36

F-18 FLT (DEX) Patient #5

Scan 1

Scan2

Scan3



SUV mean: 1.51
range:(0.85 - 2.17)

1.41
(0.75 - 1.99)

1.74
(0.90 - 2.66)

%Diff:

(Scan1 vs Scan2)
SUVmax = -8.29

(Scan2 vs Scan3)
SUVmax = 33.7

(Scan1 vs Scan3)
SUVmax = 22.6