FDG PET Imaging: Measuring Response to Therapy

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Limitations of conventional imaging:

- Residual mass due to fibrosis
- Therapy-related new findings
- Anatomical regression of tumor takes time

Role of PET

- Metabolic changes occur before anatomical changes and PET allow evaluation of metabolic changes and therefore of early response
- For example: FDG PET can characterize residual masses as metabolically active or not
PET and Tumor Response to Therapy

- **Metabolic characteristics:**
  - Cellular proliferation (high bg in BM and liver): e.g. FLT
  - Cellular oxygenation-hypoxia: e.g. FMISO, Cu-ATSM
    - Hypoxia increases resistance to XRT
    - Hypoxia leads to phenotypic heterogeneity
  - Hormone dependency
  - Drug binding-sensitivity
  - Receptor status: e.g. estrogen receptors for breast cancer
  - Gene expression/Gene therapy:
  - Cellular metabolism: e.g. FDG
  - Cell death

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Measuring Response to Therapy with PET

- Residual tumor at surgical site or post-surgical staging
- Response to radiation therapy
- Response to chemotherapy
  - Early
  - After completion
- Response to neo-adjuvant therapy
Monitoring Response to Therapy with FDG PET: Timing in Relation to Surgical Therapy

**Surgery:**
- ~ 2 months for surgical site
- Anytime for staging elsewhere.
Patients s/p gastrectomy for lymphoma 2 weeks prior

Diagnosis: FDG uptake in healing surgical incision

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Patient with esophageal cancer s/p surgery 2 months earlier with still inflamed scar
39-year-old with unresectable head and neck carcinoma, s/p recent tracheostomy

Diagnosis: Tracheostomy

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62 year-old male s/p resection of recurrent lymphoma of the small bowel 2 weeks earlier.

Diagnosis: post-operative changes
39-year-old male with a history of recurrent melanoma s/p lymphadenectomy of the right axilla

Diagnosis:
1) Post-operative changes
2) Internal mammary LN
Monitoring Response to Therapy with FDG PET: Timing in Relation to Radiation Therapy

- More than 6 months after completion of radiation:
  - FDG uptake indicates tumor recurrence
- Early after radiation (within 2 months…up to…..):
  - FDG uptake matching the radiation port due to inflammatory changes
- Recommendations:
  - Wait as long as possible after radiation before performing FDG PET
  - Comparison to baseline PET is helpful
  - Knowledge of radiation ports is helpful.
62-year-old female with RUL NSCLC s/p remote XRT to the primary and to the upper lumbar spine for a skeletal metastasis.

Diagnosis: Residual tumor at the primary site and additional bone metastases.
45-year-old man with SCC of the larynx 2 months after radiotherapy

Biopsy: Inflammatory changes and chondronecrosis

69-year-old female with carcinoma of the base of the tongue s/p chemo and radiation

Diagnosis: Recent radiation changes (2 weeks) matching the radiation port

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81-year-old male with large cell carcinoma treated with radiation therapy

Diagnosis: Radiation pneumonitis

65 year-old with lung cancer s/p XRT to mediastinum 1 week earlier

Radiation esophagitis

Curvilinear photopenia along diaphragm due to motion of diaphragm

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45-year-old man after completion of neo-adjuvant chemoradiation therapy for SCC of the right tonsil

Diagnosis: thrombophlebitis in right internal jugular vein

Monitoring Response to Therapy with FDG PET: Timing in Relation to Chemotherapy

Physiological uptake in response to therapy

- For 2-4 weeks: Bone marrow and spleen due to regenerating bone marrow (hyperplasia)
  - Worse if bone marrow stimulating factors have been administered with chemotherapy (e.g. G-CSF, neupogen)
- Possible transient cellular stunning
- Possible inflammatory response: metabolic flare

Recommendation:

- At least 2 weeks after last chemotherapy or just before next cycle
- 2-months after completion of therapy
14-year-old boy who just completed chemotherapy for lymphoma

Diagnosis: Reactive bone marrow hyperplasia

A 42-year-old female who underwent a left mastectomy for breast carcinoma followed by chemotherapy presented with rising tumor markers.

Diagnosis: Severe bone marrow uptake related to administration of G-CSF the day before.

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Diagnosis: Thymic hyperplasia
15 year-old male with lymphoma

Pre-Therapy

After 2 cycles

After completion

6 months F/U

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16-year-old boy s/p completion of chemotherapy for NHL

Diagnosis: Thymic hyperplasia
FDG PET: Thymic Uptake

- 168 patients with retrosternal lesions attributable to thymus
  - Children with malignancies pretherapy: n = 15, mean age = 12
    - Increased FDG uptake in 73%
  - Children with malignancies after chemotherapy: n = 12, mean age = 10
    - Increased FDG uptake in 75%
  - Adults with lymphoma before therapy: n = 37, mean age = 43
    - No FDG uptake
  - Adults with lymphoma 1-4 months after chemotherapy: n = 104, mean age = 41
    - Increased FDG uptake in 5%, eldest was 25 year of age

Sources of False-positives Interpretations

◊ Physiologic FDG uptake
  ▪ GU tract
  ▪ GI tract
  ▪ Muscular system

◊ Inflammation
  ▪ Therapy-related
  ▪ Infection
  ▪ Trauma
  ▪ Granulomatous diseases
FDG PET(/CT) Imaging Reports

- Brief history including
  - Timing from therapy
  - Reason for referral
  - Relevant findings on physical examination

- Comparative studies available

- Blood glucose level at the time of FDG administration

- Documentation of drugs and radiopharmaceuticals

- Type of equipment and imaging protocol

- Findings on PET and correlative findings on CT

  - (Additional incidental findings on transmission CT)

- Diagnostic impression

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Image Interpretation and Analysis

Do We Need Quantification?

- Visual analysis
- Semi-quantitative analysis using ratio of activity in two ROI: Lesion/background or right/left
- Semi-quantitative analysis: Standard uptake value

\[
\text{Activity in ROI (microcuries/ml)}
\]
\[
\text{SUV} = \frac{\text{Dose (mCi)}}{\text{Weight (kg)}}
\]

- Absolute quantification using kinetic analysis and compartmental modeling

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Standard Uptake Value

- Affected by tumor size because of partial volume effects.
- Depend on:
  - Plasma glucose levels
  - Body weight
  - Body composition
  - Time of imaging after FDG administration
  - ROI size: SUV max versus SUV avg
  - Resolution capability of the scanner
- Requires measurements of absolute concentration of positron emitter (in microCi/cc) in region of interest.

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Quantitative PET: Absolute concentration

Depends on:
- Detector normalization and calibration
- Correction for artifacts related to the scanner:
  - Deadtime correction
  - Random correction
  - Scatter correction
- Image reconstruction
- Correction for artifacts related to the object or subject
  - Partial volume effects
  - Attenuation correction
Correction for Attenuation Artifacts

Methods:

- Calculated attenuation correction: e.g. Brain
- Measured attenuation correction using various transmission sources: best XR source

Quality of the images with AC: accuracy of registration of the emission and transmission scan.

Problems:

- Inaccurate repositioning of the patient between scans
- Motion of the patient and motion of internal organs
- Type of source and reconstruction
Standard Uptake Value

- Reproducibility of the SUV depends on:
  - Rigorous quality control of the PET system
  - Imaging protocol.

- For absolute measurement of metabolic rate
  - Analysis of dynamic data over tumor
  - Arterial input function is also needed:
    - Arterial sampling
    - Or dynamic scanning over the heart
  - Patlak analysis: simplify computation by assuming that FDG is trapped intracellularly
  - Not practical clinically
FDG PET to Monitor Therapy: Clinical Data

- Brain Tumors
- Lung cancer
- Head and neck
- Sarcoma
- Germ cell tumors
- Lymphoma
- Breast cancer
- Esophageal cancer
- Colorectal cancer
- Regional therapy to hepatic tumors

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Brain Tumors: FDG PET

Tumor Recurrence vs Radiation Necrosis

- Delayed radiation necrosis usually occurs 6 months after radiotherapy (5000 rads)
- CT and MRI changes mimic tumor recurrence

Diagnosis: High grade tumor recurrence


Patronas NJ et al. Radiol 1982;144:885
FDG PET for Brain Tumors
Monitoring Radiotherapy

- 14 patients with gliomas:
  - FDG PET at baseline and 2 weeks post-XRT
- Low MRglc at baseline correlates with longer survival
  - No correlation between MRglc post-XRT and survival: Hypothesis:
    - Apoptosis requires energy
    - Inflammatory infiltrate

FDG PET for Brain Tumors
Tumor Recurrence versus Radionecrosis after Stereotactic Surgery

✧ 47 patients: mean time between XRT and FDG PET ~ 6 months*
  - To predict tumor recurrence:
    ✧ Sensitivity FDG PET: 75%, improves to 86% with MRI co-registration
    ✧ Specificity FDG PET: 81%

✧ 19 cerebral tumors in 8 patients both primary and metastatic**:
  - Starting 4 H after stereotactic surgery: Increase in phosphorylation process

FDG PET for Lung Carcinoma: Monitoring Therapy

- Locally advanced NSCLC (stage IIIB and IV): 25-40%: Poor survival

- After completion of induction chemotherapy:
  - FDG PET > CT to detect residual disease
  - Persistent FDG + indicates poor prognosis

- Neoadjuvant chemoradiation can downstage and allow for subsequent treatment resulting in improved survival in 30% of patients.
  - FDG PET can monitor response


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65-year-old male with non small cell carcinoma stage 3- s/p neoadjuvant chemo-radiation

Pre-therapy

Post-therapy

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FDG PET for H&N cancer: Monitoring Therapy

- Treatment advance stage (III and IV): chemo- and XRT
- Degree of FDG uptake pre-T predicts aggressiveness and poor survival*:
  - Pre-Therapy SUV > 7 predicts poor response
  - Post-therapy SUV >4 indicates residual disease and poor survival
- FDG PET can monitor radiation therapy **
  - FDG – at 4 months more accurate than at 1 months
  - FDG PET is reasonably accurate at 6 weeks post chemo-radiation #
- FDG PET can monitor neoadjuvant therapy***
  - To predict residual disease: sensitivity 90%, specificity 83%

FDG PET for Advanced H&N cancer: Monitoring Therapy

- 26 patients with stage III or IV HNSCC
- FDG PET at baseline and 6 weeks after completion of radiation and chemotherapy compared to histology or 6 months F/U

Results:
- FDG PET T+ (n=10): residual tumor, metastases or 2d primary (5 of which were occult clinically)
- FDG PET T- (n = 14)
- FDG PET F+ (n = 1)
- FDG PET F- (n = 1)
- Sensitivity: 90.9%
- Specificity: 93.3%


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FDG PET for Sarcomas: Monitoring Neo-adjuvant Therapy

- Heterogenous group of tumors: osteosarcoma is most common primary malignant bone sarcoma
- The response to neo-adjuvant chemotherapy
  - Important prognostic factor in osteogenic and Ewing’s sarcomas.
- Poor response to neo-adjuvant chemotherapy:
  - Higher failure rate of limb-salvage procedures instead of amputation.

FDG PET for Bone and Soft Tissue Sarcomas: Monitoring Therapy

- FDG PET can differentiate responders from non-responders in 80-90% of patients.
- Persistent uptake in benign therapy related changes has been reported.
- SUV post-therapy and ratio SUV pre-/ post-therapy correlate with histological response.

Gastrointestinal Stromal Tumors (GIST)

- Leiomyosarcoma from interstitial cells of the myenteric plexus
- Extremely poor prognosis.
- Express growth factor with tyrosine kinase activity.
- Imatinib (STI571 or Glivec, Novartis) is a selective tyrosine kinase inhibitor
- FDG PET: decreased uptake after a few days of therapy:
  - Phase II Trial of neoajuvant STI-571 for primary and recurrent operable malignant GIST expressing the KIT receptor tyrosine kinase (CD117).
- Study of 21 patients:
  - 13 responders by PET at 8 days (EORTC criteria) and 10 by CT at 8 weeks (RECIST)*
  - PET responders associated with better progression free survival (92% versus 12%)


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FDG PET for Germ Cell Tumors
Restaging and Monitoring Therapy

- Non-seminomatous germ cell tumors (NSGCT): 60%
  - embryonal carcinomas, choriocarcinomas, mixed histologies, teratomas

- Advanced disease: 60-85% have residual mass after completion of systemic therapy
  - NSGCT: 20-25% have residual tumor and 30-40% teratomas
    - Surgery indicated
    - FDG PET: good PPV, poor NPV because false – teratomas
    - FDG PET: kinetic analysis improve teratomas vs necrosis*

Spermon JR et al. BJU Int 2002;89:549-556.

**Sugarawa Y et al. Radiology 1999;211:249-256.**

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FDG PET for Germ Cell Tumors
Restaging and Monitoring Therapy

✦ Seminomas: 40%
  ✦ < 3cm usually benign,
  ✦ > 3 cm: 27-41% have viable tumor, surgery indicated
  ✦ FDG PET: good PPV and NPV*

✦ Timing of FDG PET after therapy: less F- after 2 weeks**

✦ Detection of recurrence when elevated tumor markers
  ■ FDG PET : Good PPV, good NPV, localize***

✦ Prediction of response to therapy for relapsed GCT#

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A 20-year-old male with a history of testicular ca presented with elevated tumor markers and normal CT scan.


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Recommendations of EORTC for Determining Tumor Response with FDG PET

- **Progressive metabolic response:**
  - Increase of SUV > 25%
  - Increase of extent of FDG uptake

- **Stable metabolic disease**
  - Increase of SUV < 25% or decrease < 15%
  - No visible change in extent

- **Partial metabolic response**
  - Decrease of a minimum of 15-25% SUV after 1 cycle of chemotherapy or greater than 25% after more than 1 cycle

- **Complete metabolic response:** No FDG uptake

Monitoring Response to Therapy with FDG PET:

Important:

- A negative FDG PET scan does not exclude residual microscopic disease
- Chemotherapy (with or without radiation) should be completed as planned based on histology/stage.
Applications for FDG PET Imaging in Oncology Approved by HCFA for Medicare Reimbursement

- Non-small cell carcinoma*
- Esophageal cancer*
- Colorectal cancer*
- Lymphoma*
- Melanoma* (excluding evaluation of regional LN)
- Head and Neck cancers* (excluding CNS)
- Thyroid cancer, follicular type (post-surgery, Tg > 10, WB $^{131}$I-)
- Breast cancer (excluding diagnosis, including monitoring therapy)
- Refractory seizures (presurgical evaluation only)
- Myocardial viability and perfusion

Covered for diagnosis, staging and restaging, not for monitoring therapy
Limited to selected high performance PET scanners only

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