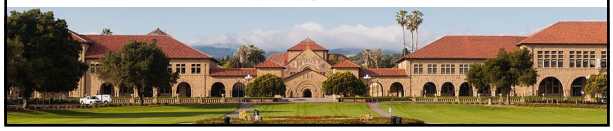
Department of Radiation Oncology
School of Medicine
Stanford University

PET Based Biological Adaptive Radiation Therapy: Current State of Art

AAPM 2022 Annual Meeting
Bin Han, Ph.D.



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Disclosure

- Currently receiving research funding support from:
  - Viewray
  - RefleXion

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Outline

- PET imaging / functional imaging
- PET-based ART for HN, Lung, Cervical and Prostate
- PET/CT/Linac for offline/online ART

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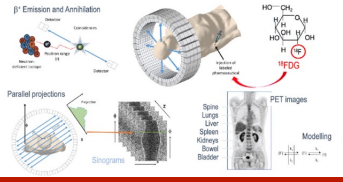
Positron emission tomography (PET)

- PET is a functional imaging technique that uses radiotracers to visualize changes in metabolic processes, and activities including blood flow, regional chemical composition, and absorption.
- A radiotracer is injected into the body. The e-p annihilation process emits gamma rays and the signals are detected by detector arrays to form 3D PET images.
- Tracer: 18F-FDG → cancer and GTV delineation, NaF-F18 → bone formation, oxygen-15 → measure blood flow



Beyer et al, 2020 Cancer imaging

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Patient preparation and FDG Dosage

- No caloric uptake for 4 - 6 hours before FDG injection
- Typical dose of FDG is 10 mCi intravenously injected
- Typical dose to patient is 10~30 mSv
- Uptake time (45 to 60 min), quiet & relaxed environment to minimize muscle uptake
- PET is performed following the CT study with same patient position
  - The CT study takes ~ 1 minute, while PET study takes 30~45 minutes depending on the coverage required

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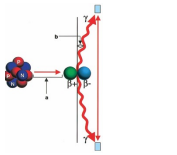
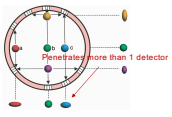
^{18}F FDG PET CT

- Image artifacts
  - CT attenuation correction artifacts
    - Mismatch between PET and CT due to patient motion
    - Metal artifacts in CT
  - Positron range blurring
    - The traveling distance of position before annihilation:
    - 1~3 mm of uncertainty
  - Annihilation angle blurring
    - Two annihilating photons are not exactly 180 apart: 0.5 degree of uncertainty
  - Radial blurring
    - Ring geometry of detector
    - Non-uniform penetration by photons
    - Worse at image periphery
  - PET resolution is about 4~5 mm





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Biological Imaging in Radiation Therapy

- CT and MRI improved structure visualization with enhanced spatial resolution.
- PET imaging visualize biological and molecular level in tumor
- Wide spectrum of positron-emitting tracer to cover more disease sites with high sensitivity

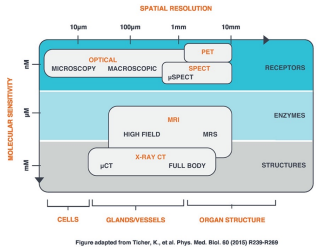

Figure adapted from Ticher, K., et al. Phys. Med. Biol. 60 (2016) R39-R369

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PET Tracers

- Metabolism tracer :
  - ^{18}F-FDG, ^{11}C-Glucose, ^{18}F-FDM. .. , Therapeutic evaluation and extension of many cancers
- Hypoxia tracer:
  - ^{18}F-MISO, ^{18}F-FAZA$_n$ and ^{64}Cu-ATSM . . . H&N, lung, brain cancers
- Proliferation tracer
  - ^{18}F-FLT…. Lymphomas and etc
- Specific membrane tracers:
  - ^{18}F-Choline, ^{11}C-Choline ^{68}Ga-PSMA…. Prostatic cancer

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Why PET based ART?

- PET imaging reveals tumor characteristics
  - Captures biological processes within the tumor → definition of the GTV
  - Captures the microscopic spread to adjacent tissues or lymph nodes → modified CTV definition strategies.
- PET-based biological response to treatment
  - Dose escalation
  - Dose de-intensification
  - Dose painting

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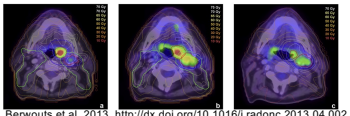
Head and Neck Cancer

- PET/CT widely used in:
  - Diagnosis of the head and neck cancer.
  - Staging: high level of accuracy in detecting nodal disease and sensitivity for distant metastases.
  - Treatment response analysis: PET imaging 12 weeks after chemoradiation to decide if surgery needed to maintain overall survival.
  - Outcome prognostication: hypoxia tracers of hypoxia are promising prognostic biomarkers.



Berwouts et al. 2013. http://dx.doi.org/10.1016/j.radonc.2013.04.002

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PET-based Adaptive Head and Neck Radiotherapy

- PET-guided response-adapted ART:
  - Dose escalation → persistent radiotracer uptake represent radio-resistance
  - Reducing the volume of disease being boosted.
- Dose escalation:
  - Duprez et al. (Red journal 2011) phase I feasibility trial:

  Dose escalated to 80 Gy to areas of persistent avidity on a PET-CT scan performed during week 2. No acute dose-limiting toxicity was encountered.
  - Berwouts el al (Red Journal 2013, 2017):

  Comparable 5 year local control (82.3% vs 73.6%, p = 0.36) but higher chronic toxicity because of the higher hotspot. So dose escalation is still an open question.

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PET-based Adaptive Head and Neck Radiotherapy

- Dose de-intensification:
  - Use interim diagnostic imaging to guide dose de-intensification in responders, with the goal to improve the acute and chronic toxicity
  - Correlating interim PET-CT tumor response → local-regional failure free survival demonstrated:

  More pronounced metabolic response by mid-treatment scan → better long-term locoregional control

  (Lin et al Radiother Oncol. 2016;120(1):87–91; Min et al, J Med Imaging Radiat Oncol. 2016;60(3):433–40)
- PEARL(NCT03935672): upcoming phase II feasibility study:
  - PET/CT scan after 2 weeks to guide reduction in target volumes as the tumor responds.
  - The biological GTVs consist of the high FDG uptake volume are automatically delineated by ATLAAS and verified by a nuclear medicine physician and a clinical oncologist.
  - Replan to deliver high dose to a smaller area of normal tissues in the mouth and throat
  - Assess the treatment outcome.

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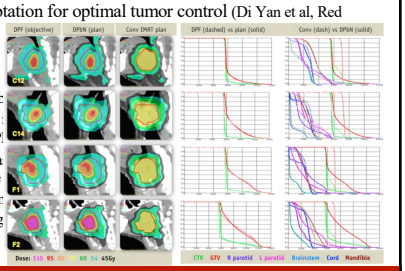
PET-based Adaptive Head and Neck Radiotherapy

- Dose painting plan adaptation for optimal tumor control (Di Yan et al, Red Journal 2019) :
  - Serial PET images for 18 6-month posttreatment
  - 4 out of 18 patient had a b
  - Treatment feedback PET prescription function (DP
  - Using tumor voxel DPF a of adaptive adaptive dose
  - The adaptive DPbN treatr with similar OAR sparing



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PET based ART for Lung Cancer

- The emerging roles of FDG-PET imaging in the management of NSCLC:
  - target definition,
  - early response assessment,
  - identification of tumor subregions that are spatially correlated with recurrence
- PET-based lung ART were used to overcome heterogeneity in response by intensifying treatment to high-risk regions defined on functional imaging.

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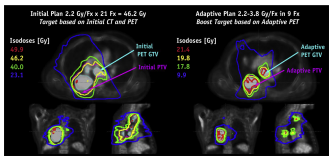
PET based ART for Lung Cancer

- RTOG 1106
  - Initial plan 2.2Gy/Fx (46.2Gy/21Fx) to PET/CT target
  - Boost up to 3.8 Gy/Fx (80.4 Gy/30Fx) to residual CT and PET volumes based on during-treatment imaging.
- Image resolution
- Need multiple adaptations



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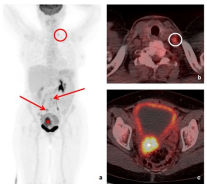
PET based ART for Cervical Cancer

- Difficulties of Radio-chemotherapy of locally advanced cervical cancer:
  - Movement of the target volumes and OARs: uterine fundus of up to 5 cm in AP, up to 2cm translation related to rectal distention.
  - Tumour volume decreases by an average of 2/3 during treatment
- PET/CT imaging is important in staging and follow-up, improves lymph node assessment compared to MRI or contrast-enhanced CT
- Potential intra-treatment FDG PET/CT ART approach:
  - identifies patients with a favorable prognosis → dose de-escalation.
  - the persistence of poor prognostic metabolic parameters → dose escalation protocols in the primary tumor or lymph nodes.



Gandy et al. Seminars in Nuclear Medicine Vol 49, (6), 2019, P461-470

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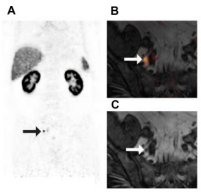
PET based ART for Prostate Cancer

- Challenges in PTV definition:
  - increased risk of toxicity if the margins are loo large
  - increased risk of recurrence if the margins are too small.
- Prostate-specific membrane antigen (PSMA) PET imaging distinguish:
  - locoregional recurrence
  - distant metastases, PET-positive lymph node and bone lesions.
- PSMA PET imaging enables dose-escalated and metastases-directed salvage radiotherapy in patients with biochemical recurrence after radical prostatectomy.



Elschot et al, PET Clinics, 2019, Vol 14, Issue 4, P487-498.

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PET for Oligometastaic disease ART

- Oligometastatic disease -- 3 to 5 or fewer metastases
- Clinical trials of 3 sited and 5 sited NSCLC shows the improved overall survival
  for 6~24 months. (Gomez 2019 JCO, Iyengar JAMA 2018)
- PET imaging reveals tumor characteristics and biological response to treatment: perfect tool biologically tracking
- Biologically tracking the oligometastases: Redefining the role for radiotherapy in metastatic cancer.

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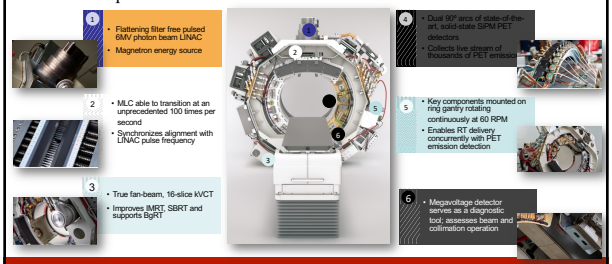
Technology Advancement for PET based ART

- The development of PET/CT-Linac



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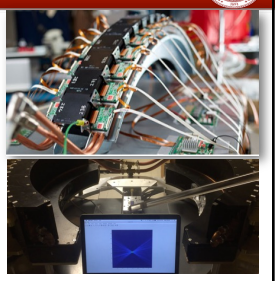
PET System Details

- Two 90° PET arcs with an axial extent of 5 cm each, provides full 360° coverage every 500ms
- Limited time sampled (LTS) images every 100ms to guide radiation beams to target
- Reconstruct full 3D PET images during treatment (Image only ~30min)
- Shares the axial plane with LINAC
- FOV 50cm transverse, 5cm longitudinal
- Resolution: 4mmx4mmx2.1mm



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PET based Planning Studies

- Lung studies by City of Hope: (Liang et al, ASTRO 2019)
  - 6 lung SBRT patients.
  - PET based PTV vs CT-based PTV SBRT, PTV volume reduced 21.5% in average.
  - OAR sparing is better for the lungs, spinal cord, esophagus, and heart
- Emory's study to investigate stability of FDG F^{18} as a "fiducial" for SBRT (Tian et al, ASTRO 2019)
  - 14 lung SBRT patients, 10Gy x 5fx
  - 3 PET/CTs acquired before the 1, 2, and 5th fx.
  - mean SUVmax change from PET1-2 = -8.2%, from PET1-3 = -7.0%.
  - [SUVmax/liver SUVmean] was stable over time; PET1-2= -0.3%, PET1-3 = +1.8%.
- Refle\Xion set SUVmax/SUVmean threshold is 2.7 for simulation in the tracking zone, 2.0 for treatment tracking.

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PET/Linac Image Quality

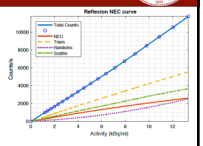
- A dual-arc, rotating PET subsystem in the PET/CT/LINAC was evaluated using the NEMA NU-2 2018 standard, operating in an imaging mode:
  - Spatial resolution: *4.3, 5.1, and 6.7 mm (FWHM) at 1, 10, and 20 cm offset.*
  - Image contrast: 29.6 to 81.2% for sphere diameter 13mm to 37mm.

Equivalent to those of typical diagnostic systems

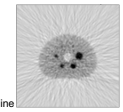
  - Sensitivity: *0.183 and 0.161 cps/kBq at the center of FOV and 10 cm off-center.*
  - Count rate:

Lower due to smaller detector area than a typical diagnostic system.

Hu et al, AAPM 2021



PET NEMA count-loss measurement



NEMA body phantom image on the PET system of a RefleXion X1 machine

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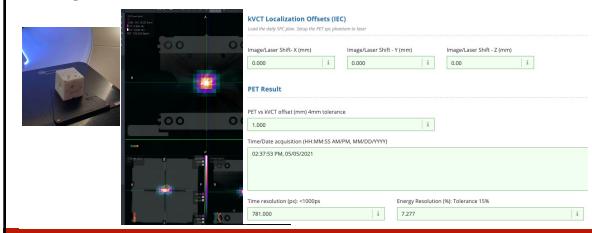
PET Image System Positioning Accuracy QA

- UMA phantom with reference source inserted. CT scan + PET scan. Assess the localization accuracy



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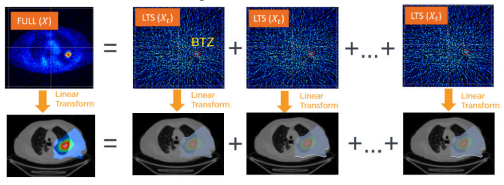
PET based Biology-guided Radiation Therapy

- Full time PET ~ 500ms (half rotation) in 60 RPM
- Limited-time-sample (LTS) PET image to track tumor: 100ms per image.
- Phantom measurement validation performed



SHIRVANI et al, 2021. BJR.

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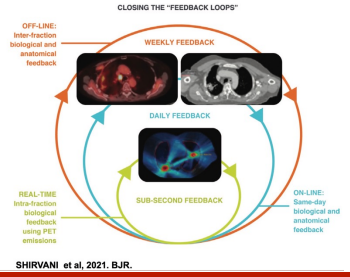
Online and Offline PET based ART



SHIRVANI et al, 2021. BJR.

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Summary

- Introduced PET imaging / functional imaging
- Reviewed PET-based ART for HN, Lung, Cervical and Prostate
- PET/CT/Linac for offline/online ART

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Acknowledgement

Stanford team:
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- Thank you for your attention
- Questions?

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