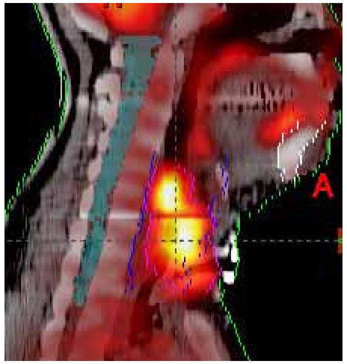


New Technologies & Functional Imaging: PET/CT and Radiation Treatment Planning

What have we been missing?

Shalom Kalnicki, MD, FACRO

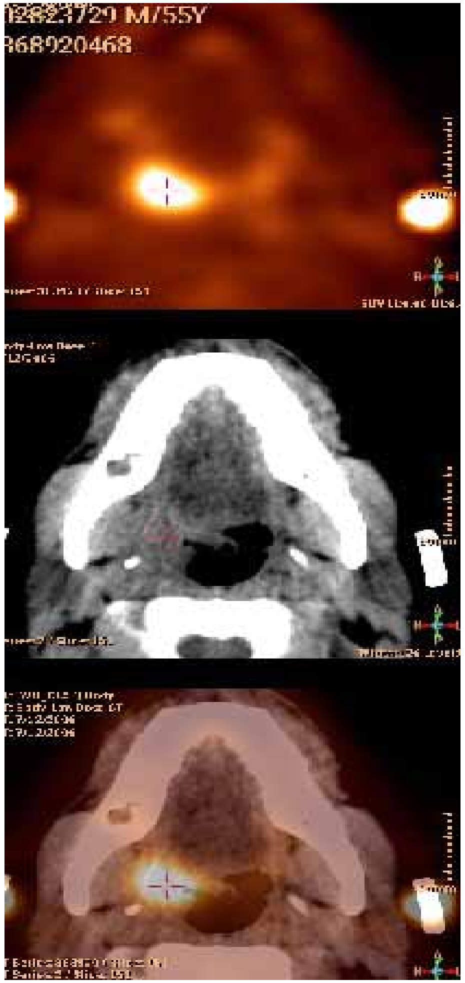
Professor and Chairman, Department of Radiation Oncology
Montefiore Medical Center
Albert Einstein College of Medicine
New York, USA

Montefiore THE UNIVERSITY HOSPITAL

EINSTEIN Albert Einstein College of Medicine OF YESHIVA UNIVERSITY

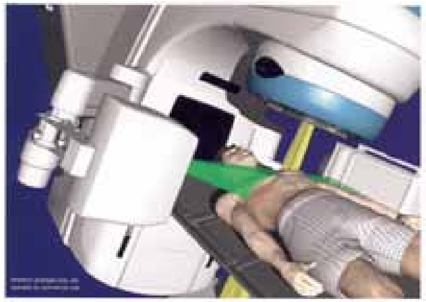
Outline

- **Modern Radiation Oncology**
- **Imaging and Radiation Oncology**
- **PET-CT in Radiation Planning**
- **PET-CT in Response Evaluation and Risk Adaptive Therapy**



Montefiore
THE UNIVERSITY HOSPITAL

EINSTEIN
Albert Einstein College of Medicine
OF YESHIVA UNIVERSITY



Historical Perspective

- Linear Accelerators: 1970's
- Computerized Treatment Planning: 1975's
- High Dose Rate Brachytherapy: 1980's
- **3-D Computerized Planning: 1980's**
- Non-Coplanar Beams: 1990's

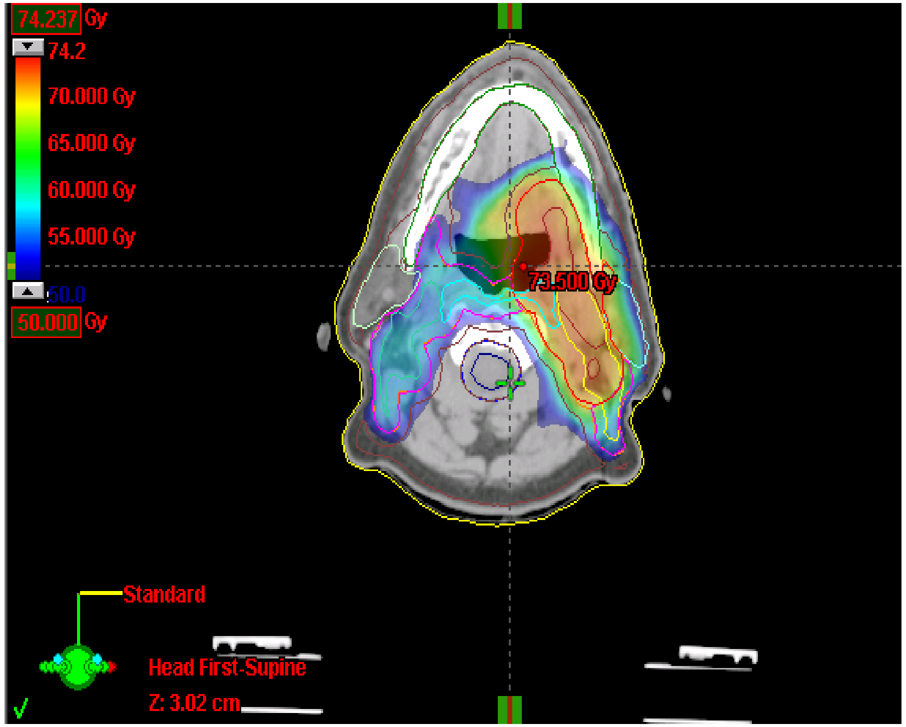
- **Inhomogeneous beams (IMRT): 1998**
- **Biological Treatment Planning (PET and PET-CT): 2000**

- Target Motion Management: 2004
- Adoptive Treatment Planning: 2006
- Integration with Targeted Therapies: 2007

Montefiore
THE UNIVERSITY HOSPITAL

EINSTEIN
Albert Einstein College of Medicine
OF YESHIVA UNIVERSITY

State of the ART: IMRT SIB "Dose Painting"



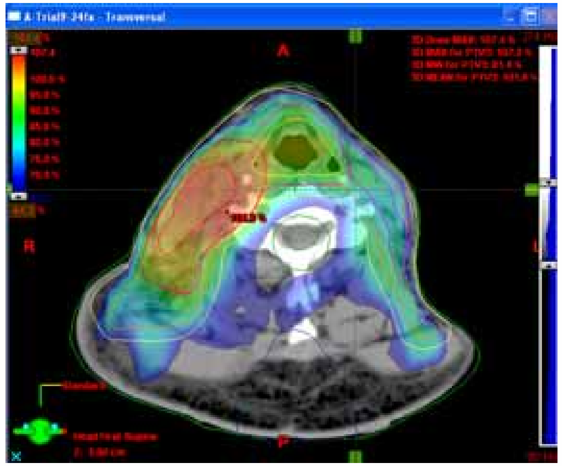
- Gross tumor (GTV) dose:
  70 Gy (2.12 Gy/Fc) to >98%
- Microscopic tumor dose (CTV):
  50 Gy (1.64 Gy/Fc) to > 98%
- Mean Right Parotid Dose:
  26 Gy
- Maximum Cord Dose:
  41 Gy

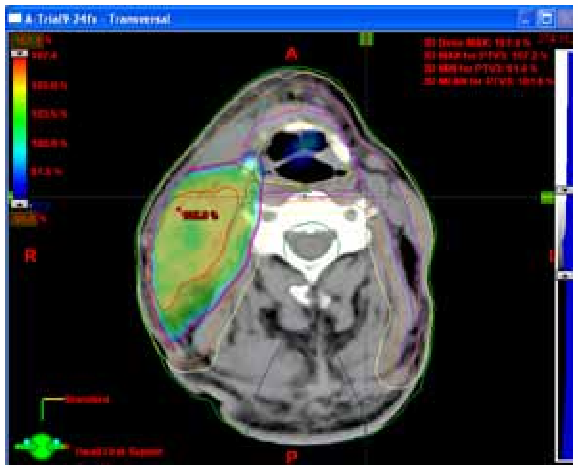
Montefiore THE UNIVERSITY HOSPITAL

EINSTEIN Albert Einstein College of Medicine OF YESHIVA UNIVERSITY

State of the ART: Dynamic Adaptive IGRT

- Sequential radiation plans developed based on new anatomic information
  - Patient weight loss
  - Tumor shrinkage
- Dramatic changes in dose distributions are seen after relatively small target volume changes
- Adaptive planning could be key to dose escalation with normal tissue sparing
- Need to develop radio-chemicals that could be used during therapy in sequential tests, unlike FDG





Montefiore
THE UNIVERSITY HOSPITAL

EINSTEIN
Albert Einstein College of Medicine
OF YESHIVA UNIVERSITY

With more precise delivery…

- Come opportunities
  - Decrease volume of normal tissue irradiated
  - Dose escalation to target
  - Improved tumor control with less morbidity

- and challenges:
  - Target delineation!
  - Target motion!
  - *Geographical miss!!!!!*

Montefiore THE UNIVERSITY HOSPITAL

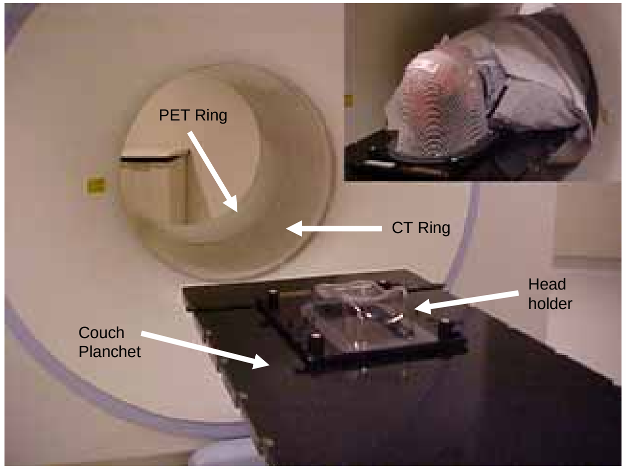
EINSTEIN Albert Einstein College of Medicine OF YESHIVA UNIVERSITY

Functional Imaging for IMRT and IGRT Treatment Planning

- Valuable addition to imaging armamentarium to define tumor and target tissues
- Inverse treatment planning algorithms would take into consideration sub-target volumes defined by different PET Specific Unit Values on PET CT treatment planning files
- Differently oxygenated tumor target areas can receive different doses of irradiation during each treatment fraction
- Issues / challenges include:
  - Resolution of PET: *Improved detectors*
  - Target mobility during long time of PET acquisition: *Gating*
  - Standardization: *To SUV or not to SUV? This is the question!*
  - 18FDG: *Generic marker*

Montefiore THE UNIVERSITY HOSPITAL

EINSTEIN Albert Einstein College of Medicine OF YESHIVA UNIVERSITY



PET-CT Simulation Technique

- Immobilization mask manufactured
- CT Simulation
- Axis laser marking
- CT data acquisition into computer treatment planning system

- Patient positioned with mask and laser system into same axis marking fiducials
- FDG PET performed in treatment position
- Data exported to radiation oncology treatment planning system

- Data import verification
- Fusion of co-registered PET CT and treatment planning CT into single data set to be used in radiation planning
- Target and normal tissues outline

Montefiore THE UNIVERSITY HOSPITAL
EINSTEIN Albert Einstein College of Medicine OF YESHIVA UNIVERSITY

Radiation Oncology Target Volumes
"Redefining the Definitions"

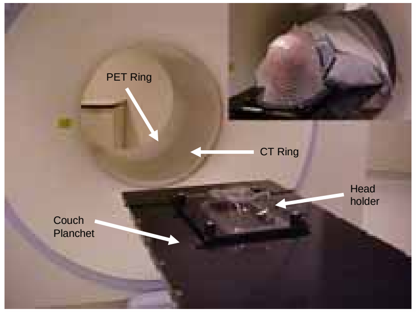
- **Gross Target Volume (GTV):** Tumor as contoured from imaging data
  - GTVc: Based on CT planning only
  - GTVp of GTVb: Based on PET-CT fusion

- **Clinical Target Volume (CTV):** Areas that have to be included for oncologic reasons (e.g. normal lymph nodes, pre-sacral space)
  - CTVc: Based on CT only, all normal anatomy
  - CTVp: Excludes areas of CTV that are transformed into GTVp through PET-CT positivity

- **Planning Target Volume (PTV):** GTVp + CTVp plus expansion for imaging and set up uncertainty
  - Needs to be expanded for PET-CT resolution at edges of PET positive areas
  - Gating significantly reduces expansion of target areas that move with respiration

Montefiore
THE UNIVERSITY HOSPITAL

EINSTEIN
Albert Einstein College of Medicine
OF YESHIVA UNIVERSITY



Important Practical Tips

- Set up patient on flat table, in the same immobilization device
  - Patient comfort crucial for PET CT (treatment is faster)
  - Precise reproduction important for co-registration
- Align the patient with radiation oncology lasers
- Perform PET CT:
  - Maximal technique desired
  - Perfect co-registration a must
  - Low dose vs. diagnostic grade CT
- Concentrate on anatomical details
  - Anatomy is key for co-registration perfection
- Determine clear uptake levels for tumor outlines
- Special attention to boundaries with normal tissues

Clinical Applications of PET-CT in Radiation Oncology

- Staging:
  - Extent of disease assessment
  - Prevent curative local treatment in the setting of systemic disease
- Radiation treatment planning:
  - Target delineation
  - Normal tissue sparing
- Response prediction
- Differentiation between treatment sequelae and recurrent disease

Montefiore
THE UNIVERSITY HOSPITAL

EINSTEIN
Albert Einstein College of Medicine
OF YESHIVA UNIVERSITY

Image Acquisition and Registration

- CT is the primary imaging modality in RT planning: CT images provide for both tumor delineation as well as the electron density data necessary for accurate dose calculations.

- PET, MR, etc. are considered Secondary images: will have to be registered (fused) to the primary planning CT scan.

- Fusion between both PET and CT provides anatomic information to improve the ***tumor localization*** and ***characterize*** sites of radiotracer uptake.

Montefiore THE UNIVERSITY HOSPITAL

EINSTEIN Albert Einstein College of Medicine OF YESHIVA UNIVERSITY

Rigid vs. Deformable Registration

- Rigid: Positioning a patient in the RT treatment position during the diagnostic staging PET scan acquisition on a flat couch insert, improves the accuracy of rigid registration of staging PET and RTP CT scans.

- Deformable: potential differences in image data sets such as those caused by differences in anatomical positioning are reduced by estimating the spatial relationship between the volume elements of the image sets.
- Improves accuracy of registration of a staging PET/CT and RTP CT scans in head and neck cancer patients.

Montefiore
THE UNIVERSITY HOSPITAL

EINSTEIN
Albert Einstein College of Medicine
OF YESHIVA UNIVERSITY

PET-CT and Motion Management

- Respiration can introduce artifacts in CT images caused by the interaction between the axial images acquisition and the motion of the tumor and healthy tissues.
- In PET imaging, the data are usually collected for 3-7 minutes per bed position (field of view) and therefore are time-averaged over many breathing cycles.
- Respiratory motion will result in blurring of the lesion, consequently underestimating the corresponding SUV ***(Specific Uptake Value)*** and overestimating the lesion volume.
- ***Careful attention must be paid to the*** artifacts introduced by breathing motion can lead to overestimation of target volumes.

Spatial mismatch and respiratory motion

- Another cause for reduced SUVs is the spatial mismatch between PET and CT, which results in inaccurate attenuation correction.

- Caused by difference in the image acquisition times between PET and CT:
  - CT image is collected at a distinct phase of the respiratory cycle
  - PET image is a time-averaged image over many breathing cycles.

- ***Caution:***
  - Potential mislocalization of the lesion
  - Inaccurate quantification of SUV values.

Motion Artifact Correction for PET-CT Imaging

- Combination of techniques for respiratory motion management in PET and CT scans.

- 4D PET/CT:
  - CT and PET acquired with respiratory motion tracking
  - Both spatially match at each phase of the breathing cycle
  - 4D-CT is acquired and sorted into 10 groups, according to their corresponding phase of the breathing cycle
  - PET also acquired using gating
  - Both 4D-CT and 4D-PET are correlated according to the respiratory phase.

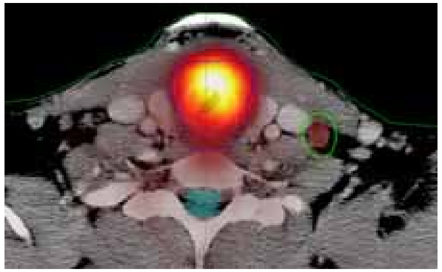
- Deep-inspiration BH PET/CT: shown to significantly reduce motion artifacts, enabling better target localization, as well as to increase SUV values.

Motion Artifact Correction for PET-CT Imaging

- Attenuation correction in PET images by average CT (ACT)
  - Improves spatial matching
  - Does not correct for motion.

- ***Caution:*** Gated PET exhibits reduced statistics ***due to longer acquisition time compared to*** clinical PET.

- Several approaches being studied in order to improve image statistics by combining counts from all gated PET bins at same time preserving temporal resolution.



Head and Neck Cancer

Integration of PET/CT into Radiation Treatment Planning

Montefiore
THE UNIVERSITY HOSPITAL

EINSTEIN
Albert Einstein College of Medicine
OF YESHIVA UNIVERSITY

Let's not treat large "generic" anatomical areas to low doses…

- Areas of GTV are commonly expanded by 0.5-1.5 cm in all three dimensions in order to account for microscopic extension of disease (CTV) and for set up error to define a planning target volume (PTV)

- Any changes in delineated GTV greatly amplifies the volume that receives high radiation dose.

- In the head and neck, tumors are in close proximity to normal tissues with low tolerances for radiation, it is essential to define volumes that are both ***necessary and sufficient*** for tumoricidal dose delivery.

Montefiore THE UNIVERSITY HOSPITAL

EINSTEIN Albert Einstein College of Medicine OF YESHIVA UNIVERSITY

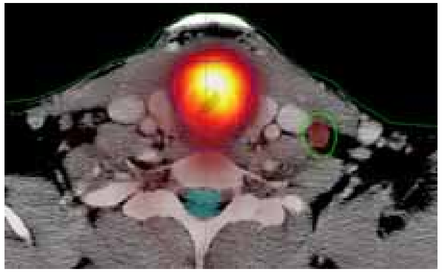
But without missing the tumor!

- *The converse of increased dose conformality is the possibility of geographic miss of gross tumor at the primary site.*

- Sensitivity for cancer at the primary site in the head and neck:
  - CT: 50 - 95%
  - MRI: 68 - 92%
  - *PET-CT: 90 – 95%*

- Sensitivity for neck node metastasis:
  - CT: 65 - 95%
  - MRI: 35-90%
  - Both together: 60 - 90%
  - *PET-CT: 75% - 90%*

- For CT and MRI, specificity is a function of the size of the primary mass as well as that of any suspicious nodes



Basic Objectives

- Better delineation of primary tumor: GTVc → GTVp
  - Identification of unknown primary
  - Differentiation with inflammatory changes
  - CT and MRI not precise in soft tissue areas
- Outline of hypoxic areas in tumors:
  - Need for increased radiation dose
  - Simultaneous Integrated Boosts (SIB)
- Diagnosis of nodal disease: CTVc ↔ GTVp
  - Non-enlarged tumor containing nodes
  - Enlarged inflammatory nodes
- Diagnosis of distant metastasis:
  - Avoidance of local therapy for patients who don’t benefit
- Prediction of therapeutic outcome

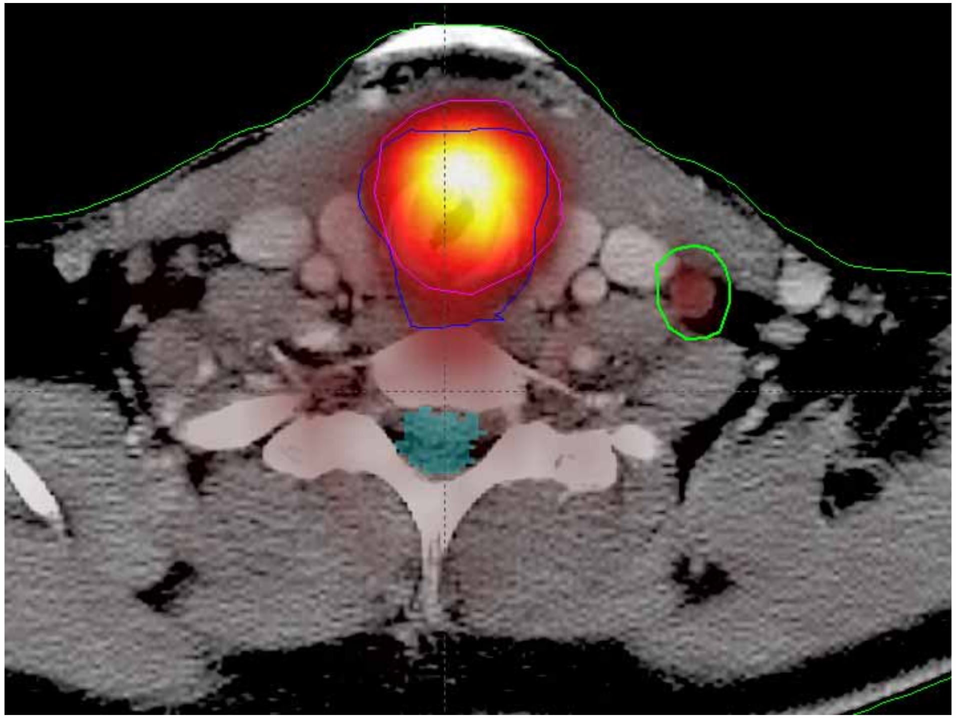
Montefiore THE UNIVERSITY HOSPITAL

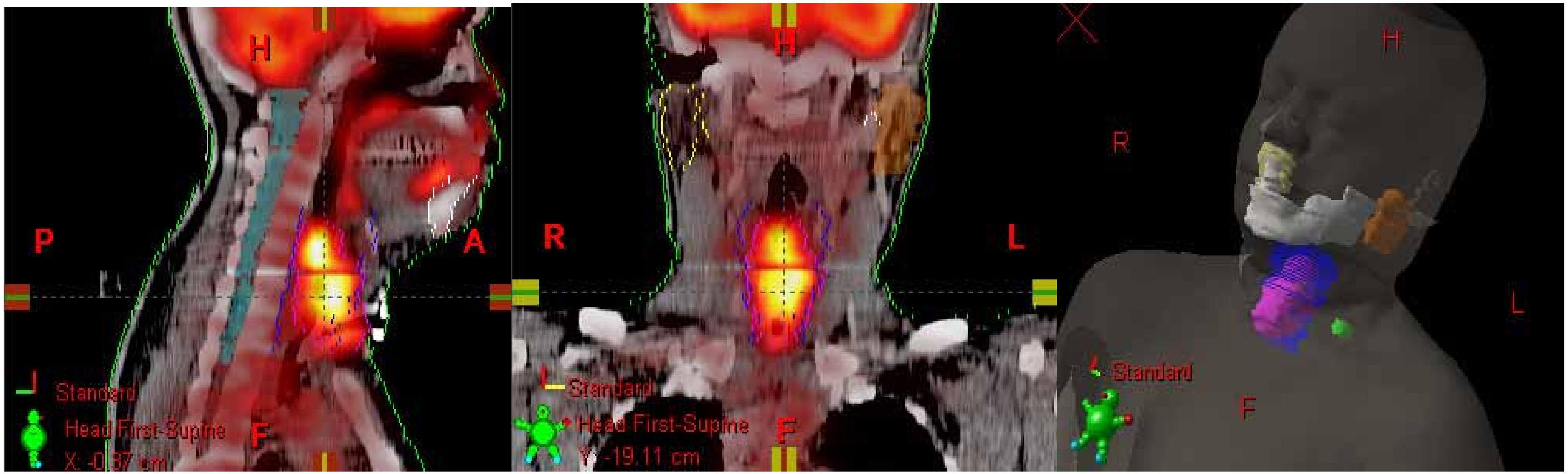
EINSTEIN Albert Einstein College of Medicine OF YESHIVA UNIVERSITY

Primary Detection: Base of Tongue

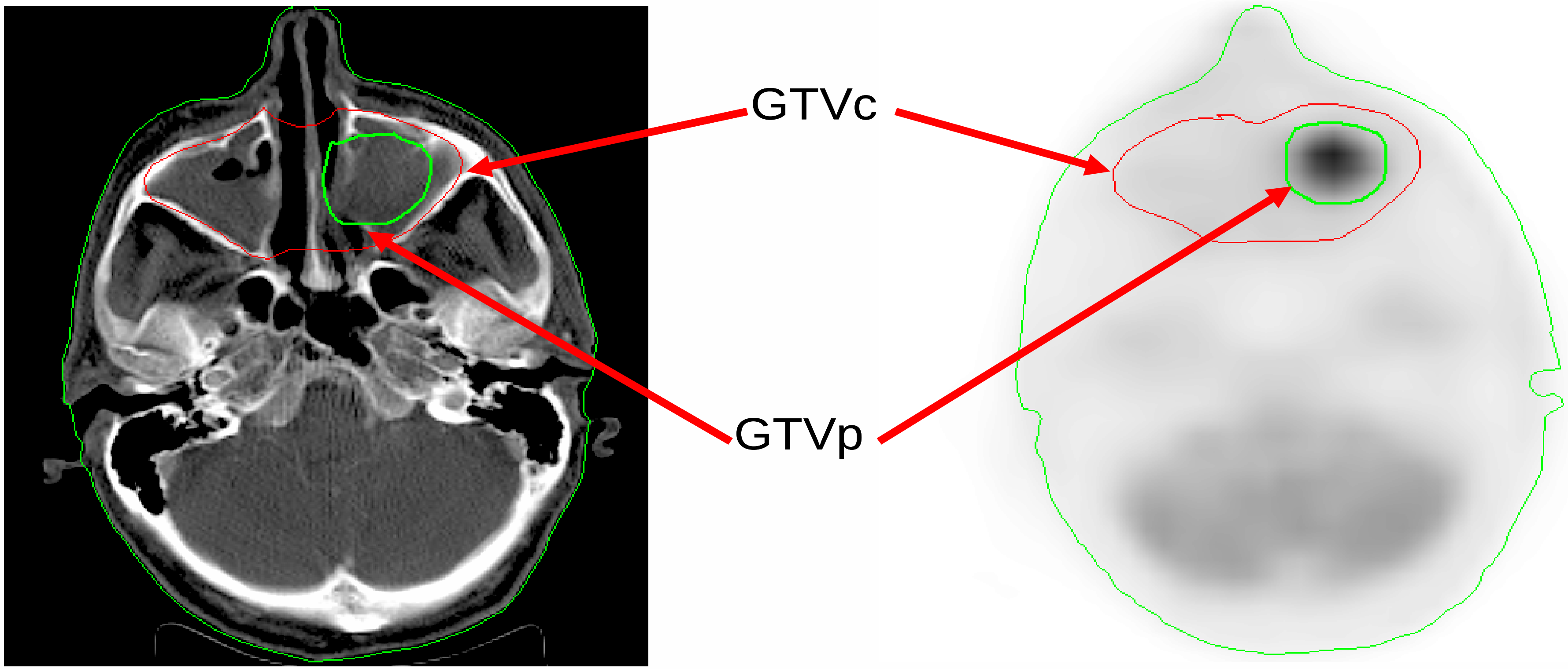
- Pt with palpable neck node, no lesion on exam
- CT: enlarged L neck node
- PET CT: clear delineation of base of tongue primary

Example:
Laryngeal Cancer *($T_3N_0M_0$)*





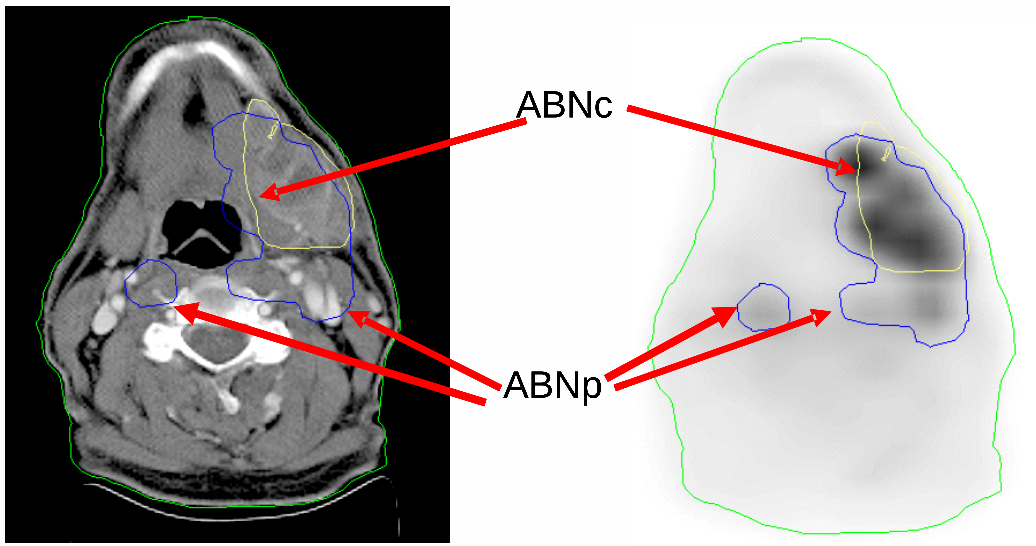
Ethmoid Sinus Cancer ($T_4N_0M_0$)



Hybrid PET-CT Simulation For Radiation Treatment Planning In H&N Cancers: A Brief Technical Report

Heron, Kalnicki, Avril et al: U of Pittsburgh

- 21 patients.
- Threshold based on Liver uptake.
- Abnormal areas of FDG uptake contoured on PET for the gross tumor volume (GTVp) and abnormal nodal region (ABNp).
- These compared with the same CT gross tumor volumes (GTVc) and abnormal nodal region (ABNc).



Int. J. Rad. Onc. Biol. Phys 2004; 60(5):1419–1424

Montefiore THE UNIVERSITY HOSPITAL

EINSTEIN Albert Einstein College of Medicine OF YESHIVA UNIVERSITY

Heron et al: Results
PET-CT Fusion IMRT Planning

- In patients with lymph node metastases:
  PET identified the primary site in <u>all cases</u> **<u>AND</u>** a greater number of involved lymph nodes (than CT)

- PET showed a greater number of high-risk areas (primary and involved nodal sites), which were generally smaller in volume than that seen on CT

- The average ratio of GTVc/GTVp was 3.1 (range, 0.3–23.6), whereas for ABNc/ABNp was 0.7 (range, 0–4).

- Volumes for the primaries were significantly larger (about 1.8 times) on CT than on PET (*p* 0.002) but not for nodal regions (*p* 0.5).

Montefiore
THE UNIVERSITY HOSPITAL

EINSTEIN
Albert Einstein College of Medicine
OF YESHIVA UNIVERSITY

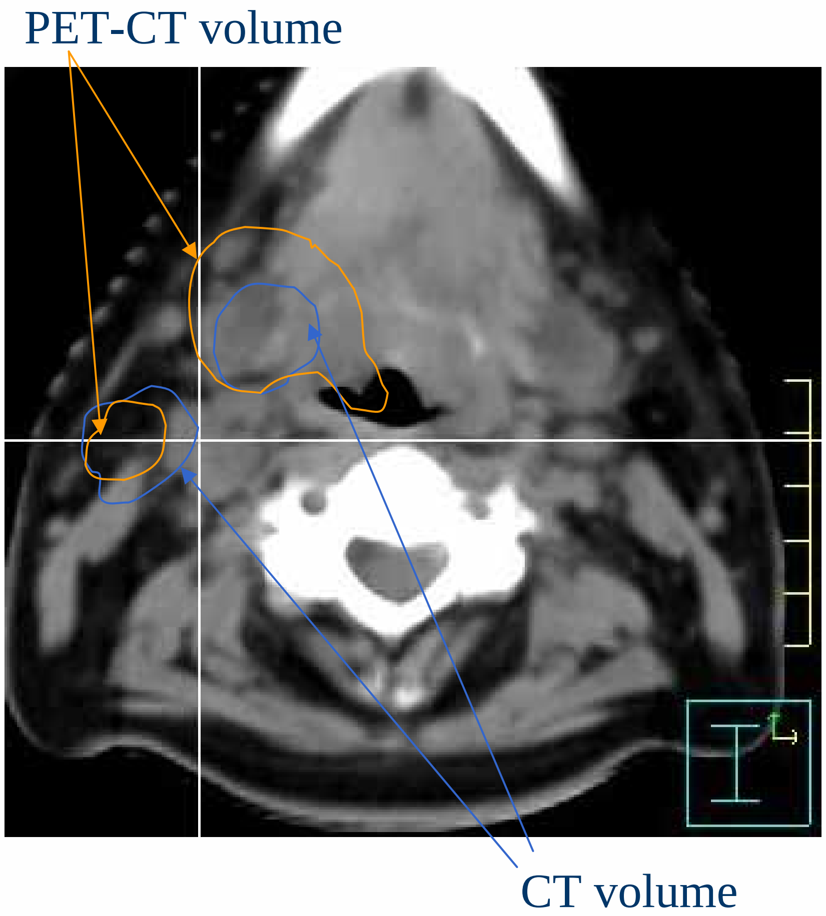
Head and Neck PET CT Fusion
Montefiore-Einstein Experience

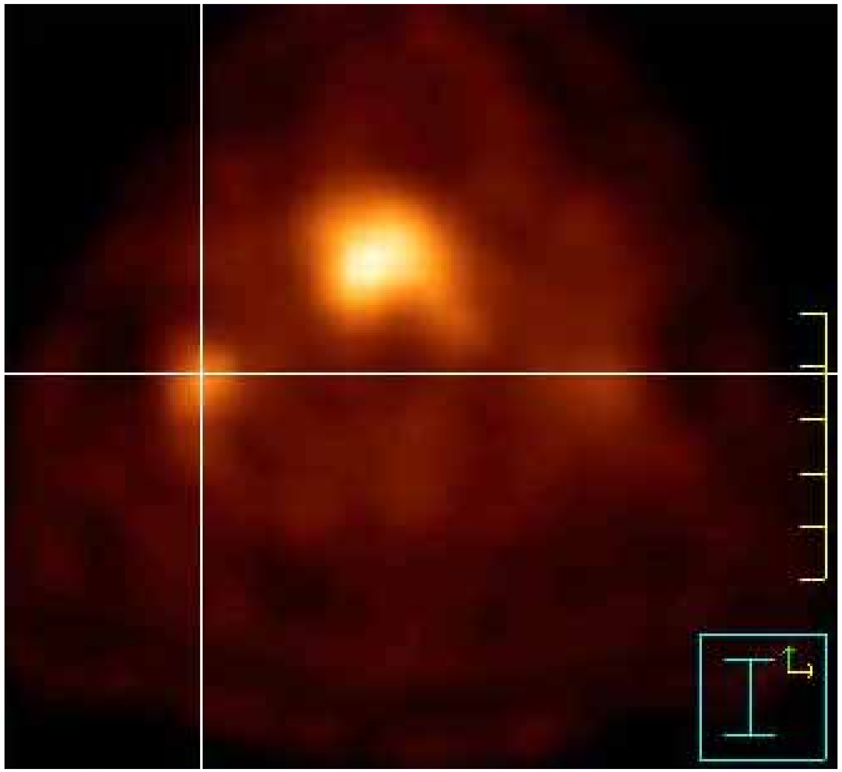
- Detailed analysis of the first 52 patients with head and neck cancer underwent CT-PET for radiation treatment planning
- Volume differences were charted for primary site and neck nodes
- CT and PET images fused in treatment planning position
- Volumes independently assessed and contoured by CT and PET CT
- Radiation planning volumes and radiation dose changes charted and analyzed

Montefiore
THE UNIVERSITY HOSPITAL

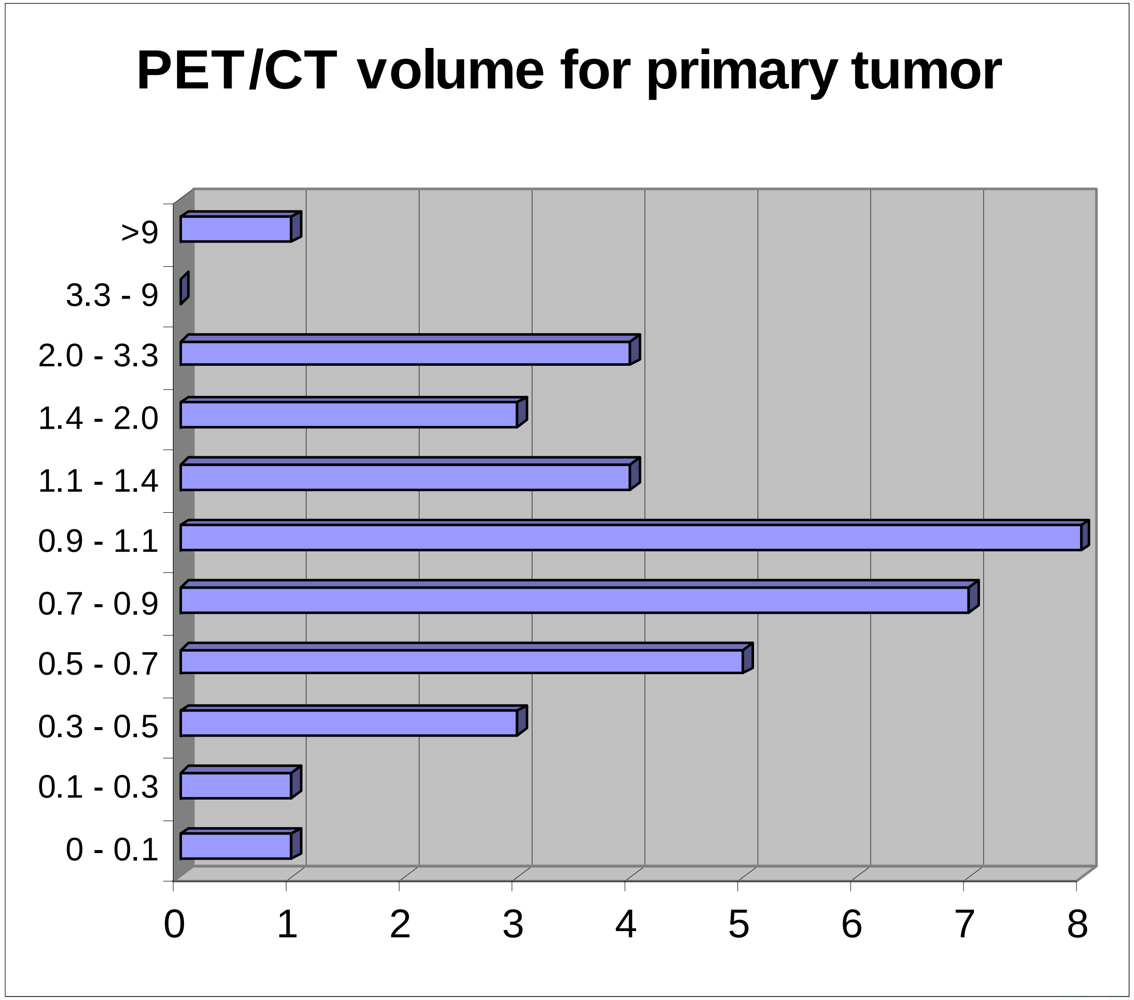
EINSTEIN
Albert Einstein College of Medicine
OF YESHIVA UNIVERSITY

Outline of Volume Methodology





Primary Disease Volume Outline
CT vs. PET GTV Comparison



Larger in 32%

Smaller in 46%

Montefiore THE UNIVERSITY HOSPITAL

EINSTEIN Albert Einstein College of Medicine OF YESHIVA UNIVERSITY

Primary Disease Volume Outline
CT vs. PET GTV Comparison

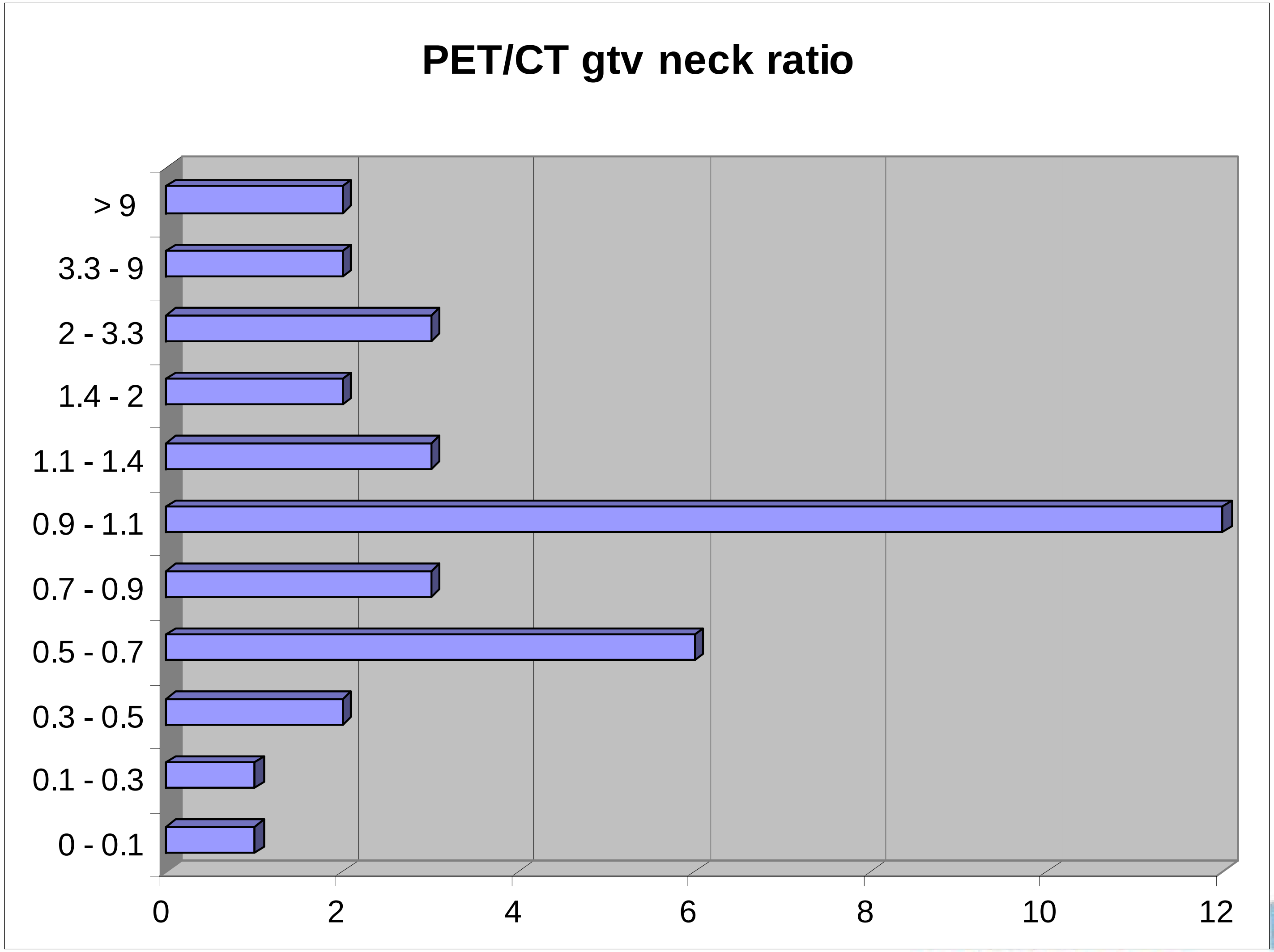
CT-GTV
41.3 mm3

PET-GTV
45.8 mm3
11% larger than CT

CT+PET GTV
Boolean volume
62.1 mm3
50% greater than CT-GTV

Ratio of CT+PET GTV and CT GTV– 1.5 (SD ± 0.73) - p=0.008

PET CT GTV Neck Node Ratios



32% larger

35% smaller

THE UNIVERSITY HOSPITAL

EINSTEIN
Albert Einstein College of Medicine

Neck Disease
CT Compared to PET Volumes

CT-neck GTV
21.5 mm3

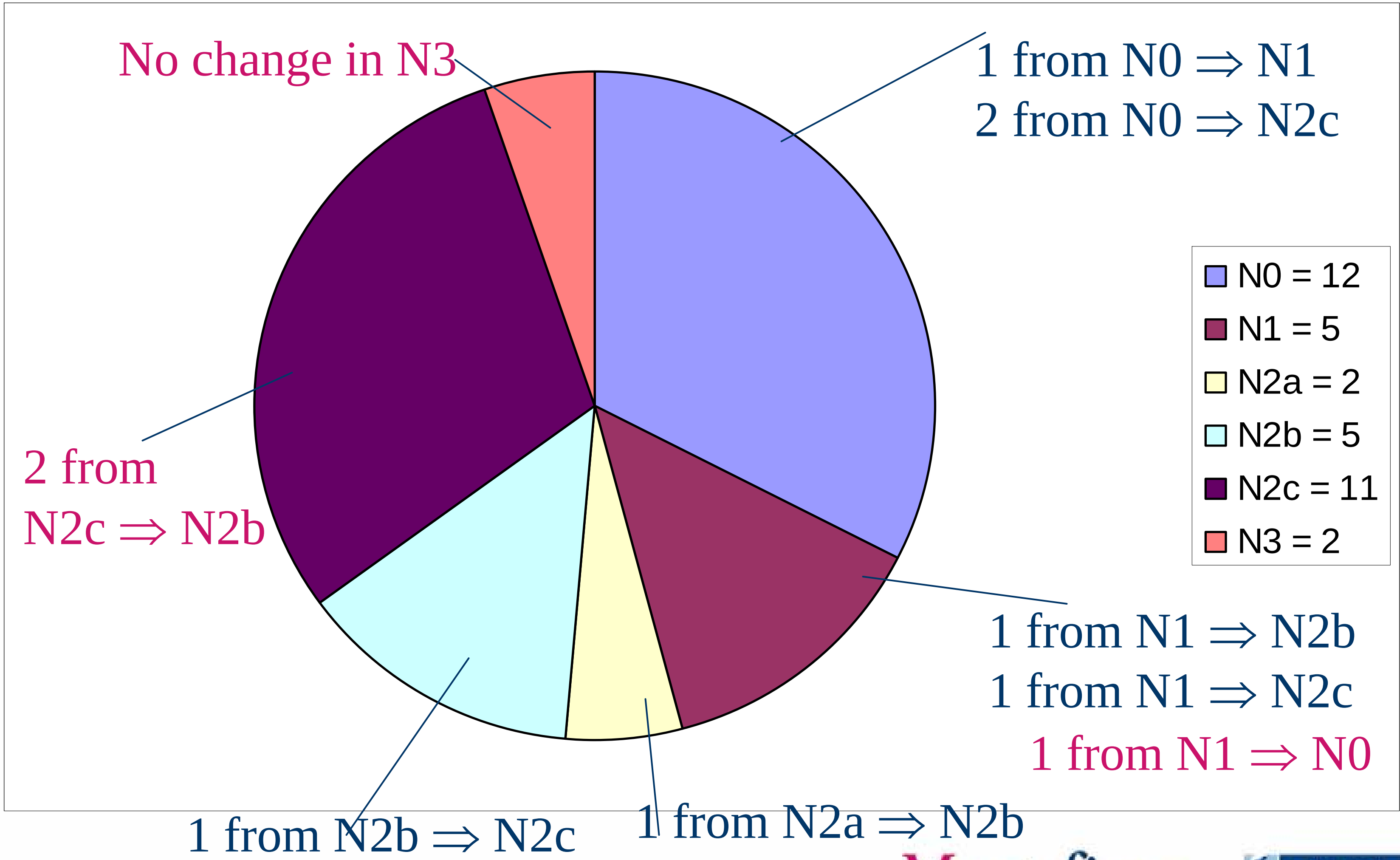
PET-neck GTV
20.9 mm3
3% smaller than CT

CT+PET neck GTV
Boolean volume
31.6 mm3
47% greater than CT-GTV

Ratio of CT+PET GTV and CT GTV– 1.5 (SD ± 0.73) , p=0.27

Montefiore THE UNIVERSITY HOSPITAL
EINSTEIN Albert Einstein College of Medicine OF YESHIVA UNIVERSITY

Nodal Status Change after PET CT Planning



Montefiore
THE UNIVERSITY HOSPITAL

EINSTEIN
Albert Einstein College of Medicine

GTV based on PET-CT

	Same (± 10%)	Larger	Smaller
Emory	**8%**	**18%**	**75%**
Vanderbilt		**40%**	**60%**
Wisconsin		**56%**	**44%**
Pittsburgh		**20%**	**80%**
Montefiore Einstein	***22%***	***32%***	***46%***

Montefiore THE UNIVERSITY HOSPITAL
EINSTEIN Albert Einstein College of Medicine OF YESHIVA UNIVERSITY

Montefiore-Einstein Experience
Summary of Results (Ahn et al)

- Number of neck nodes detected on PET-CT vs. CT:
  - Increased in 21% of patients
  - Decreased in 14%

- Target volume drawn on PET-CT vs. CT:
  - Larger in 23% of patients (>110%)
  - Smaller in 54% (<90%)

- While there was no significant population difference seen between PET-CT and CT outlined volumes, there is large variability in volumes on an individual basis

Head and Neck Montefiore Einstein Experience: *Conclusions*

- Image fusion between FDG-PET and CT is useful in GTV, CTV and PTV determination.

- PET-CT resulted in upstaging of neck in 6 (23%) and down staging in 2 (8%) patients respectively.

- Boolean CT+PET GTV volume was 15% greater than the CT-GTV volume.

Montefiore-Einstein Experience
Comments: Target Volume

- PET-CT volumes tend to be smaller than CT ones as one clearly separates inflammatory mucosal and sub-mucosal components of the mass lesion

- In a smaller number of cases, especially base of tongue, PET-CT adds volume by identifying disease lying within or adjacent to muscle layers and infiltrative neoplastic processes which appear normal on CT.

Montefiore-Einstein Experience
Comments: Nodes

- There is little volume variability
- PET-CT adds value by identifying abnormal uptake in nodes that appear normal on CT by volume only (smaller than 1 cm.)
- In this patients there is a transformation of CTV dose into GTV dose, potentially greatly affecting relapse and cure rates.

Montefiore-Einstein Experience: *Summary of Changes*

- Accounting for differences in *target volumes* and *dose distributions*, the addition of PET-CT to CT and/or MRI significantly changed radiation planning in approximately ***60%*** of head and neck cancer patients.

- The impact on the therapeutic program, survival and quality of life is dramatic.

Practical Tips
Head and Neck Cancer

- Very precise set up and position of immobilization mask

- Perform PET CT as usual
  - Maximal technique desired
  - Perfect co-registration

- Concentrate on anatomical details
  - CT may show periphery of nodal areas with precision
  - Only PET CT will show boundaries of tongue, oropharyngeal and laryngeal lesions
  - Extreme attention to base of skull and Waldeyer's ring

- Review nodal areas with extreme care
  - Differentiate between positive submental nodes and salivary glands
  - Remember: a normal size node with uptake needs higher radiation dose

- Be quick to add and slow to subtract anatomy
  - CTV definition extremely important

Montefiore THE UNIVERSITY HOSPITAL

EINSTEIN Albert Einstein College of Medicine OF YESHIVA UNIVERSITY

Lung Cancer

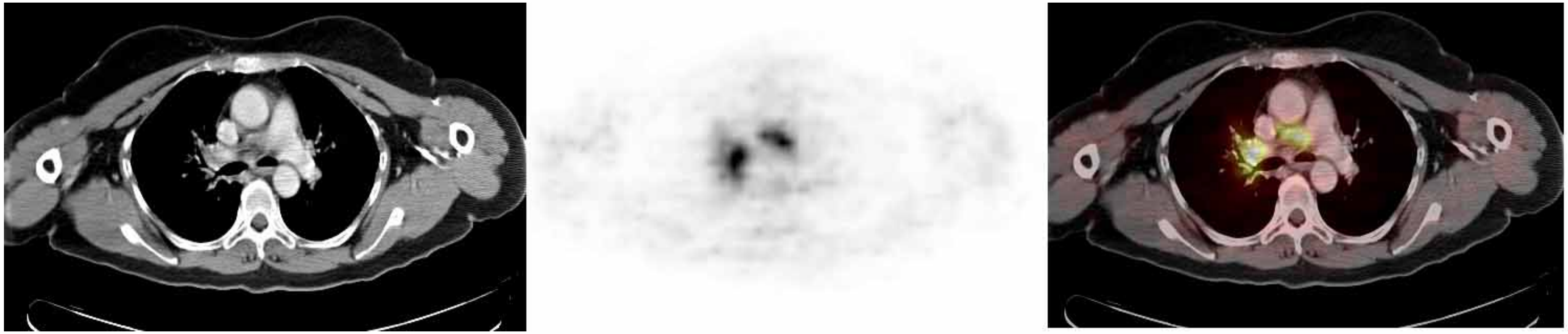
Integration of PET/CT into Radiation Treatment Planning

Montefiore
THE UNIVERSITY HOSPITAL
EINSTEIN
Albert Einstein College of Medicine
OF YESHIVA UNIVERSITY

Objectives

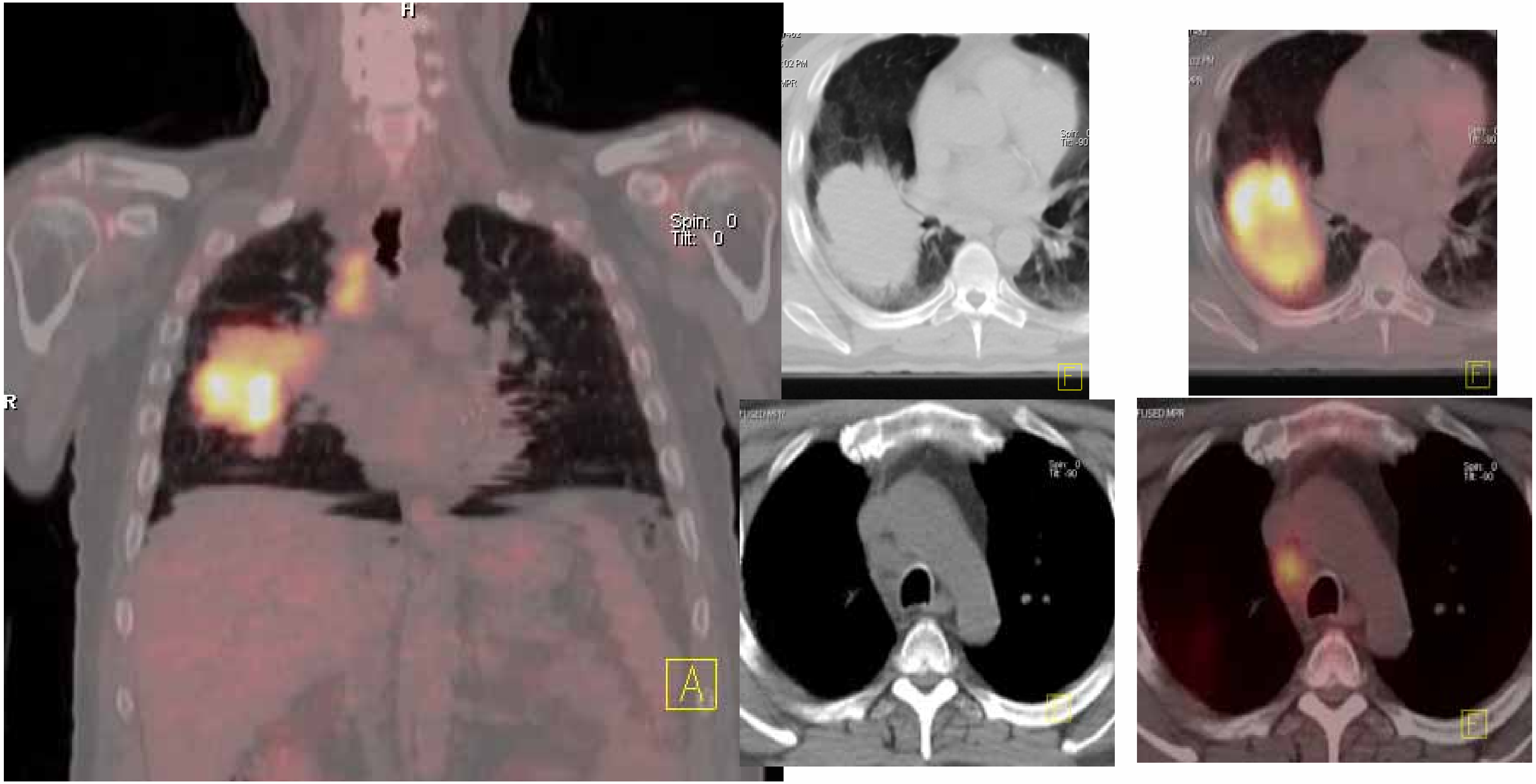
- Staging and treatment planning in one test
  - Best method to diagnose unsuspected metastatic disease
- Delineation of primary tumor
  - Plus: tumor vs. lung collapse
  - Minus: motion during acquisition time
  - Necrosis and hypoxia inside large lesions
- Detection of nodal involvement
  - Non enlarged lymph nodes
  - Necrotic lymph nodes
- Evaluation of therapeutic response
  - Extremely important in neo-adjuvant chemo irradiation

Improved Localization of Nodal Disease

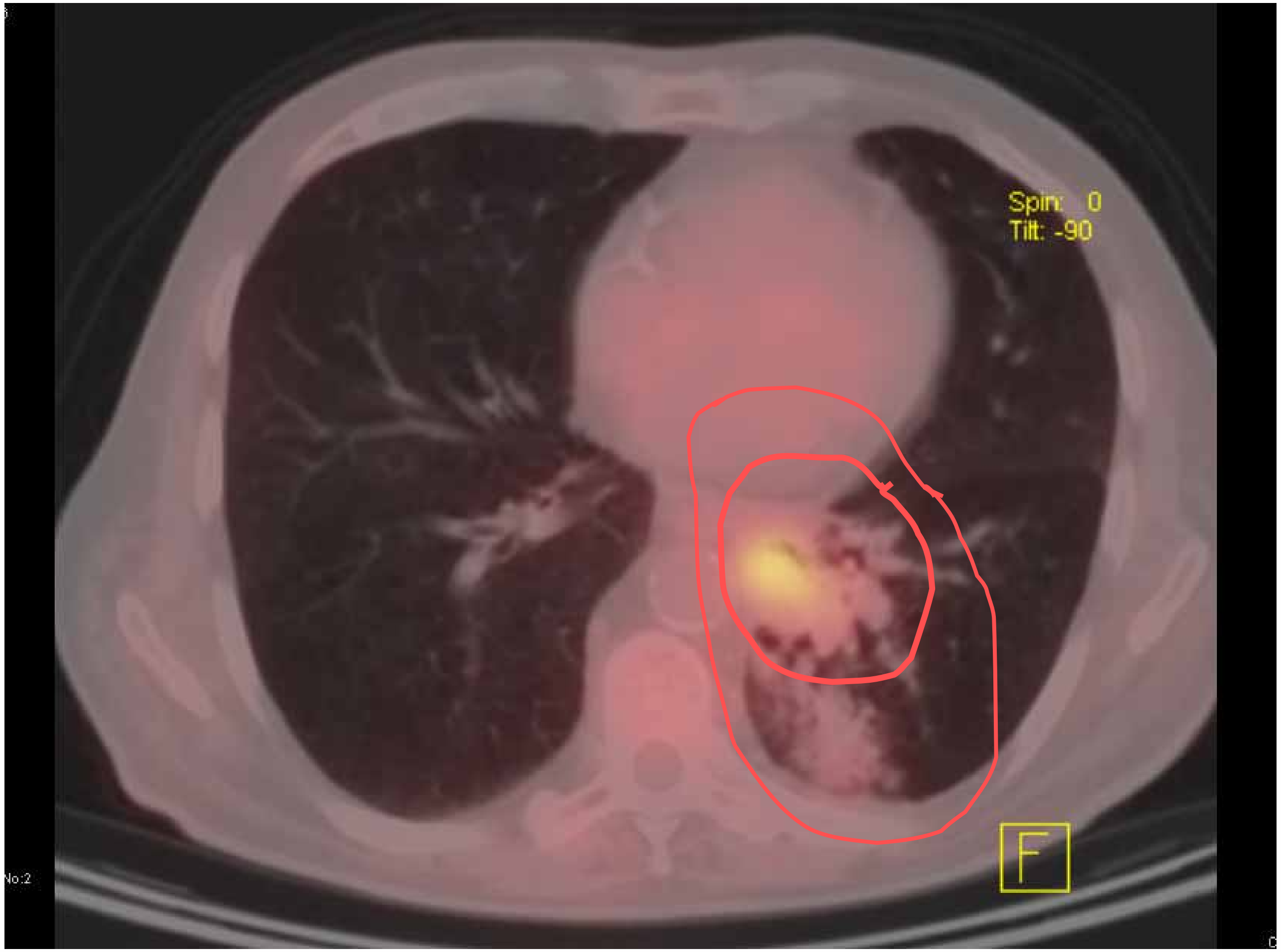


- CT scan shows normal mediastinal nodal complexes
- PET shows abnormal uptake
- PET CT fusion clearly shows abnormal uptake in unsuspected mediastinal nodes

Lung Ca:
Tumor necrosis and nodes



Lung Cancer:
Central neoplasm with peripheral collapse



Montefiore THE UNIVERSITY HOSPITAL
EINSTEIN Albert Einstein College of Medicine OF YESHIVA UNIVERSITY

Impact of FDG-PET on radiation treatment volumes in NSCLC

- Hebert (*Amer J of Clin Oncol. 1996;19:416-421*): 20 patients
  - 3/12 had CT/CXR changes larger than PET
  - 2/12 had PET volumes larger than CT/CXR
- Kiffer *(Lung Cancer. 1998;19:167-177*):
  - Coronal PET images with the anterior–posterior (AP) simulator image on which the RT volume had been marked
  - 4/15 patients had RT volume influenced by the PET findings
- Nestle (*Int J Radiat Oncol Biol Phys. 1999;44:593-597*):
  - Retrospective study used PET-C based planning
  - Reduction in the radiation portals in 12 of 34 patients (35%)
- Munley (*Lung Cancer. 1999;23:105-114*):
  - FDG-PET influenced 34%(12/35) of the RT plans examined
  - Resulted in enlarging portions of the beam

Impact of FDG-PET on radiation treatment volumes in NSCLC

- Multiple series demonstrated changes in treatment volumes from 15 to 60 % if FDG PET information was utilized

- Reviews on PET/CT utilization for radiotherapy planning in lung cancer maintained a range of 30-60% differences between PET derived contours versus CT only target volumes

Practical Tips
Lung Cancer

- Gating helps: 4D planning
  - Tumor motion is always a problem
  - Composite target with motion and deformation

- Tumor vs. lung collapse definition
  - Sparing of normal lung increased
  - Extremely important for new SRS programs

- Mediastinal lymph node boosts
  - Large area / low dose being replaced by…
  - Targeted radiation with higher doses to smaller areas, concomitant with chemotherapy

Gynecologic Oncology

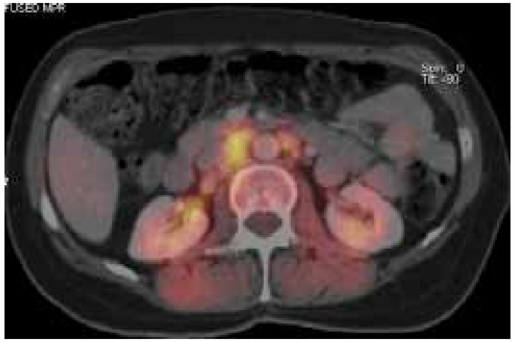
Integration of PET/CT into Radiation Treatment Planning

Objectives

- Staging and treatment planning in one test
- Clarification of CT and MRI densities in patients who underwent multiple abdominal surgical procedures
  - Extremely important in asymptomatic rising CA-125
- Detection of nodal involvement
  - Analysis of para-aortic nodes
  - Differentiation of nodes vs. fibrosis
- Delineation of uterine and cervical primary tumor
- Evaluation of therapeutic response
  - Reduction in exploratory laparotomies

Cervical Carcinoma

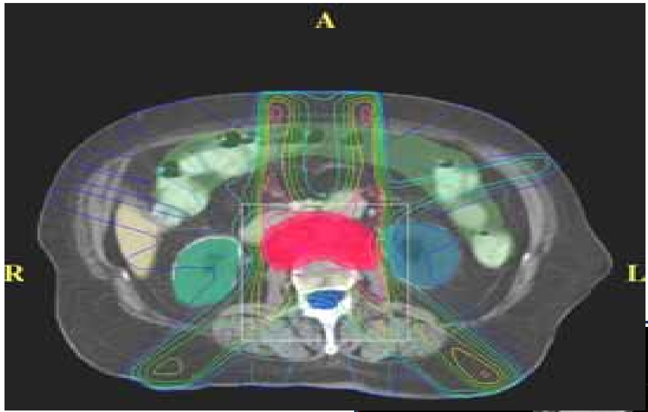
Detection of CT-negative Metastatic Disease

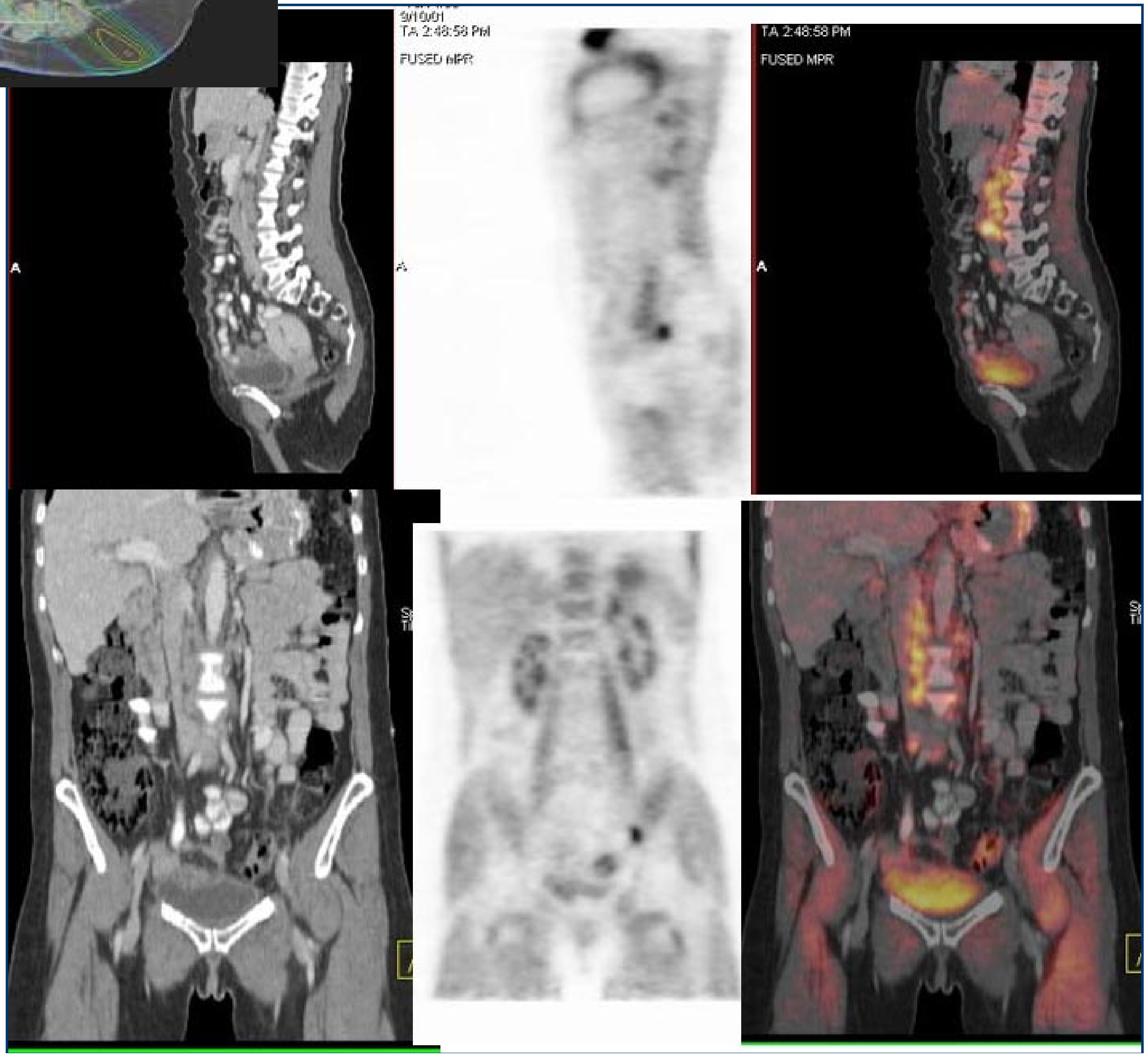


Montefiore
THE UNIVERSITY HOSPITAL

EINSTEIN
Albert Einstein College of Medicine
OF YESHIVA UNIVERSITY

Detection of unsuspected Para aortic nodes





EINSTEIN
Albert Einstein College of Medicine
OF YESHIVA UNIVERSITY

Fibrosis vs. Recurrent Disease

Axial CT, PET, Fused PET-CT demonstrate the detection of an occult nodal recurrence in the pelvis that was not appreciated on the CT. This area corresponds to the site of a previous pathologically proven nodal metastases prior to the adjuvant radiotherapy treatment (45 Gy) to the pelvis in December 2000.

Montefiore THE UNIVERSITY HOSPITAL

EINSTEIN Albert Einstein College of Medicine OF YESHIVA UNIVERSITY

PET/CT planning for locally advanced cervical cancer: *Montefiore experience*

- 22 patients with locally advanced cervical cancer
- Pretreatment CT and PET/CT scans
  - Blinded by an unbiased observer
  - Two radiation oncologists read the CT and PET/CT of all the patients in a blinded fashion to create the PTV
- Isodose curves were generated from the blinded treatment fields
- PTV, the V95, and mean dose to bladder and rectum compared between the CT and PET/CT

PET/CT planning for locally advanced cervical cancer: *Results*

- PTV Volume:
  - Mean PTV (CT): 1501.43 ± 589.85 cm^3
  - Mean PTV (PET/CT): 1631.61 ± 505.39 cm^3
  - PET/CT increase in PTV: 8.33%±13.45(p=0.01).
- V95 (PTV volume receiving a minimum 95% dose)
  - Mean V95 (CT): 97.3%
  - Mean V95 (PET/CT): 96.9% (p=0.09)
- Mean rectal dose:
  - CT: 43.60 Gy
  - PET/CT: 44.57 Gy
- Mean bladder dose:
  - CT: 45.70 Gy
  - PET/CT: 45.45 Gy

Montefiore THE UNIVERSITY HOSPITAL

EINSTEIN Albert Einstein College of Medicine OF YESHIVA UNIVERSITY

PET/CT planning for locally advanced cervical cancer: *Results*

- PET/CT treatment planning increases the treatment volume by 8.33%.
- More importantly, PET/CT identified foci of metastatic disease allowing for expansion of the target volume.
- PET/CT treatment planning did not significantly increase the dose to bladder or rectum.
- Radiation planning provided adequate dose coverage as indicated by the minimal change in V95.
- Further prospective study for clinical ramifications is warranted.

Montefiore
THE UNIVERSITY HOSPITAL
EINSTEIN
Albert Einstein College of Medicine
OF YESHIVA UNIVERSITY

Practical Tips
Gynecologic Oncology

- Abdominal pelvic immobilization a challenge
- Care with motion in liver and upper abdomen: gated PET CT and gated IMRT important
- Careful look ad diagnostic CT for correlation
- Localization of recurrent disease important
- Careful tailoring of change in GTV and CTV

Where do we go next?

- New radiotracers
  - Apoptosis: Aposense study
  - Cell proliferation (thymidine)
  - Hypoxia
  - C11
  - Gene expression markers

- Improved technology
  - New detectors: better resolution and higher speed
  - Better CT base: 64 slice helical scans
  - Gated acquisition: correlate with gated delivery

- Improved targeting
  - Adaptive treatment planning
  - PET based (SUV?) contouring tools

- Outcome studies

The Future:
Settle normalization?

- Emory
  - ***50% intensity level relative to the tumor maximum***
- Pittsburgh
  - ***Threshold based on Liver uptake***
- Vanderbilt
  - ***Average threshold was 50% of image maximum intensity***
- Wisconsin
  - ***An increased abnormal uptake with standard uptake value (SUV) of more than 2.5***
- Montefiore/Einstein
  - ***Image normalized to the FDG uptake in the liver without background subtraction***

Montefiore
THE UNIVERSITY HOSPITAL

EINSTEIN
Albert Einstein College of Medicine
OF YESHIVA UNIVERSITY

Acknowledgements:
Our PET CT Nuc Med / Rad Onc Team

- **Nuclear Medicine**
  - David Miltstein, MD
  - Suman Jana, MD
  - Renee Moadel, MD
  - Lenard Freeman, M.D.
  - M. Donald Blaufox, MD, PhD
- **Radiation Oncology**
  - Madhur Garg, MD
  - Chandan Guha, MD, PhD
- **Physics/Dosimetry**
  - Ravindra Yaparpalvi, MS
  - Paola Godoy Scripes, MS
  - Jin Shen, MS
  - Joe Lee, MS
  - Ekeni Miller, MS
- **Residents**
  - Peter Ahn, MD
  - Keyur Mehta, MD
- **Radiology**
  - Kievan Shifteh, MD
- **Administrative / Integral PET**
  - M.Stromer
  - T. Huvane
  - R. Lissak
  - M. Lissak
  - B. Lissak
  - K. Ortega

Montefiore THE UNIVERSITY HOSPITAL

EINSTEIN Albert Einstein College of Medicine OF YESHIVA UNIVERSITY

PET-CT and Response Evaluation

- Quickly established as one of the key elements of detection for primary and metastatic disease
- First readily available method to evaluate tumor biology:
  - Metabolic and reproductive activity
  - Hypoxia
  - Tumor subpopulations
- Initially thought not to be effective for evaluation of therapy results
  - Post operative changes and inflammation
  - Post chemotherapy and radiation changes
- Supposed "problems" with PET during and post treatment may become valuable assets in therapeutic evaluation!

Surgical Questions

- Pre-operative
  - Is the tumor highly aggressive? *Neo-adjuvant therapy*
  - Is the tumor hypoxic or hyper- vascular? *Post operative adjuvant therapy*

- Post-operative
  - Is the lesion completely resected?
  - Are there any new uptakes seen? *Too small or redistribution of FDG*

- Clinical consequences:
  - Elimination of unnecessary surgical procedures
  - Better planning of neo adjuvant and adjuvant therapies
  - Better comprehension of natural history of disease

Radiation Therapy Questions

- Primary tumor:
  - Size, shape, volume: *inter-observer discrepancies*
  - Hypoxia: *dose painting*
- Lymph nodes:
  - Better diagnosis: *normal looking nodes with uptake*
- Response evaluation: ***"Risk-Adaptive Radiation Therapy"***
  - Delayed: *appropriate time for determination of local control*
  - During therapy:
    - *elimination of non-responders when there is an option for surgical resection*
    - *Changes in tumor biology that require adjustments in target dosing, volume and shape*

Chemotherapy Questions

- Most neo-adjuvant and adjuvant regimens are “pre-set”:
  - Breast cancer: Adriamycin / Cytoxan X4 + Taxol X4
  - Breast cancer Her-2-neu+: add Herceptin X12
  - Colorectal cancer: FOLFOX X6
- Most curative regimens are also preset:
  - Lymphoma: R-CHOP X6
- Changes of dose and cycles have only been allowed for toxicity
- PET may allow for true ***“Risk-Adaptive Chemotherapy”***

But there are a few problems…

- Strict standards are needed if one takes comparative PET-CT scanning beyond crude imaging reports
- Timing between scans needs to be very well integrated into practices
- Proper markers need to be developed and evaluated for specific applications: e.g.., apoptosis, hypoxia
- Clinical pathways have to incorporate scans so payer relations are possible

Montefiore
THE UNIVERSITY HOSPITAL

EINSTEIN
Albert Einstein College of Medicine
OF YESHIVA UNIVERSITY

Impact of the definition of peak standardized uptake value on quantification of treatment response.
Vanderhoek M, et al. J Nuc Med 2012 (Madison, WI)

- PET-based treatment response assessment typically measures the change in maximum standardized uptake value (SUV(max)), which is adversely affected by noise.
- Peak SUV (SUV(peak)) has been recommended as a more robust alternative, but its associated region of interest (ROI(peak)) is not uniquely defined.
- Authors investigated the impact of different ROI(peak) definitions on quantification of SUV(peak) and tumor response.

- 17 patients with solid malignancies were treated with a receptor tyrosine kinase inhibitor (Tarveva®) resulting in a variety of responses.
- (18)F-FLT) PET/CT scans were acquired prior to and during treatment.

Montefiore THE UNIVERSITY HOSPITAL
EINSTEIN Albert Einstein College of Medicine OF YESHIVA UNIVERSITY

Impact of the definition of peak standardized uptake value on quantification of treatment response.
Methods

- (18)F-FLT-avid lesions (~2/patient) were segmented on PET images, and tumor response was assessed via the relative change in SUV(peak).
- For each tumor, 24 different SUV(peaks) were determined by changing the ROI(peak):
  - Shape: circles vs. spheres
  - Size: 7.5 vs. 20 mm
  - Location: centered on SUV(max) vs. placed in highest-uptake region
- Variations in the 24 SUV(peaks) and tumor responses were measured within each tumor: coefficient of variation (CV), standardized deviation (SD), and range.
- For each ROI(peak) definition, a population average SUV(peak) and tumor response were determined over all tumors.

Montefiore
THE UNIVERSITY HOSPITAL

EINSTEIN
Albert Einstein College of Medicine
OF YESHIVA UNIVERSITY

Impact of the definition of peak standardized uptake value on quantification of treatment response.
Results

- Significant variation in both SUV(peak) and tumor response resulted from changing the ROI(peak) definition.

- Intratumor SUV(p) variation: 49% above - 46% below mean (CV, 17%)
- Intratumor SUV(p) response var: 49% above - 35% below mean (SD, 9%).

- Population average SUV(p) variation: 24% above - 28% below mean (CV, 14%)
- Population average SUV(p) response var: 3% above - 3% below mean (SD, 2%)

- Size of ROI(p) caused more variation in response than location or shape.
- Population average tumor response was independent of size, shape, and location of ROI(peak).

- Quantification of individual tumor response using SUV(peak) is highly sensitive to the ROI(peak) definition, which can significantly affect the use of SUV(peak) for assessment of treatment response.

Montefiore
THE UNIVERSITY HOSPITAL

EINSTEIN
Albert Einstein College of Medicine
OF YESHIVA UNIVERSITY

Head and Neck Cancer

- Confirmation of response in primary
  - Unnecessary biopsies
- Analysis of the enlarged node on CT
  - Post radiation neck dissection
- Prediction of response
  - Apoptosis marker clinical trials

Prediction of Therapy Outcome

Brun E, et al (2002):Head and Neck 24: 127-135

Table 3. Metabolic values (MR FDG Mol μmol/min/100 g) and SUV FDG at PET_1 and PET_2 in primary tumors and in metastases. *P* values for comparison of distributions by response status, complete remission (CR) or not complete remission (no CR).

	CR			no CR			
	n	Median	Range	*n*	Median	Range	*p*
PET_1							
MR tumor	36	23	4.5–79	9	27	24–67	.14
MR metastasis	29	16	6.1–51	9	22	9.6–116	.62
SUV tumor	36	8.0	1.4–25	9	12	7.4–19	.027
SUV metastasis	29	5.7	2.4–20	9	6.4	4.2–32	.36
PET_2							
MR tumor	36	14	2.0–41	9	27	14–69	.001
MR metastasis	29	11	3.0–33	9	23	9.9–55	.008
SUV tumor	36	4.4	1.0–13	9	7.7	2.8–16	.07
SUV metastasis	29	4.3	1.0–11	9	5.4	12–14	.28

- 47 patients with St II-IV H&NSCC
- Two PET exams – one before and one 1-3 wks after definitive treatment; metabolic rate (MR) and standardized uptake value (SUV) measured
- Median follow-up time 3.3 years
- ***Lower MR and SUV were significantly associated with CR***

Montefiore THE UNIVERSITY HOSPITAL

EINSTEIN Albert Einstein College of Medicine OF YESHIVA UNIVERSITY

Therapy Outcome Following RT

Yao M et al: Int J Rad Onc Biol Phys 2004; 59(4):1001-1010

- **To study the ability of post–RT FDG PET imaging to predict the status of residual lymphadenopathy after non-surgical management of regionally advanced neck disease.**
- **41 patients**
- ***All patients with negative post RT PET or those with a SUV <3 had negative pathology either on ND or FNA.***
- **Neck Dissection can be avoided post RT on the basis of a negative PET scan.**

Patient	Pre-RT lymph node (cm)*	Post-RT lymph node (cm)*	Post-RT FDG PET	Interval RT to FDG PET (days)	Procedure	Largest lymph node recovered (cm)†	Pathology
1	6.0	3.6	Negative	97	ND	5.3	Negative
2	3.9	1.6	Negative	98	ND	3.5	Negative
3	4.0	1.2	SUV 2.7	103	ND	2.5	Negative
4	1.5	1.4	SUV 6.9	85	ND	2.4	Positive
5	4.5	2.6	SUV 4.8	95	ND	5.5	Negative
6	2.0	2.0	SUV 3.5	91	ND	4.0	Positive
7	4.5	1.3	SUV 3.6	74	ND	2.6	Positive
8	5.2	5.0	Negative	75	ND	6.0	Negative
9	1.3	1.2	SUV 5.2	101	FNA	N/A	Positive
10	4.0	1.8	Negative	91	FNA	N/A	Negative
11	1.5	1.1	SUV 2.9	180	FNA	N/A	Negative
12	1.1	1.1	Negative	115	FNA	N/A	Negative

Prediction of Therapy Outcome

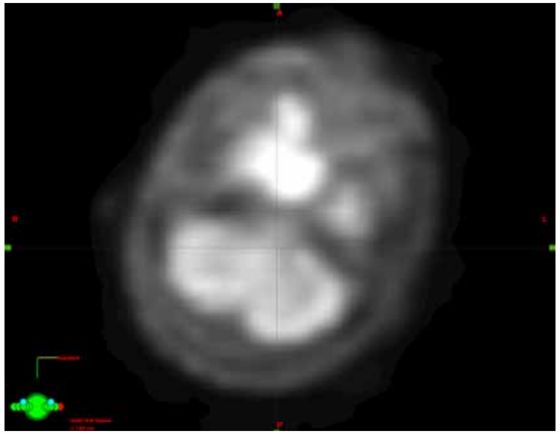
Andrade R, et al (2006):Int J Rad Onc Biol Phys 65: 1315-1322

- Post-treatment FDG-PET/CT was performed in 28 patients on average 8 weeks (range,4 to 15.7 weeks) after completing definitive radiation therapy.

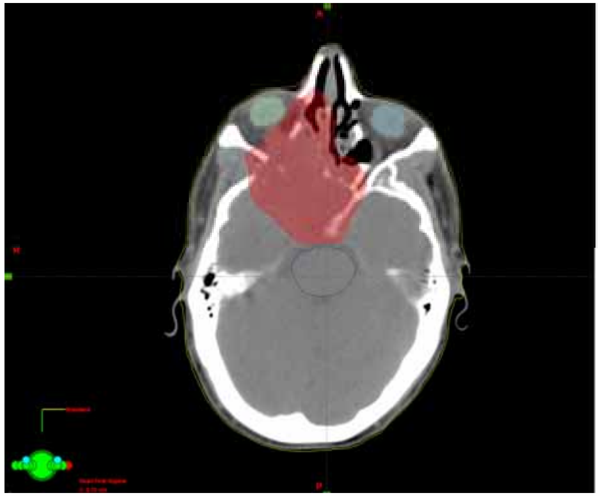
Residual Disease	**PET CT 4-8 weeks**	**CT 4-8 weeks**	**PET CT > 8 weeks**	**CT > 8 weeks**
Sensitivity	66.7%	88.9%	100%	100%
Specificity	87.5%	62.5%	100%	28.6%
+ Predictive Value	85.7%	72.7%	100%	44.4%
- Predictive Value	70.0%	83.3%	100%	100%
Accuracy	76.5%	76.5%	100%	54.5%

Therapy outcome
(Sinonasal Undifferentiated Carcinoma)

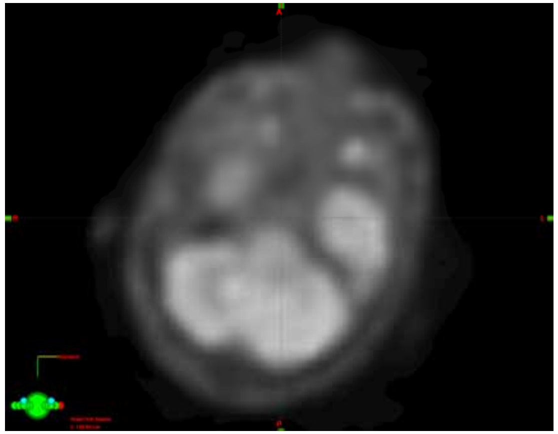
02/07

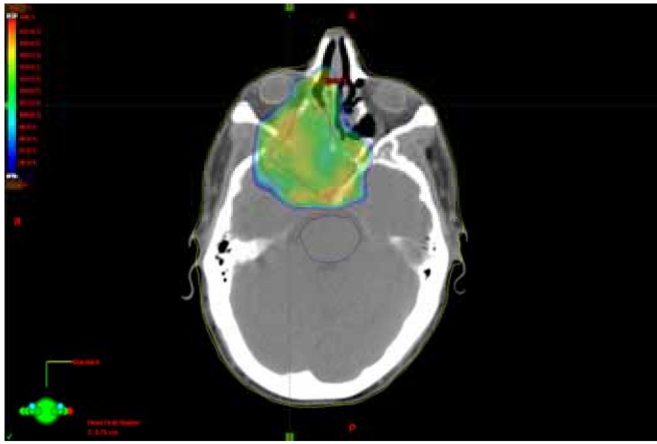


02/07-04/07



08/07





ntefiore
ERSITY HOSPITAL

EINSTEIN
Albert Einstein College of Medicine
OF YESHIVA UNIVERSITY

Response assessment by combined PET-CT scan versus CT scan alone using RECIST in patients with locally advanced head and neck cancer treated with chemoradiotherapy.
Passero VA et al. Ann Oncol 2010 (Pittsburgh)

- 53 patients with previously untreated stages III-IVb SCCHN treated with primary concurrent chemoradiotherapy

- Response was assessed by clinical exam, computed tomography (CT), and PET portions of combined PET-CT scan ~8 weeks after completion of chemoradiotherapy.

Response assessment by combined PET-CT scan versus CT scan alone using RECIST in patients with locally advanced head and neck cancer treated with chemoradiotherapy.
Passero VA et al. Ann Oncol 2010 (Pittsburgh)

- CR rates:
  - Clinical exam: 42/53 (79%)
  - CT: 15/53 (28%)
  - PET-CT: 27/53 (51%)

- CR as assessed by PET, but not as assessed by clinical exam or CT using RECIST, correlated significantly with progression-free status (PFS) (P < 0.0001)

- The 2-year PFS for patients with CR and without CR by PET was 93% and 48%, respectively (P = 0.0002).

Montefiore THE UNIVERSITY HOSPITAL

EINSTEIN Albert Einstein College of Medicine OF YESHIVA UNIVERSITY

Breast Cancer

- Evaluation of response after neo adjuvant chemo irradiation for advanced disease
  – Eliminating mastectomies in progressive disease
  – Allowing breast conserving therapy in good response

- Risk adaptive therapy?

Montefiore
THE UNIVERSITY HOSPITAL

EINSTEIN
Albert Einstein College of Medicine
OF YESHIVA UNIVERSITY

Case in Point: Breast Cancer

- 52 year old female with T2N2bM0 Stage III breast carcinoma
- Biopsy shows poorly differentiated adenocarcinoma with positive axillary nodes

- Would like to try breast conserving therapy
- Neoadjuvant therapy started
- Patient has complete clinical response after neoadjuvant chemotherapy

- Can she have breast preserving surgery?
- Does she need additional post-operative chemotherapy or radiation?

Triple-Negative Breast Cancer: Early Assessment with 18F-FDG PET/CT During Neoadjuvant Chemotherapy Identifies Patients Who Are Unlikely to Achieve a Pathologic Complete Response and Are at a High Risk of Early Relapse.
Groheux D. et al. J. Nuc Med 2012 (Paris, France)

- Prospective study investigated whether early changes in (18)F-FDG tumor uptake during neoadjuvant chemotherapy (NAC) can predict outcomes.
- 20 patients underwent (18)F-FDG PET/CT at baseline and after the second cycle.
- NAC was completed irrespective of PET results.

Triple-Negative Breast Cancer: Early Assessment with 18F-FDG PET/CT During Neoadjuvant Chemotherapy Identifies Patients Who Are Unlikely to Achieve a Pathologic Complete Response and Are at a High Risk of Early Relapse.

Groheux D. et al. J. Nuc Med 2012 (Paris, France)

- At surgery, 6 patients had pathologic CR, 14 had residual tumor.
- 4 patients showed early relapse (<2 y after surgery).
- 11 metabolic responders and 9 non-responders (42% decrease in SUVmax).

	NonResp	Resp	P
Risk of residual tumor at surgery	100%	45%	0.014
Risk of early relapse	44%	0%	0.024

Early prediction of response: Risk Adaptive Therapy

- Protracted chemotherapy regimens
- Shift from chemotherapy and radiation to surgery
- Risk adaptive doses of chemotherapy and radiation

Montefiore
THE UNIVERSITY HOSPITAL

EINSTEIN
Albert Einstein College of Medicine
OF YESHIVA UNIVERSITY

Case in Point:
NSCLC and Radiation Therapy

- 64 year old male, smoker, COPD, with pulmonary nodule
- Biopsy shows non small cell lung cancer Stage II
- Technically resectable but borderline operable as per PFTs
- Is radiation therapy an option?

Montefiore THE UNIVERSITY HOSPITAL
EINSTEIN Albert Einstein College of Medicine OF YESHIVA UNIVERSITY

Combined PET/CT image characteristics for radiotherapy tumor response in lung cancer.

Vayida M. et al. Radiother Oncol 2011 (St. Louis, MO)

- Multimodality image-feature approach for predicting post-radiotherapy tumor progression in NSCLC.
- 27 patients with pre-treatment FDG-PET-CT studies
- 32 tumor region features based on SUV or HU, intensity-volume-histogram (IVH) and texture characteristics were extracted.
- Statistical analysis was performed using Spearman's correlation (rs) and multivariable logistic regression.

Montefiore THE UNIVERSITY HOSPITAL
EINSTEIN Albert Einstein College of Medicine OF YESHIVA UNIVERSITY

Combined PET/CT image characteristics for radiotherapy tumor response in lung cancer.

Vayida M. et al. Radiother Oncol 2011 (St. Louis, MO)

- For loco-regional recurrence, IVH variables had the highest univariate association. In PET, IVH-slope reached rs=0.3426 (p=0.0403).

- For loco-regional and local failures, a 2-parameter model of PET-V(80) and CT-V(70) yielded rs=0.4854 (p=0.0067) and rs=0.5908 (p=0.0013), respectively.

- Multimodality image-feature modeling provides better performance compared to existing metrics and holds promise for individualizing radiotherapy planning.

Montefiore
THE UNIVERSITY HOSPITAL

EINSTEIN
Albert Einstein College of Medicine
OF YESHIVA UNIVERSITY

Using FDG PET/CT to assess tumor volume during RT for NSCLC and its potential impact on adaptive dose escalation and normal tissue sparing.
Feng M et al. Int J Radiat Oncol Biol Phys 2009 (Univ of Michigan)

- Quantify changes in FDG-avid tumor volume on PET/CT during RT
- To examine its potential use in adaptive radiotherapy for tumor dose escalation or normal tissue sparing

- 14 patients with Stage I-III NSCLC underwent FDG-PET/CT before RT and after 40-50 Gy
- Gross tumor volumes were contoured on CT and PET scans obtained before and during RT.
- RT plans were generated for each patient, first using only pretreatment CT scans. Mid-RT PET volumes were then used to design boost fields.

Using FDG PET/CT to assess tumor volume during RT for NSCLC and its potential impact on adaptive dose escalation and normal tissue sparing.
Feng M et al. Int J Radiat Oncol Biol Phys 2009 (Univ of Michigan)

- Mid-RT PET scans were useful in the 10/14 patients.
- Mean volume decreases: CT=26%, PET=44%
- Designing boosts based on mid-RT PET allowed for a meaningful dose escalation of 30-102 Gy (mean, 58 Gy).

- Tumor metabolic activity and volume can change significantly after 40-50 Gy of RT
- Using mid-RT PET volumes, tumor dose can be significantly escalated or NTCP reduced.
- Clinical studies evaluating patient outcome after PET-based adaptive RT are ongoing.

Functional Imaging of Factors Affecting Therapeutic Response

- Certain tumor characteristics may affect response to chemotherapy and radiation

- These include
  - Hypoxia
  - Necrosis
  - Tumor bed effect

- Is there a role for PET-CT in those circumstances?

Montefiore
THE UNIVERSITY HOSPITAL

EINSTEIN
Albert Einstein College of Medicine
OF YESHIVA UNIVERSITY

A Prospective, Multicenter Study, to Evaluate the Efficacy and Safety of [18F]-ML-10, a PET Imaging Radiotracer, in Early Detection of Response of Non-Hematological Tumors to Concurrent Chemoradiotherapy.

- To evaluate a new apoptosis marker for early diagnosis of responsiveness in two patient populations

- Previously untreated, locally advanced non small cell lung cancer (NSCLC), who will receive concurrent chemoradiotherapy as definitive treatment.

- Previously untreated, locally advanced squamous cell carcinoma of the head and neck (SCCHN), who will receive concurrent chemoradiotherapy as definitive treatment.

Montefiore
THE UNIVERSITY HOSPITAL

EINSTEIN
Albert Einstein College of Medicine
OF YESHIVA UNIVERSITY

Aposense study sessions

- Each patient will undergo two PET/CT sessions at the time points defined below, each following intravenous (IV) administration of a single [^{18}F]-ML-10 injection:

- *Baseline session*: 1-13 days prior to initiation of treatment.

- *Follow-up session:* 11±1 days post initiation of CRT (following an accumulative radiation dose of 14.4-20.0Gy).

Montefiore
THE UNIVERSITY HOSPITAL

EINSTEIN
Albert Einstein College of Medicine
OF YESHIVA UNIVERSITY

Thank You!

Come Visit!

Montefiore
THE UNIVERSITY HOSPITAL

EINSTEIN
Albert Einstein College of Medicine
OF YESHIVA UNIVERSITY