



The UNIVERSITY of OKLAHOMA
Health Sciences Center

Utilization of FDG PET CT in Target Volume Definition and its Impact on Tumor and Normal Tissue Dose Variation

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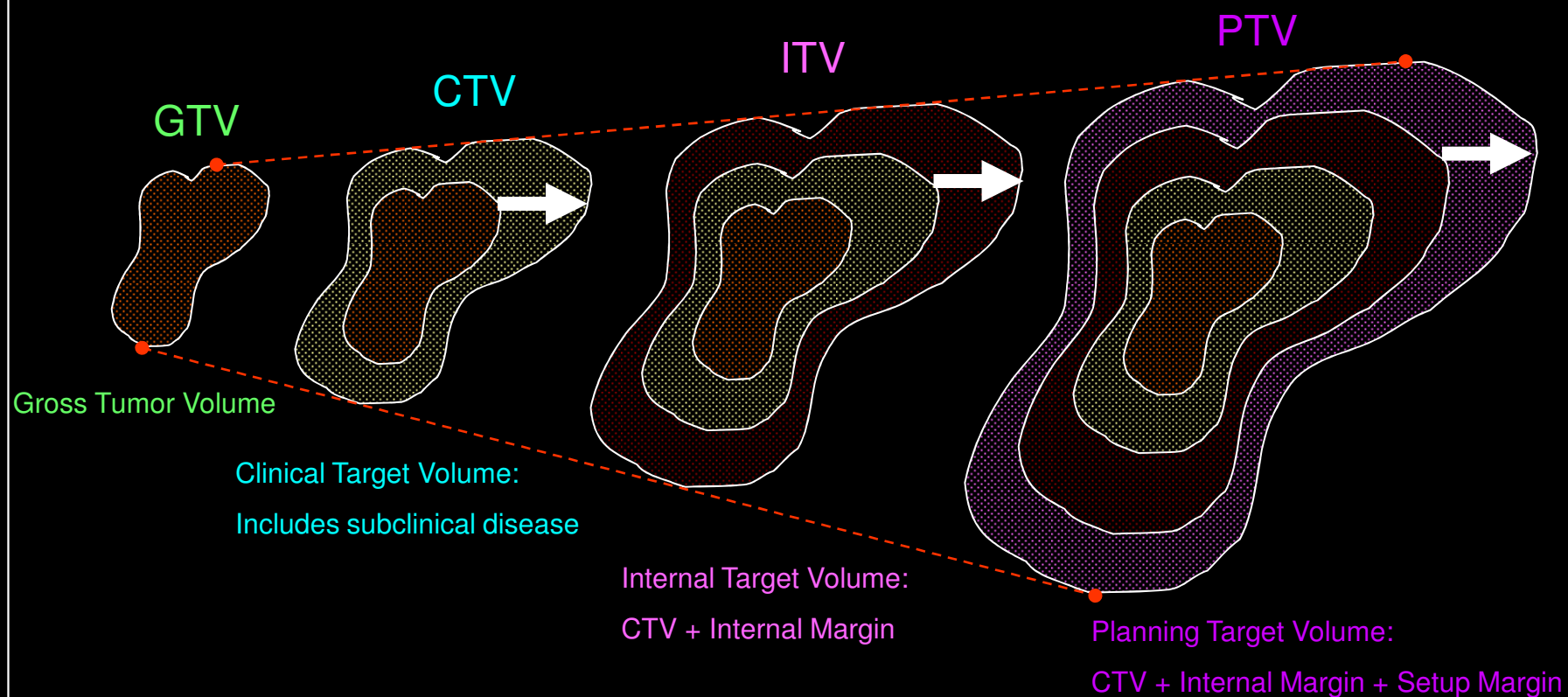
OUTLINE

- Introduction
- Materials and Methods
- Results
- Discussions
- Conclusions
- Questions

INTRODUCTION

- Radiation treatment planning is fundamentally based on imaging
- In the past, tumor and normal structures were defined on data sets generated with contrast and computed tomography (CT) and/or magnetic resonance imaging (MRI)
- For radiation therapy to be effective, the target volume must be encompassed as accurately as possible by high radiation dose to yield a successful tumor control and avoid damaging neighboring critical structures

ICRU REPORT 62: Prescribing and Reporting Photon Beam Therapy

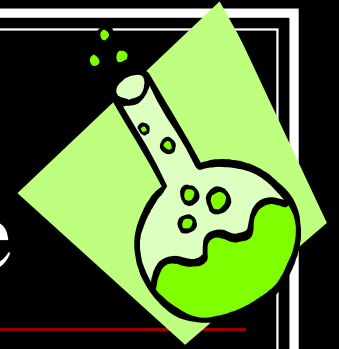


Tools for Tumor Definition



- The definition of the CTV is the most important component in the treatment planning process
- The doses delivered to the tumor area and to the healthy tissues near it depend on it, and the radiation oncologist relies on imaging tools that are essential for accomplishing this task
- With the readily available Fluorine-18-FluoroDeoxyGlucose (18F-FDG) radiopharmaceutical, the positron emission tomography (FDG PET) combined with computed tomography (CT) can provide structural and biological information useful in the definition of tumor and radio-resistant regions of tumor that can be treated to higher doses

Fluorine-18-FluoroDeoxyGlucose



- ^{18}F -FDG is an analogue of glucose that can accumulate in high concentration in metabolically active tumors
- It's overall **sensitivity** for NSCLC is about 90% for primary tumors and 83% for nodes, and **specificity** may range from 79 to 93% for primary tumors and 89% for nodes¹
- It is approved by the Center for Medicare and Medicaid Services for diagnosis, staging and re-staging of several cancers, lung cancer among them
- It is produced in a cyclotron, the half life is 110 minutes, and it is commercially available throughout the U.S in unit dose quantities

¹ Clinical use of PET-CT data for radiotherapy planning: What are we looking for?

Arturo Chiti, Margarita Kirienko, Vincent Grégoire, Radiotherapy and Oncology 96 (2010) 277-279

Fluorine-18-FluoroDeoxyGlucose



- PET potentially can provide diagnostic information over biochemically changing tumors before visually structural changes occur
- ^{18}F -FDG is not a specific tumor agent and it may accumulate in different organs and areas of infection
- The image interpreter must be aware of the high uptake by benign tumors that may exceed the accumulation in malignant tumors² (giant cell tumor, fibrous dysplasia of bone, adenomatous polyps in colon)
- A look into the patient's history and appropriate patient preparation for the scan to avoid artifacts should support an accurate interpretation of the images scanned

HOWEVER...



- Treatment planning is based on the physician's clinical interpretation of the tumor volume
- The tumor and normal tissue doses received by a patient may vary significantly when the treatment plan is based on CT images alone or on CT images fused with ^{18}F FDG PET, **AND**, are absolutely dependent on the observation by the experienced clinician
- In this study, we looked at the differences in tumor volumes, in tumor and mean lung doses, and the volume of lung receiving 20Gy or higher calculated for treatment plans based on targets defined by physician T and physician H, on CT and PET-CT images

MATERIALS AND METHODS

Patient Data



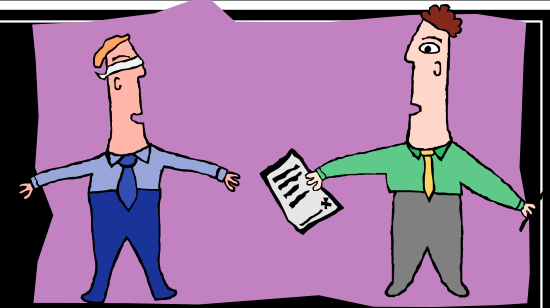
- This study uses retrospective data from twenty lung cancer patients who had CT and PET imaging for treatment plan preparation
- The median age for this group was 59 years (range = 46 to 72 years)
- In this group of studied subjects:
 - 10 had tumors in the left lung
 - 6 had tumors in the right lung
 - 1 had a central tumor, 1 had a left central tumor, and 2 had right central tumors

Imaging Equipment



- Sim CT: GE LightSpeed CT Scanner, 4 Slice
- ^{18}F FDG PET-CT: GE Discovery STE, 16 slice, BGO crystal
 - Lung scan technique, free breathing, patient's immobilization device, and arms up
 - for $\text{BMI} \leq 40$, ^{18}F FDG dose is 10mCi
 - for $\text{BMI} \geq 41$, ^{18}F FDG dose is 20mCi

Target Volumes



- Both physicians were asked to contour the target volumes on the CT scans first
- Then, they were asked to contour the target volumes again on the PET-CT fused scans independently of what they had done before for each patient
- Treatment plans were created for the CT and PET-CT set of target volume contours for both physicians

Treatment Planning

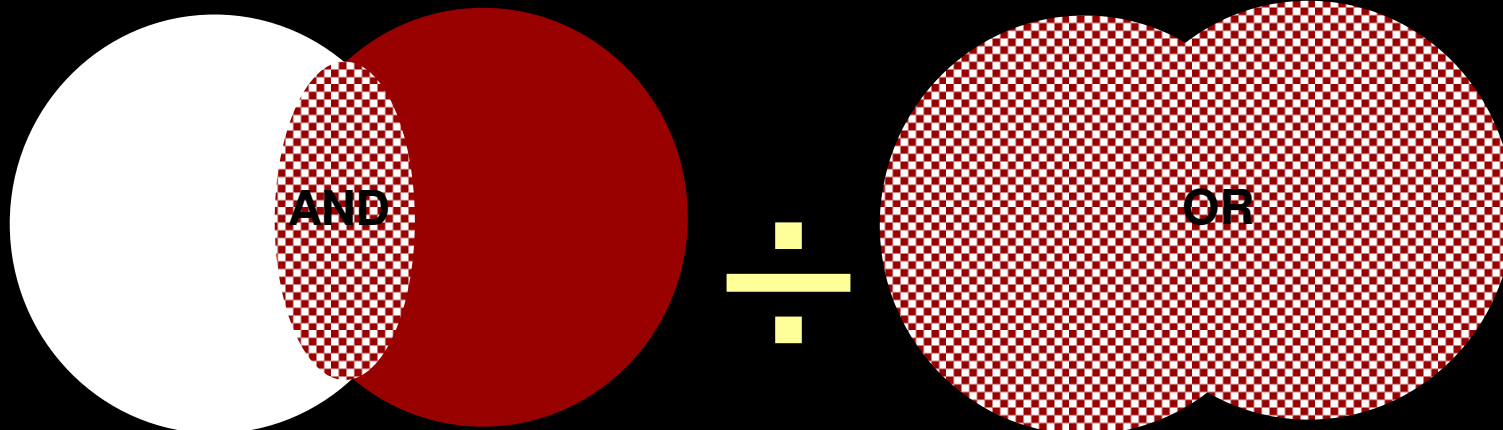


- The treatment plans used non-opposing co-planar beams of four to seven fields
- The prescribed dose was 70.2 Gy in 39 fractions
- The doses to the CT contoured structures were obtained from plans that were originally planned based on the contours from the PET-CT fused images
- *...in other words...the PET-CT-image-based-contoured-treatment-plans* were used as the base for comparison

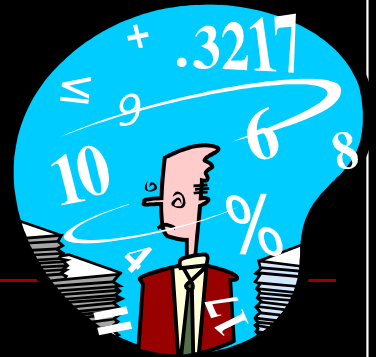
Index of Agreement (IoA)



- The tumor volumes of PET-CT and CT were compared by an index of agreement (IoA) that ranges from 0 (no agreement) to 1 (total agreement)
- The volume shared by CT and PET-CT plans (intersection) divided by their union



Index of Agreement (IoA)



- IoA intra-observer: $(CT) \cap (PET-CT) \div (CT) \cup (PET-CT)$
- IoA inter-observer: $(CT)_H \cap (CT)_T \div (CT)_H \cup (CT)_T$
- IoA inter-observer: $(PE-CT)_H \cap (PET-CT)_T \div (PET-CT)_H \cup (PET-CT)_T$
- Minimum and mean doses to the tumor and mean lung dose
- V_{20} (volume of lung receiving dose above 20 Gy)
- Student's t-test (paired, two tails, significance with p-value < 0.05)

RESULTS



Three cases chosen randomly

- Physician H

CT volumes are in orange

PET volumes are in red

- Physician T

CT volumes are in purple

PET volumes are in cyan

SUBJECT 5

Physician H

CT volume = 379.52 cm³

PET/CT volume = 235.73 cm³

V₂₀ = 6% (both volumes)

IoA = 0.38

Physician T

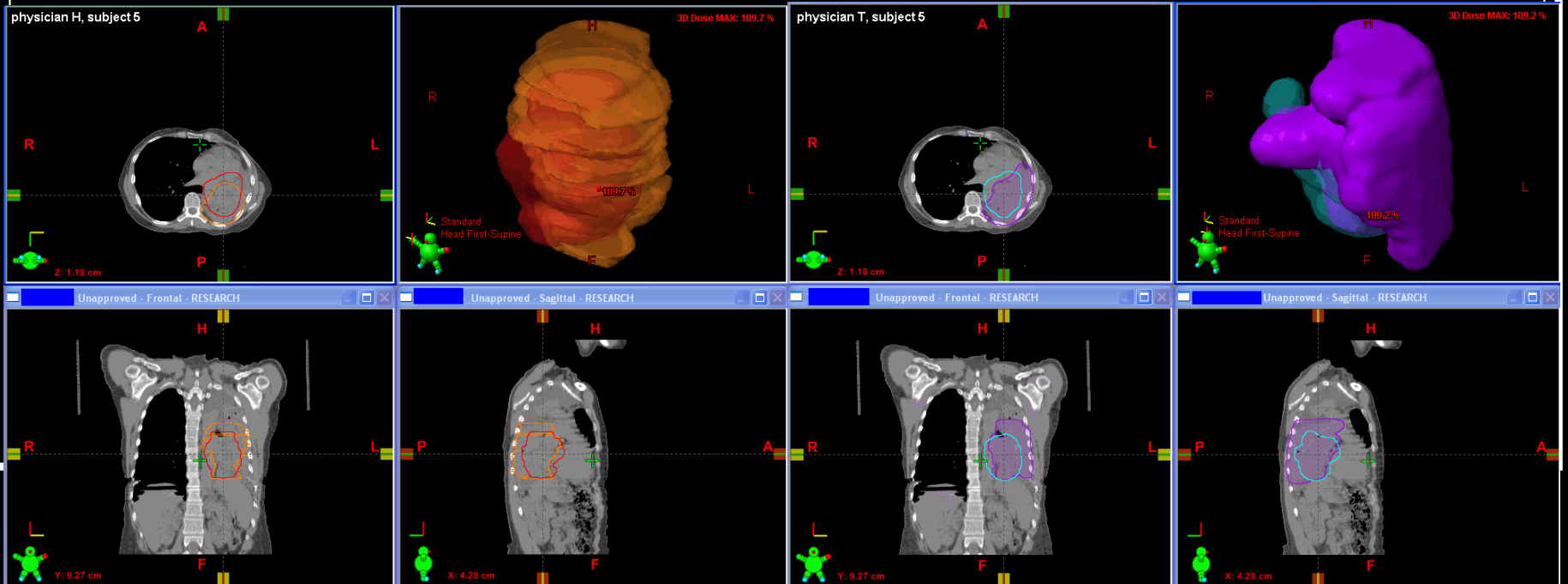
CT volume = 658.83 cm³

PET/CT volume = 249.19 cm³

V₂₀ = 9% (both volumes)

IoA = 0.31

Inter-observer variation: for CT = 0.51, and for PET/CT = 0.81



SUBJECT 8

Physician H

CT volume = 269.08 cm³

PET/CT volume = 202.18 cm³

V₂₀ = 3%

IoA = 0.36

Physician T

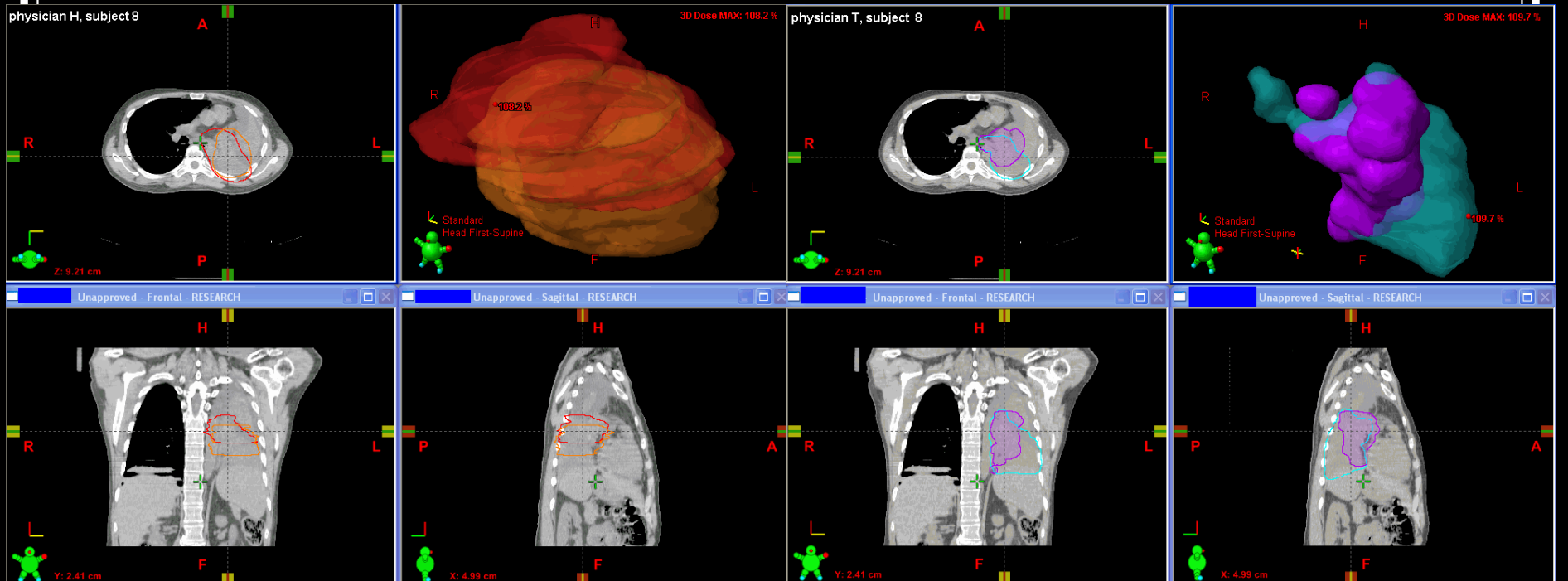
CT volume = 276.32 cm³

PET/CT volume = 533.65 cm³

V₂₀ = 8%

IoA = 0.25

Inter-observer variation: for CT = 0.29, and for PET/CT = 0.28



SUBJECT 11

Physician H

Physician T

CT volume = 567.22 cm³

PET/CT volume = 378.71 cm³

V₂₀ = 13.9 -14.6%

IoA = 0.45

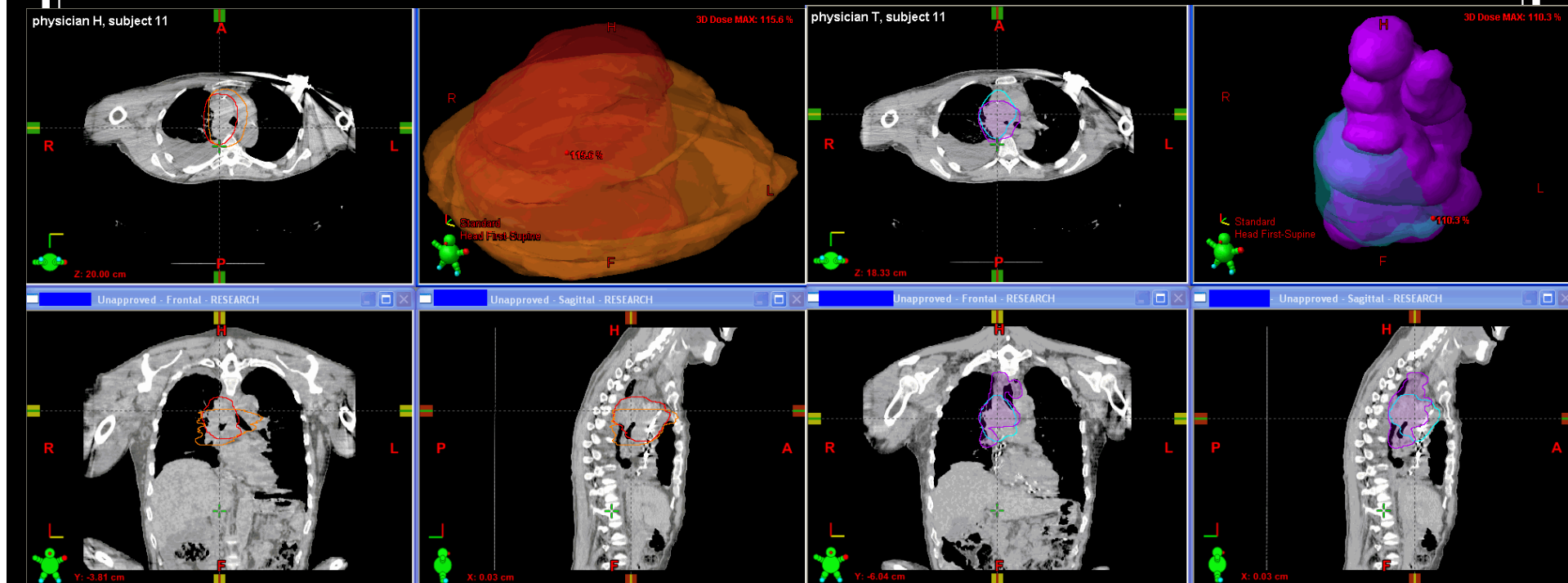
CT volume = 464.51 cm³

PET/CT volume = 279.14 cm³

V₂₀ = 11.5 -11.8%

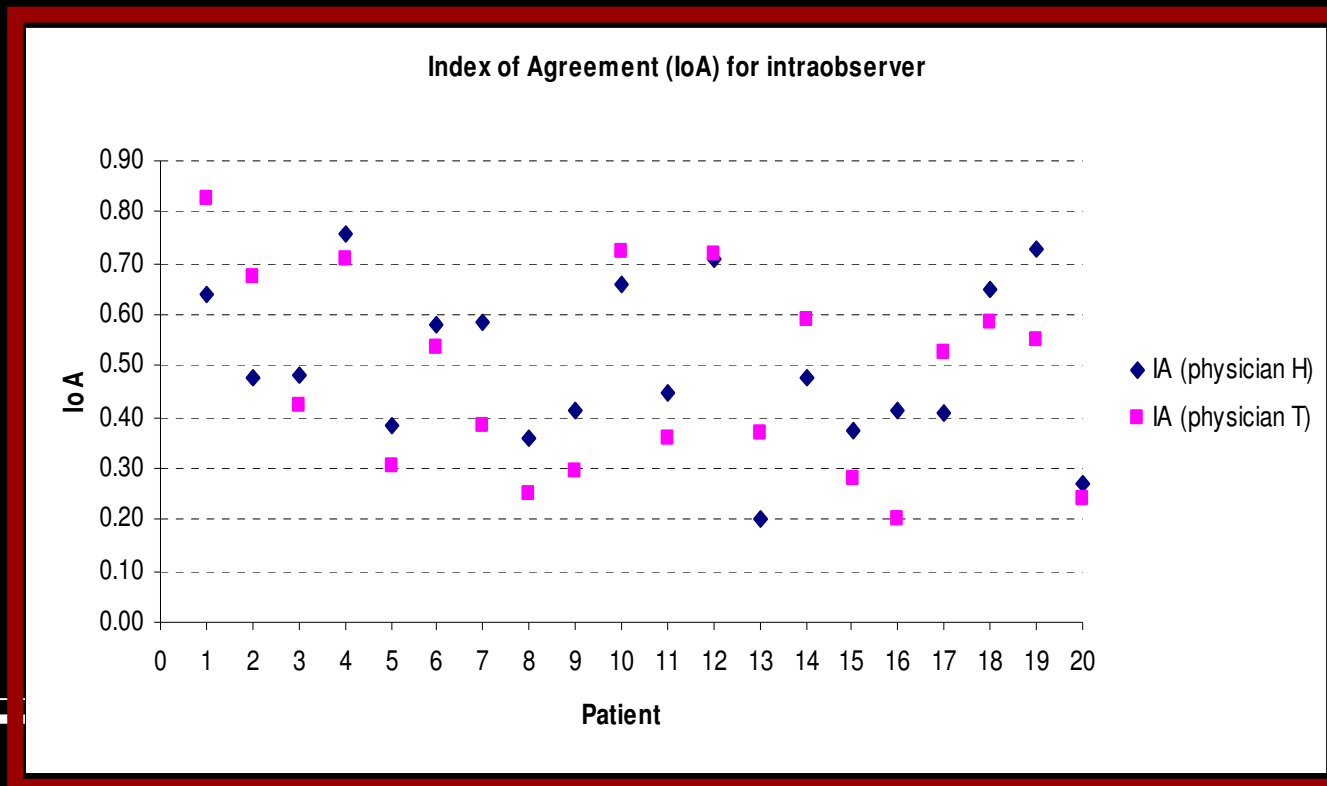
IoA = 0.36

Inter-observer variation: for CT = 0.34, and for PET/CT = 0.72



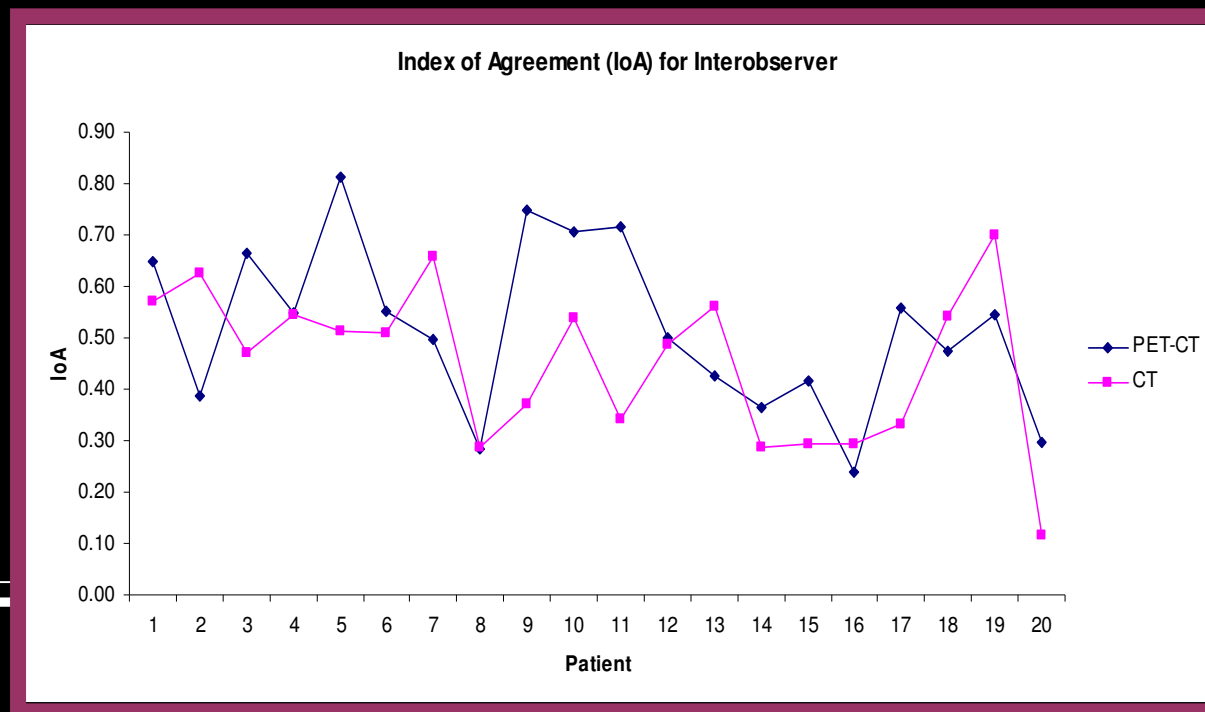
Level of agreement on the CT and PET-CT volumes for each physician

- The mean intra observer IoA value was approximately 0.50 for both physicians



Level of agreement on the CT and PET-CT volumes for both physicians

- The mean inter observer IoA value was 0.45 for CT and 0.52 for fused PET-CT tumor outlining respectively



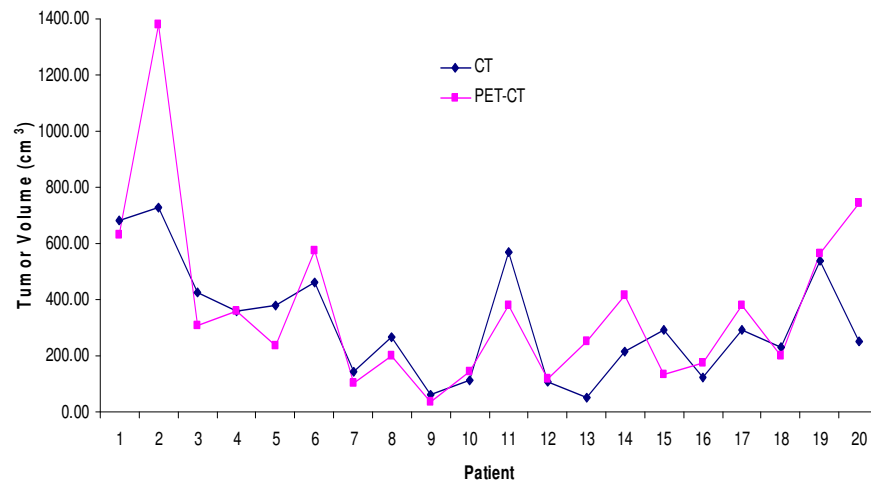
Tumor Volume Contouring Variation for CT and PET-CT

- The average percent difference in the volumes drawn by physician H was 14.16% (*p value* = 0.278)

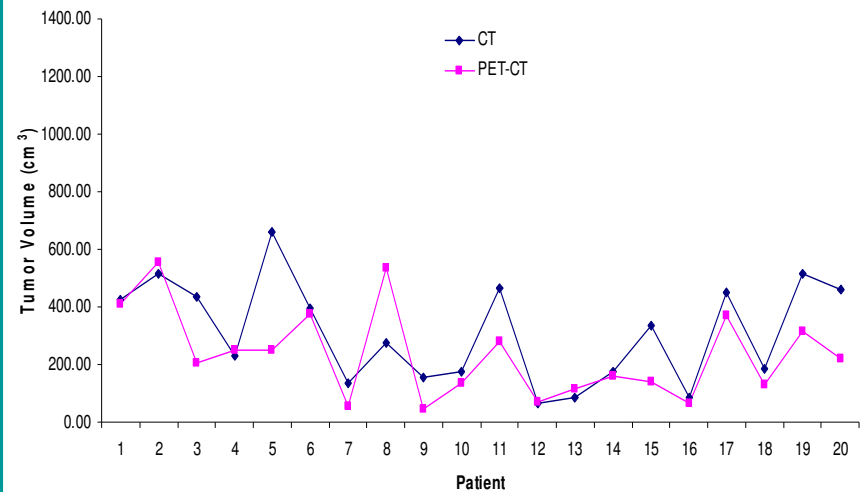
- The average percent difference in the volumes drawn by physician T was -32.95% (*p value* = 0.023)

$$\% \Delta = 100 \times [(PET-CT)vol - CTvol] \div (PET-CT)vol$$

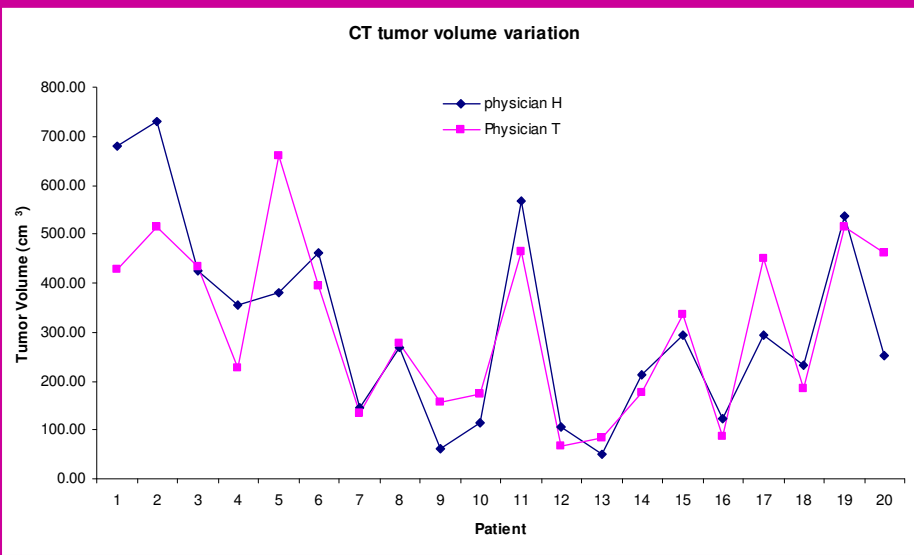
Tumor Volume Variation (physician H)



Tumor Volume Variation (physician T)



CT Tumor Volume (cm³)

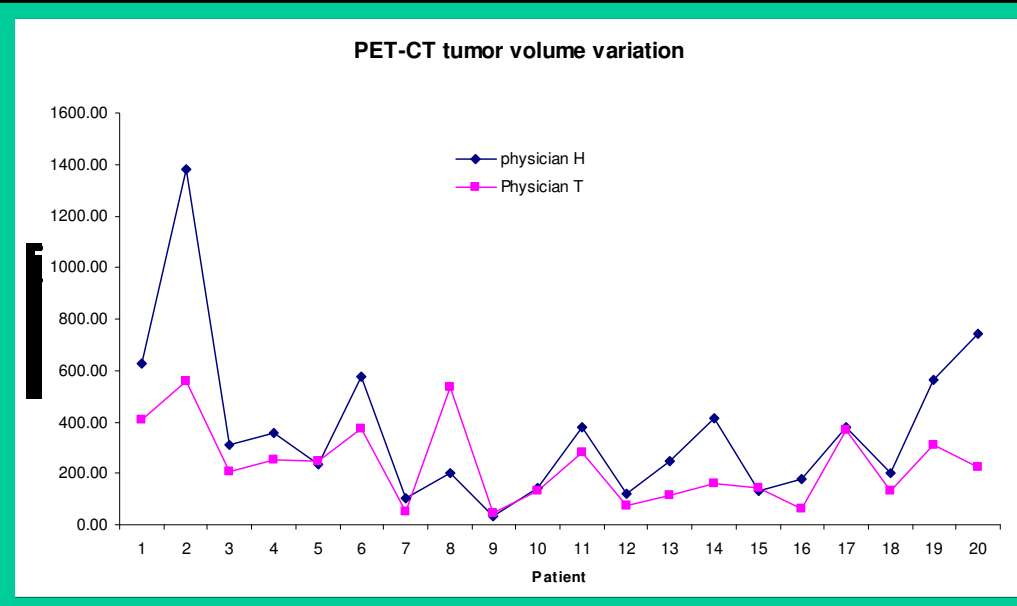


Subject	Physician H	Physician T	% difference
1	680.43	426.88	37.26
2	728.82	515.60	29.26
3	424.67	434.04	2.21
4	356.61	227.69	36.15
5	379.52	658.83	73.60
6	460.49	394.85	14.25
7	145.59	135.30	7.07
8	269.08	276.32	2.69
9	62.33	156.19	150.59
10	114.68	173.71	51.47
11	567.22	464.51	18.11
12	106.40	67.01	37.02
13	51.53	84.46	63.90
14	213.01	176.31	17.23
15	293.54	336.75	14.72
16	123.95	87.46	29.44
17	292.38	450.71	54.15
18	231.29	183.67	20.59
19	536.91	514.59	4.16
20	252.90	461.34	82.42

p-value = 0.910

$$\% \Delta = 100 \times [(H-CT)_{vol} - (T-CT)_{vol}] \div (H-CT)_{vol}$$

PET-CT Tumor Volume (cm³)



Subject	Physician H	Physician T	% difference
1	628.23	407.90	35.07
2	1379.38	557.49	59.58
3	309.31	205.52	33.56
4	357.45	251.17	29.73
5	235.73	249.19	5.71
6	575.07	374.69	34.84
7	104.49	53.51	48.79
8	202.18	533.65	163.95
9	36.19	46.34	28.05
10	142.56	135.25	5.13
11	378.71	279.14	26.29
12	119.59	71.99	39.80
13	250.23	112.72	54.95
14	414.82	160.80	61.24
15	132.63	142.10	7.14
16	175.83	64.45	63.35
17	379.44	371.00	2.22
18	200.12	130.67	34.70
19	562.02	313.28	44.26
20	744.93	222.37	70.15

p-value = 0.018

$$\% \Delta = 100 \times [(H-PET-CT)_{vol} - (T-PET-CT)_{vol}] \div (H-PET-CT)_{vol}$$

% Δ in average minimum and mean doses for PET-CT and CT plans

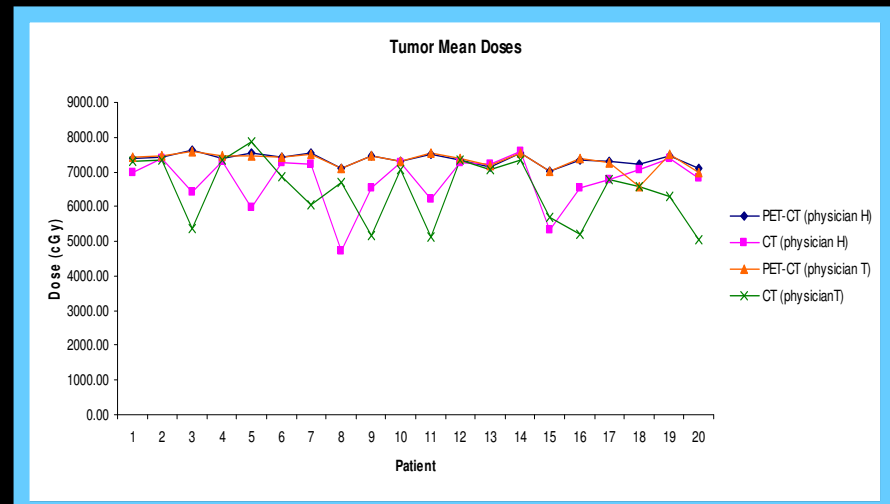
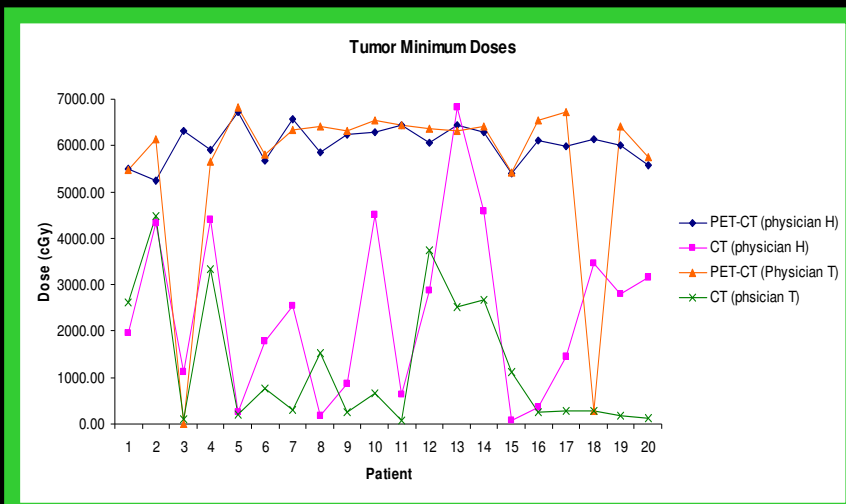


■ Physician H:

- Minimum dose = 60.1%
- Mean dose = 8.1%

■ Physician T:

- Minimum dose = 78.4%
- Mean dose = 11.7%



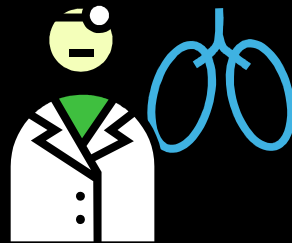
Averaged variations in mean dose to the lung for PET-CT and CT plans

■ Physician H:

- Mean dose = 5.6%
- *p-value* = 0.02

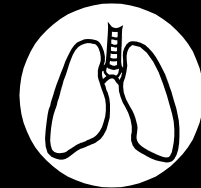
■ Physician T:

- Mean dose = 1.9%
- *p-value* = 0.53



The differences in mean dose to the lung between both physicians were
9.60% for PET-CT plans (*p-value*= 0.20)
12.74% CT plans (*p-value*= 0.15)

Percentage of Lung receiving above 20 Gy (V_{20})



Physician H (% V_{20})		
Patient	PET/CT	CT
1	25.58	27.47
2	48.87	51.64
3	13.95	15.00
4	13.95	5.59
5	6.05	6.06
6	35.36	36.09
7	11.51	10.88
8	3.05	3.05
9	8.08	7.54
10	9.85	10.41
11	14.57	13.85
12	2.29	2.65
13	14.55	16.08
14	18.70	22.00
15	2.73	2.42
16	19.89	20.30
17	13.72	13.86
18	16.14	15.81
19	22.82	22.44
20	30.40	33.34

(Range, 2.42 – 51.64) p -value = 0.680

Physician T (% V_{20})		
Patient	PET/CT	CT
1	25.50	22.21
2	31.34	30.98
3	12.96	11.77
4	7.38	8.14
5	9.33	9.42
6	28.58	28.34
7	8.79	7.89
8	7.99	7.98
9	8.50	7.05
10	9.91	9.27
11	11.80	11.51
12	3.17	3.48
13	12.20	11.72
14	17.22	16.35
15	18.70	17.09
16	17.22	16.82
17	12.60	13.28
18	17.79	17.80
19	15.31	13.37
20	22.21	20.44

(Range, 3.48 – 30.98) p -value = 0.006

DISCUSSION



- Three articles are specifically used for discussion and comparison:
 - An educational review of the integration of FDG-PET and PET-CT in TP for NSCLC
 - A phase II comparative study of GTV definition with or without PET/CT fusion (RTOG 0515)
 - A comparative study of FDG PET and CT based target volumes in NSCLC outlined by three radiation oncologists and a PET radiologist

Educational review

Practical integration of [^{18}F]-FDG-PET and PET-CT in the planning of radiotherapy for non-small cell lung cancer (NSCLC):
The technical basis, ICRU-target volumes, problems, perspectives

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- General overview of technical factors influencing PET and PET-CT data and their consequences for radiotherapy planning
- Reviews literature concerning the diagnostic value of FDG-PET in RT planning for NSCLC
- Points out the impact in GTV definition and methods of target volume contouring for primary tumor and integration of lymph node involvement in the CTV, and implications on the PTV
- Offers a view to future PET tracers for lung cancer

Major highlights...

- Most important observation was the implication of FDG-PET in the diagnosis of lymph node involvement
- False positive in the mediastinum due to inflammatory lesions might influence the GTV delineation
- FDG PET could improve the delineation of malignant tissue from atelectasis
- FDG PET the target volume can either be enlarge or reduced
- Target volumes are susceptible to the visual interpretation of the contouring physician and for the most part an SUV of 2.5 is often used as threshold for the distinction of malignant and benign tumors
- Motion artifacts blur the edges of PET contours (respiratory gating may help reduce this uncertainty)

On the definition of the CTV...

- In NSCLC the TCP increases with higher doses of radiation
- Irradiated volume is a risk for normal tissue toxicity, so high doses cannot be achieved for large target volumes
- The Elective Nodal Inclusion (ENI): prophylactic inclusion of large parts of the mediastinum into the CTV
- ENI is being replaced in favor of irradiation of the macroscopic tumor tissue alone by increasing dose of high precision

On the margins for PTV...

- Two main influencing factors: set-up variation and internal motion
- Set-up variations are not much impacted with PET-CT systems. For CT and PET systems, identical patient positioning must be assured before the images can be fused
- A conservative margin for internal margin in non-gated irradiations of 0.5 cm to 1.5 cm is added
- It might be possible to reduce the margin added to CTV to create the ITV after defining the GTV with FDG-PET; however, no tight thresholds should be used for contouring the FDG positive tissue

Table 1
Literature reports on the impact of FDG-PET on radiotherapy planning in lung cancer

Author	Study	Patients	PET/CT image fusion	Method of GTV contouring (PET)	Change of GTV, PTV using PET	Increase of GTV, PTV using PET	Decrease of GTV, PTV using PET	Comment
Hebert et al. [46] ✓	Prospective	20	Comparison X-ray, CT, PET	Visual evaluation of FDG-PET	GTV 7/20 P (35%)	GTV 3/20 P (15%)	GTV 4/20 P (20%)	PET may be useful for delineation of lung cancer
Kiffer et al. [54]	Retrospective	15	Graphical co-registration of coronal PET with AP simulator image	Visual evaluation of FDG-PET	GTV: 7/15 P (47%) PTV: 4/15 P (27%)	GTV and PTV: 4/15 P (27%)		PET detects positive lymph nodes, not useful in tumor delineation
Munley et al. [63]	Retrospective	35	CT/PET co-registered manually using transmission PET	Visual evaluation of FDG-PET	PTV: 12/35 P (34%)	PTV: 12/35 P (34%)	PET target smaller than CT not evaluated	PET complements CT information
Nestle et al. [69]	Retrospective	34	PET-portal compared to CT-portal	Visual evaluation of FDG-PET	change of field size in 12P (35%) Median 19, 3% (cm ²)	Increase of field size 9 P (26%)	Decrease of field size 3 P (9%)	Change of field size in patients with dys- or atelectasis
Vanuytsel et al. [92]	Retrospective	73 (N+)	CT-Naruke map compared with CT-PET-Naruke map and pathology	Visual evaluation of FDG-PET	GTV: 45/73P (62%)	GTV: 16/73P (22%) 11P = pathology 1P-unnecessary 4P-insufficient	GTV: 29/73P (40%) 25P = pathology 1P-inappropriate 3P-insufficient	PET data vs. pathology: 36 P (49%) = pathology 2 P (3%) inappropriate 7 P (10%) insufficient
MacManus et al. [61]	Prospective	153	PET results used for treatment planning, no image fusion	Visual evaluation of FDG-PET	GTV: 22/102 P (21%)	GTV: 22/102 P (21%) Inclusion of structures previously considered uninvolved by tumor n.e.	GTV: 16/102 P (15%) Exclusion of atelectasis and lymph nodes	Post-PET stage but not pre-PET stage was significant associated with survival
Kalff et al. [53]	Prospective	34	No image fusion	Visual evaluation	22/34 altered treatment delivery	n.e.	11/34 reduction of treatment volume	Part of a study on impact of FDG- PET on various endpoints (n = 105)
Giraud et al. [40]	Prospective	12	CT/PET image fusion	Visual evaluation of FDG-PET	GTV, PTV 5/12 P (42%)	n.e.	n.e.	4/12 P lymph nodes 1/12 atelectasis and distant meta
Mah et al. [62]	Prospective	30	Image coregistration CT-PET using external fiducial markers	50% intensity level of max. FDG uptake	GTV: 5/23 P (22%) FDG-avide lymphnodes	PTV: 30-76% of cases (varied between the 3 physicians)	PTV: 24-70% of cases (varied between the 3 physicians)	(a) Addition of PET does lower physician variation in PTV delineation

						Increase of GTV, PTV using PET	Decrease of GTV, PTV using PET	Comment	
Erdi et al. [34]	Prospective	11		Image fusion: manual method using transmission PET data compared with automated image registration based on mutual information	40% intensity level of max. FDG uptake	PTV: 11/11P (100%)	PTV: 7/11 P (36%) 19% (5–46%) cc detection of lymph nodes	PTV: 4/11 P 18%(2–48%) cc exclusion of atelectasis trimming the target vol. to spare critical structure	(b) PET-significant alterations to patient management and PTV PET improves GTV and PTV definition
Ciernik et al. [23]	Prospective	6		Integrated PET/CT	manually	GTV: 6/6 P (100%)	GTV 1/6 (17%)	GTV 4/6 (67%)	PET/CT improves GTV delineation
Bradley et al. [13]	Prospective	26	✓	Patient immobilization	40% intensity level of max. FDG uptake	PTV:14/24 P(58%)	11/24 P (46%) 10 lymph nodes, 1 tumor	3/24 P (12%) Tumor vs. atelectase	PET improves diagn. of lymph nodes and atelectasis
Van Der Wel et al. [89]	Prospective	21		PET/CT visual fusion technique		GTV and PTV: 12/21 P (57%)	0%	12/21 P (57%)	Nodal GTV decreased by PET dose escalation > increased TCP
Brianzoni et al. [14]	Retrospective	28	✓	PET/CT	40% intensity level	GTV/CTV: 11/25 (56%)	6/11	5/11	
Ashamalla et al. [7]	Prospective	19	✓	Integrated PET/CT	Halo phenomenon	GTV: 10/19 P (52%) PTV: 8/19 P (42%)	GTV: 5/19 (26%) PTV: 4/19 (21%)	GTV: 5/19 (26%) PTV: 4/19 (21%)	Improvement of interobserver variability up to 84%
Deniaud-Alexandre et al. [29]	Retrospective	101	✓	Image fusion using fiducial markers	50% intensity level of max FDG uptake	PTV: 43/101 (43%)	GTV: 24/101 (24%)	GTV: 21/101 (23%)	PET/CT has impact on treatment planning
Steenbakkers et al. [81]	Prospective	22		PET-CT	Integrated PET-CT standardized windowing	Significant reduction of mean GTV	n.e.	n.e.	Significant reduction of inter observer variation
De Ruyscher et al. [26]	Prospective	21	✓	PET-CT simulator vs. CT-simulator	Identification of affected anatomical structures by FDG	14/21 (66%)	2/21 (10%)	12/21 (57%)	with PET simulator TCP signi. higher NTCP sign. lower

n.e.: not evaluated.

A PHASE II COMPARATIVE STUDY OF GROSS TUMOR VOLUME DEFINITION WITH OR WITHOUT PET/CT FUSION IN DOSIMETRIC PLANNING FOR NON-SMALL-CELL LUNG CANCER (NSCLC): PRIMARY ANALYSIS OF RADIATION THERAPY ONCOLOGY GROUP (RTOG) 0515

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BARRY A. SIEGEL, M.D.,* JACQUELINE BRUNETTI, M.D.,|| JAMES PURDY, PH.D.,¶ SERGIO FARIA, M.D.,**
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- Designed to quantify the impact of PET-CT compared with CT on RTPs and determine the rate of elective nodal failure for PET-CT derived volumes
- Materials and Methods:
 - 47 patients who had definitive radiotherapy for NSCLC (≥ 60 Gy)
 - GTVs drawn on CT and PET-CT images, but treatment was based on PET-CT derived volumes
 - Treating Rad/Onc defined volumes on PET-CT, and CT volumes were defined by two alternating Rad/Oncs from participating institution
 - Measured differences analysis on GTV, No. of involved nodes, MLD, V_{20} , and MED (esophageal)
- Results:
 - GTV was statistically significantly smaller for PET-CT tumors ($p < 0.0001$)
 - MLDs: 19.0 Gy (CT), 17.8 Gy (PET-CT)
 - No. involved nodes: 2.1 (CT), 2.4 (PET-CT)
 - V_{20} : 32% (CT), 30.8% (PET-CT)
 - MED: 28.7 Gy (CT), 27.1 Gy (PET-CT)
- Conclusions:
 - PET-CT tumor volumes were smaller than CT volumes
 - PET CT changed nodal GTV contours in 51% of patients
 - Elective nodal failure rate for GTVs from PET-CT is low supporting the RTOG standard of limiting the target volume to the primary tumor and involved nodes, because failure rate was less than 5%

¹⁸F-FLUORODEOXYGLUCOSE POSITRON EMISSION TOMOGRAPHY/COMPUTED TOMOGRAPHY-BASED RADIOTHERAPY TARGET VOLUME DEFINITION IN NON-SMALL-CELL LUNG CANCER: DELINEATION BY RADIATION ONCOLOGISTS VS. JOINT OUTLINING WITH A PET RADIOLOGIST?

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- Investigated volumetric and positional variations in GTV using planning PET-CT among 3 Rad/Oncs and 1 PET radiologist

■ **Materials and Methods:**

- RTP PET-CTs of 28 NSCLC patients (stage IA-IIIB)
- Three Rad/Oncs and one PET radiologist with a fourth Rad/Onc's help with countouring
- GTVs on CT and fused PET-CT images
- % volume change between GTV_{CT} and GTV_{PET-CT} for the Rad/Oncs and PET radiologist
- CI to asses positional and volume change between both GTVs in one measurement

■ **Results:**

- For all patients, a significant difference in % volume change from GTV_{CT} and GTV_{PET-CT} exists between Rad/Oncs (median, 5.9%) and the PET radiologist (median, -0.4%, $p = 0.001$)
- No significant difference in median concordance index (for GTV_{CT} and GTV_{fused} for individual cases, $p = 0.088$)
 - PET radiologist (CI = 0.73)
 - Rad/Oncs (CI = 0.66)

■ **Conclusions:**

- % volume change from GTV_{CT} to GTV_{PET-CT} were lower for the PET radiologist than for the Rad/Oncs
- Suggesting lower impact of PET-CT volume delineation for the PET radiologist than for the Rad/Oncs
- Guidelines are needed to standardize the use of PET-CT for tumor delineation in RTP

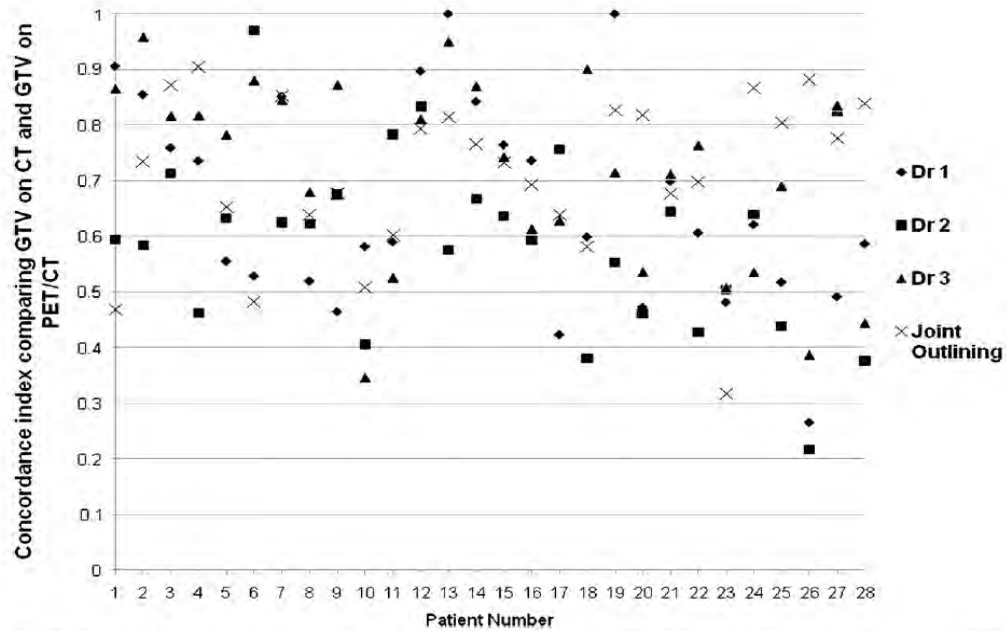
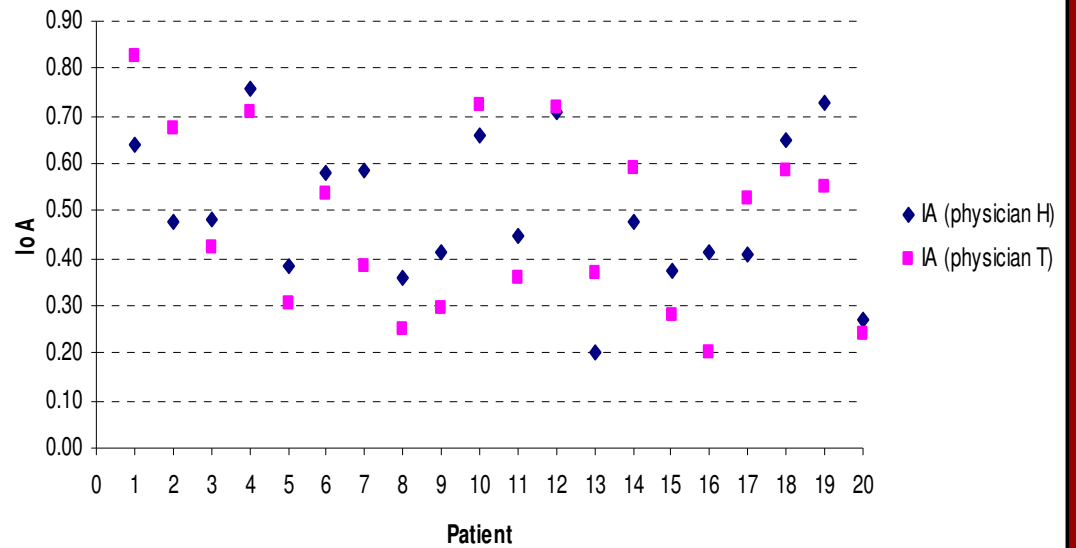


Fig. 7. Concordance index measurement comparing gross tumor volume (GTV) delineated on computed tomography (CT) alone with GTV delineated on positron emission tomography (PET)/CT. The values for the three radiation oncologists (denoted by Dr. 1, Dr. 2, and Dr. 3) are shown along with the values for the joint outlining.

Index of Agreement (IoA) for intraobserver



CONCLUSIONS



- The volumes created on PET-CT images by two experienced physicians were greatly different compared to the volumes created on CT images only, resulting in extreme differences in calculated doses
- The outlining of the tumor based on PET-CT showed a slight improvement of agreement between both physicians

CONCLUSIONS



- The incorporation of PET and CT has the potential of improving the treatment planning process, especially, if both technologies are merged and gated so uncertainties due to target volume movement and deformation are reduced
- This may show higher agreement in inter-observer variation, but ultimately it is the observer's clinical perception and experience that has the greatest impact on the target coverage, and normal tissue involvement
- To this day, there exists no conclusive data demonstrating the superiority of PET-CT over CT based planned treatments on patient outcomes of tumor control and normal tissue toxicities
- Nevertheless, radiation therapy treatment planning is recommended to be based on PET-CT as this imaging combination currently provides the best assessment for cancer patients

ON BEHALF OF...



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THANK YOU FOR YOUR ATTENTION

QUESTIONS?

