WORKSHOP

Trattamenti integrati nel NSCLC III stadio

Imaging morfo-funzionale nell'identificazione dei volumi clinici

Cinzia Iotti

Arcispedale S. Maria Nuova – IRCCS – Reggio Emilia

To have a chance for success

- Good patient selection

- The high-dose treatment volume must include all gross tumor deposits

- Elective nodal irradiation is not recommended
    - *Less toxicity*
    - *More room for dose escalation*

Recommendation for target delineation in locally advanced NSCLC

Radiation Therapy Simulation, Planning, and Delivery

- Simulation should be performed using CT scans obtained in the RT treatment position with appropriate immobilization devices. IV contrast with or without oral contrast is recommended for better target/organ delineation whenever possible in patients with central tumors or nodal disease. Because IV contrast can affect tissue heterogeneity correction calculations, density masking or use of a pre-contrast scan may be needed when intense enhancement is present.
- PET/CT significantly improves targeting accuracy,[76] especially for patients with significant atelectasis and when IV CT contrast is contraindicated. A randomized trial of PET/CT versus CT-only RT planning demonstrated improved preemption of futile radical RT, decreased recurrences, and a trend toward improved overall survival with PET/CT RT planning.[77] Given the potential for rapid progression of NSCLC,[78,79] PET/CT should be obtained preferably within 4 weeks before treatment. It is ideal is to obtain PET/CT in the treatment position.
- Tumor and organ motion, especially owing to breathing, should be assessed or accounted for at simulation. Options include fluoroscopy, inhale/exhale or slow scan CT, or, ideally, 4D-CT.

European Organisation for Research and Treatment of Cancer Recommendations for Planning and Delivery of High-Dose, High-Precision Radiotherapy for Lung Cancer

Dirk De Ruysscher, Corinne Faivre-Finn, Ursula Nestle, Coen W. Hurkmans, Cécile Le Péchoux, Allan Price, and Suresh Senan

VOLUME 28 · NUMBER 36 · DECEMBER 20 2010

JOURNAL OF CLINICAL ONCOLOGY

resolution digitally reconstructed radiographs and facilitates accurate tumor delineation

The use of intravenous contrast can improve the delineation of centrally located primary tumors and lymph nodes

The use of data from a planning 4D-CT scan is strongly preferred for treatment planning

PET scanning

FDG-PET re... lymph no... the proce...

Strictly star... cooperati... medicine... are used

FDG-PET scans for radiotherapy treatment planning should be acquired in radiotherapy position and coregistered with a planning CT using rigid methods

Contrast enhanced CT

PET-guided RT

Correction of motion artifacts

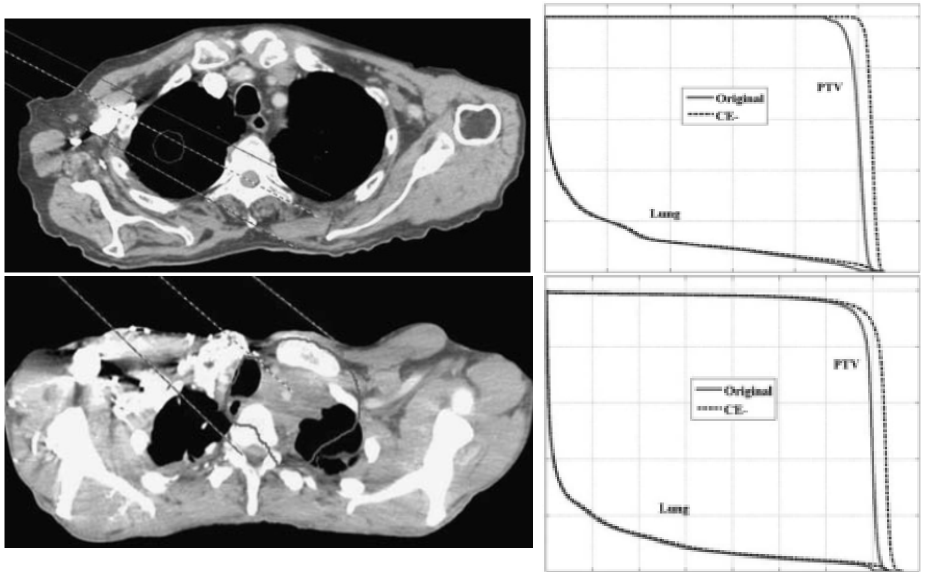
For NSCLC, selective nodal irradiation on the basis of CT and FDG-PET is the recommended standard as it results is a less than 5% of isolated failures, and this should take into consideration all data obtained using endoscopy, ultrasound-guided fine-needle aspiration, or mediastinoscopy

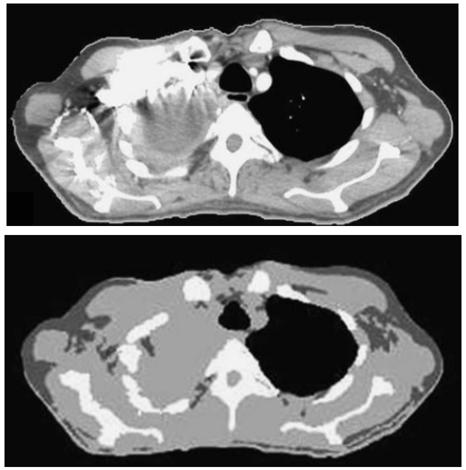
American Journal of Clinical Oncology • Volume 35, Number 2, April 2012

Intravenous Contrast Agent Influence on Thoracic Computed Tomography Simulation Investigated Through A Heterogeneous Dose Calculation Method Using 5-Bulk Densities

Anneyuko I. Saito, MD, PhD,* Jonathan G. Li, PhD,† Chihray Liu, PhD,†
Kenneth R. Olivier, MD,‡ Shinsuke Kyougoku, MD, PhD,* and James F. Dempsey, PhD§

Only 2 of 17 patients with a strong injection artifact in the PTV or beam showed >3% discrepancy in the target dose.
No significant changes were observed for critical structure doses.

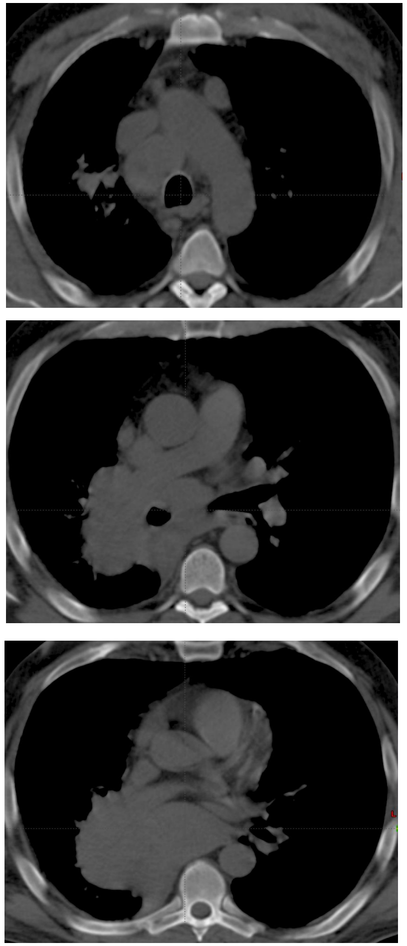


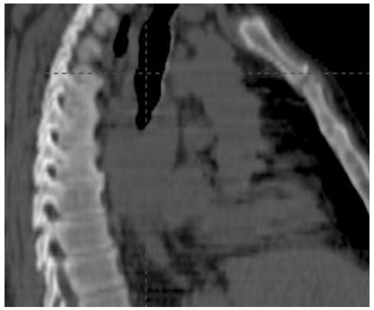


However, the injection artifact has the potential to cause large errors. Thus, a method to reduce the streak artifact must be considered.

Contrast enhancement and CT planning

W/out contrast
enhancement





With contrast
enhancement

FDG-PET/CT and RT planning for NSCLC

Several studies have proven the clinical efficacy of FDG/PET in the workup of patients with NSCLC.

Tumori, 98: 66-78, 2012

Radiotherapy in Italy for non-small cell lung cancer: patterns of care survey

Sara Ramella[1], Ernesto Maranzano[2], Paolo Frata[3], Cristina Mantovani[4], Grazia Lazzari[5], Claudia Menichelli[6], Piera Navarria[7], Stefano Pergolizzi[8], and Fabrizio Salvi[9]

65 of 143 Italian centers responded to the questionnaire

FDG-PET was routinely used by 51% of centers for diagnostic and contouring phases.

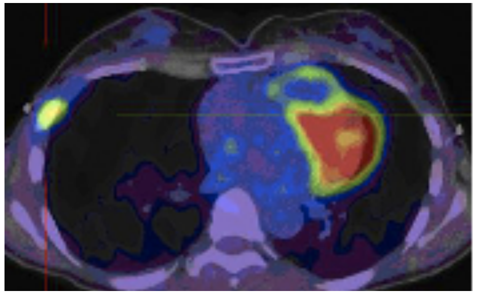
The result emphasized the emergent necessity of PET availability, in particular to help radiation oncologists to deliver modern higher doses to selected volumes, while waiting for biological target definition

Stage distribution	No. patients (%)
I	367 (8.70)
II	235 (5.50)
IIIA	862 (20.3)
IIIB	1067 (25.2)
IV	1529 (36.0)
ECOG at start of RT treatment	
0-1	56.3%
2	28.6%
3	14.4%
Application of PET in diagnostic phases	
Routinely	51%
In cN2 CT-defined patients	4%
In cN1-N2 CT-defined patients	21%
In case of atelectasia	24%
Use of PET for simulation	
Never	54%
In selected cases	37%
Always	9%

Advantages of PET for patients candidates for RT

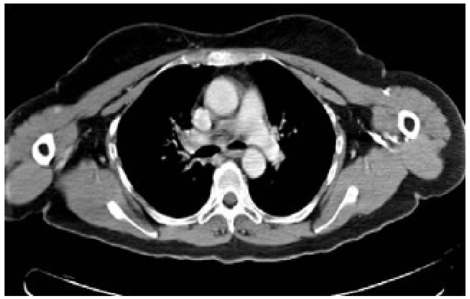
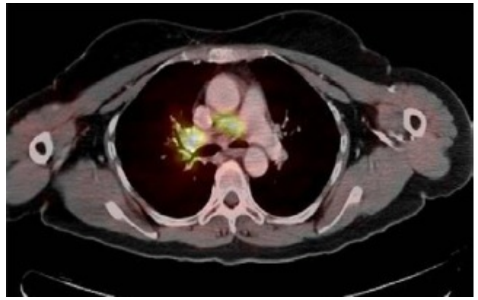
Advantages of PET for patients candidates for RT

1) Potential to detect distant metastasis (~24% in stage III)

2) Very high negative predictive value

Sensitivity and specificity in patients with non-enlarged, but positive, nodes were 82% and 93%, respectively.

However, in the presence of enlarged lymph nodes, PET-CT becomes less specific and its ability to detect truly negative nodes become reduced. Pathological confirmation of PET-positive mediastinal nodes should be obtained by mediastinoscopy or EUS-FNA

PET is better than CT but not perfect

The effects of PET in patients candidates for RT

A variety of studies using different selection criteria, end points, and methodologies.

Despite the varied study design, it is clear that in each study PET profoundly influenced the delivery of RT.

Table 1 Studies With >20 Patients That Evaluated the Impact of PET or PET/CT in RT Planning for NSCLC

Author	Patients	Parameter Studied	Change in RT*
Munley et al[31]	35	RT field	>34%
Nestle et al[32]	34	RT field	35%
Vanuytsel et al[33]	73	GTV	62%
Caldwell[34]	30	GTV	100%
Mac Manus et al[21]	102	GTV	38%
Mah et al[35]	23	PTV	100%
Bradley et al[36]	24	GTV	58%
Van Der Wel et al[37]	21	GTV	100%
De Ruysscher et al[38]	21	RT Field RT dose deliverable with equal toxicity	100% 55.2 Gy RT 68.9 Gy PET
Deniaud-Alexandre et al[25]	92	GTV	48%
Faria et al[39]	32	GTV	56%
Pommier et al[40]	119	Change in RT plan	31%
Kolodziejczyk et al[24]	75	Geographic miss	27% if PET not used
Bradley et al[41]	47	GTV	51%

The effects of PET in patients candidates for RT

The predominant effect is to upstage patients.

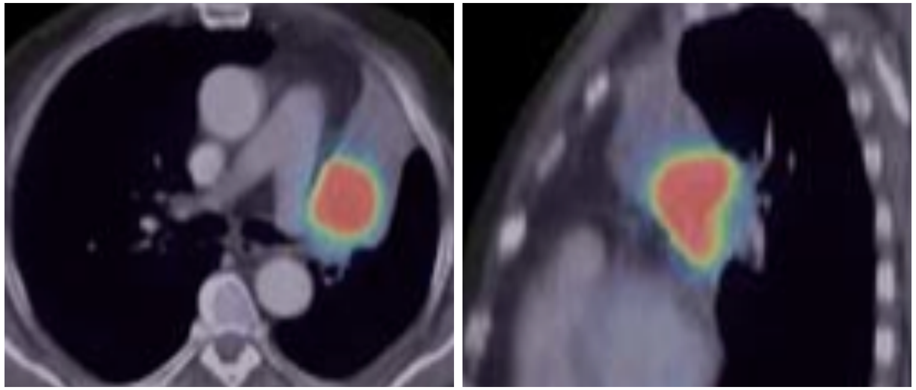
Approximately 1/3 of patients were found to be unsuitable for definitive RT, either because of distant metastasis or mediastinal disease being too extensive to be encompassed in a tolerable RT target volume.

↓

Impact on treatment intent/ patient selection

The effects of PET in patients candidates for RT

1) When the **primary tumor** was considered, the greatest effect was seen in patients with atelectasis



2) Otherwise, the most common reason for changes in RT delivery was an alteration in the perceived **nodal status**

3) In those studies where treatment volumes were considered, there has been a trend toward smaller target volumes but when small lymph nodes were found to be FDG positive, an overall increase in treatment volume could occur.

The effects of PET in patients candidates for RT

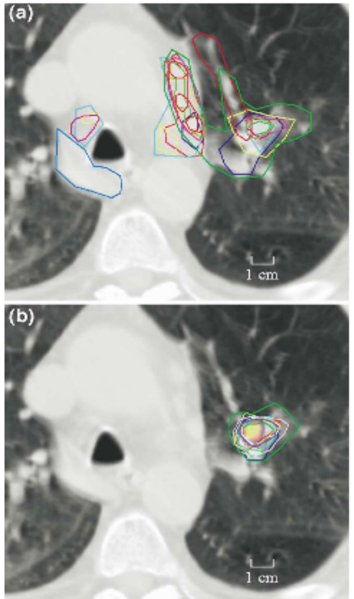
The effect of PET/CT on RT planning is likely to be greatest at centers where RT target volumes are tightly shaped around tumor deposits (in other words, highly conformal) and lowest at centers where large target volumes with wide margins around tumors and/or ENI are used

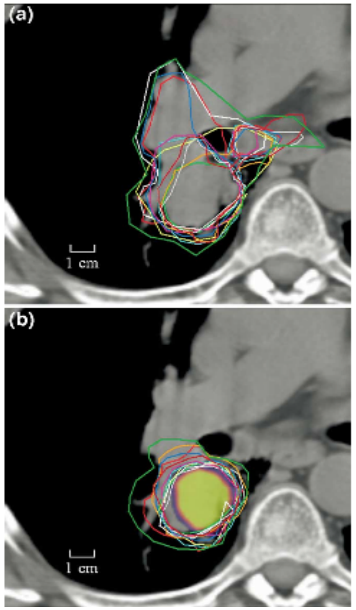
The effects of PET in patients candidates for RT

Int. J. Radiation Oncology Biol. Phys., Vol. 64, No. 2, pp. 435–448, 2006

REDUCTION OF OBSERVER VARIATION USING MATCHED CT-PET FOR LUNG CANCER DELINEATION: A THREE-DIMENSIONAL ANALYSIS

Roel J. H. M. Steenbakkers, M.D.,* Joop C. Duppen,* Isabelle Fitton, Ph.D.,*
Kirsten E. I. Deurloo, Ph.D.,* Lambert J. Zijp,* Emile F. I. Comans, M.D., Ph.D.,[†]
Apollonia L. J. Uitterhoeve, M.D.,[‡] Patrick T. R. Rodrigus, M.D.,[§]
Gijsbert W. P. Kramer, M.D.,[‖] Johan Bussink, M.D., Ph.D.,[¶] Katrien De Jaeger, M.D., M.Sc.,*
José S. A. Belderbos, M.D.,* Peter J. C. M. Nowak, M.D., Ph.D.,[#]
Marcel van Herk, Ph.D.,* and Coen R. N. Rasch, M.D., Ph.D.*





The overall 3D IOV was reduced from 1.0 cm (SD) for the first phase (CT only) to 0.4 cm (SD) for the second phase (matched CT-PET). **The largest reduction in the observer variation was seen in the atelectasis region.**

However, IOV in delineation was still a major source of geometric error.

It seems obvious that improving patient selection and reliably hitting the target must inevitably improve the results of RT in NSCLC, however there is little information on long-term patient outcomes

Int. J. Radiation Oncology Biol. Phys., Vol. 82, No. 1, pp. 435–441, 2012

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

JEFFREY BRADLEY, M.D.,* KYOUNGHWA BAE, PH.D.,† NOAH CHOI, M.D.,‡ KEN FORSTER, PH.D.,§ BARRY A. SIEGEL, M.D.,* JACQUELINE BRUNETTI, M.D.,|| JAMES PURDY, PH.D.,¶ SERGIO FARIA, M.D.,** TONI VU, M.D.,†† WADE THORSTAD, M.D.,* AND HAK CHOY, M.D.‡‡

Phase II prospective trial designed to quantify the impact of PET/CT on RTPs and to determine the rate of EN failure for PET/CT-derived volumes.

52 patients accrued, 47 evaluable. Tumor staging: II=6%, IIIA=40%, IIIB=54% . Each patient had 2 RT plans, one with (delivered) and one w/out PET information

Results: The $GTV_{PET/CT}$ was statistically significantly smaller and median lung doses slightly lower. Nodal contours were altered by PET/CT for 51% of patients.

Only a patient (2%) developed an elective nodal failure

Conclusions: … The elective nodal failure rate for GTVs derived by PET/CT is quite low, suggesting that **PET-assisted RT planning rendered ENI unnecessary**

About the selective nodal irradiation

More studies, with long term follow-up, are needed to demonstrate the appropriateness (or otherwise) of this policy, especially in patients treated with IMRT, where the dose to neighboring macroscopically unaffected lymph node regions may be reduced compared to standard 3D conformal techniques.

Radiotherapy and Oncology 106 (2013) 292–298

The use of fused PET/CT images for patient selection and radical radiotherapy target volume definition in patients with non-small cell lung cancer: Results of a prospective study with mature survival data

Michael P. Mac Manus [a,b,*], Sarah Everitt [c], Mike Bayne [d], David Ball [a,b], Nikki Plumridge [a,b], David Binns [e], Alan Herschtal [f], Deborah Cruickshank [a], Mathias Bressel [f], Rodney J. Hicks [b,e]

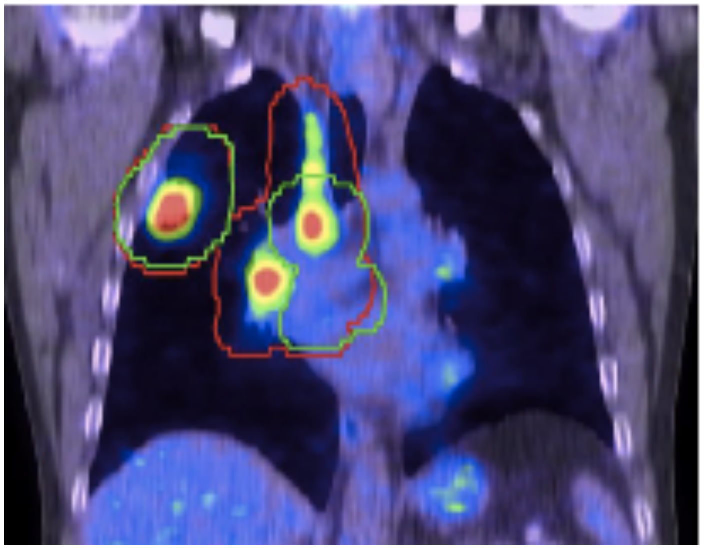
The study investigated the impact of PET/CT on management of NSCLC

76 eligible patients (March 2004 and February 2007)

after PET/CT:

50 (66%) received radical chemoRT

26 (34%) received palliative therapies because advanced disease detected



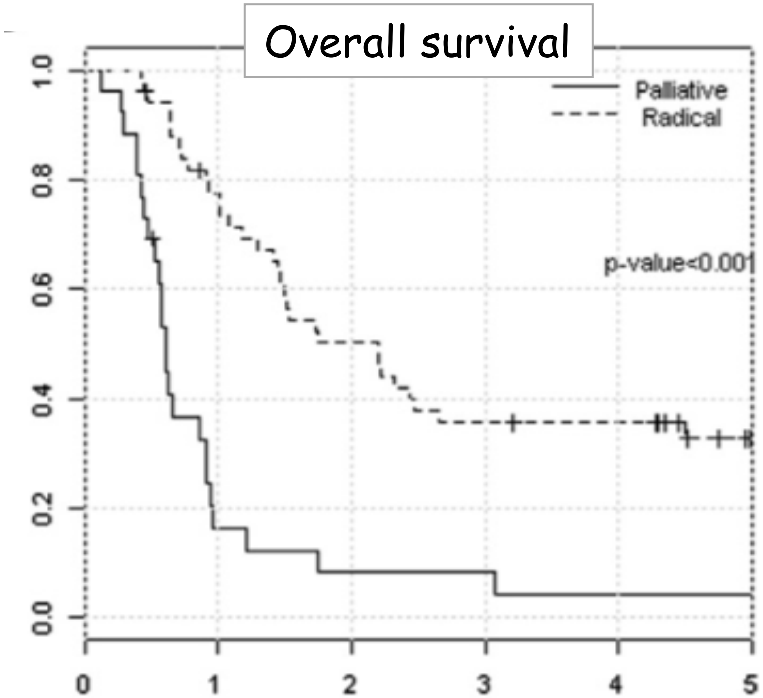
Significant variation between the two modalities

Green: CT-defined PTV
Red: PET/CT-defined PTV

Overall Survival

pts given chemoRT: 77.5% and 35.6% at 1 and 4 years, respectively
(for stage IIIA at 4 years 32%)

pts treated palliatively: 16.3% and 4.1% at 1 and 4 years, respectively ($P < 0.001$)



These results suggest that PET/CT was used appropriately to select patients for chemoRT.

Mac Manus 2013

To separate the effects of superior patient selection and RT-planning with PET/CT a randomized trial would be necessary, in which PET/CT information was used for staging but was only randomly made available for RT planning.
But such a trial would now be unethical based on existing knowledge, because of the proven superior accuracy of PET

Mac Manus 2013

How integrate PET/CT imaging in the treatment planning

Indirect Planning

It combines the PET/CT data with a planning CT acquired on a separate occasion
There are logistical and financial reasons why indirect planning may be the preferred option.

Anyway, it is recommended that a dedicated planning PET/CT scan is acquired for fusion with a planning CT once custom-made immobilization devices have been prepared

Pay attention: the registration of PET or CT component of PET/CT with the planning CT can cause alignment errors.
Non-rigid algorithms may be able to account for a degree of interscan motion, but these techniques have not been widely validated, particularly for PET data, and should be used with caution.

These errors may make the "indirect planning" unsuitable for advanced IMRT applications such as dose-painting

Somer 2012

All too often, the process of diagnosis and pretreatment evaluation is prolonged in NSLC, and the initial staging PET/CT scan can be many weeks old when treatment commences.

In a study of 21 patients with NSCLC who had separate staging and RT planning PET/CT scans, a median of 24 days apart, the probability of upstaging within 24 days was calculated to be 32%. Treatment intent changed from curative to palliative in 6 (29%) cases *(Everitt 2010)*

Consider the opportunity to repeat the PET/CT scan for radiation treatment purpose when the interval time is long (> 4 weeks)

How integrate PET/CT imaging in the treatment planning

Direct Planning

The CT component of the PET-CT scan can replace the CT planning scan

The PET-CT scanner has to be passed the QC requirements for radiotherapy planning

Despite the increased logistical challenges, direct planning remains the preferred option.

QC requirements:

- *provision of external lasers*
- *careful assessment of scanner couch motion*
- *PET-CT gantry alignment confirmed*
- *data transfer and display, including any DICOM radiotherapy objects, within the TPS validated*

Somer 2012

Radiotherapy and Oncology 108 (2013) 86–90

Does enhanced CT influence the biological GTV measurement on FDG-PET images?

CrossMark

Pierre Vera [a,*], Romain Modzelewski [a], Sebastien Hapdey [a], Pierrick Gouel [a], Hervé Tilly [b], Fabrice Jardin [b], Su Ruan [a], Isabelle Gardin [a]

Objectives: To test the influence of media injection in PET/CT on the functional or gross tumor volume measurement.

Conclusion: The functional volume could be measured in PET/CT when CT was performed with enhanced media.

Caution should be taken when using the volume delineation method.
The delineation volume using the relative or adaptative method should be preferred when contrast media are used for PET/CT.

PET/CT – practical issues

The methodology for contouring tumor margins remains controversial.

Two main approaches

1. Visual methods that require human judgment (widely used)

2. Automated/semiautomated methods
   - Thresholding methods (various levels of SUV, SUV thresholds, lesion-to-background ratio)
   - Other more complex methods (Variational approaches, Learning methods, Stochastic models)

CATEGORY	Pro	Cons
Manual techniques	Based on the experience Very simple to use	Time consuming. High IOV and poor reproducibility. Close cooperation between disciplines is essential

CATEGORY	Pro	Cons
Automated techniques	High efficiency. Low IOV	Different methods can give different contours in the same patient; no consensus as to which performs best Hard decision making. Too sensitive to PVE, tumor heterogeneity and motion artifacts.

Fully automated contouring can sometimes be 100% reproducible but 100% wrong

Such methods should prove a useful starting point for the human observer to work on

In any case

- **Lymph nodes identification: by detectability rather than by SUV.**

- Omit RT planning after induction chemotherapy due to the risk of false-negative FDG uptake

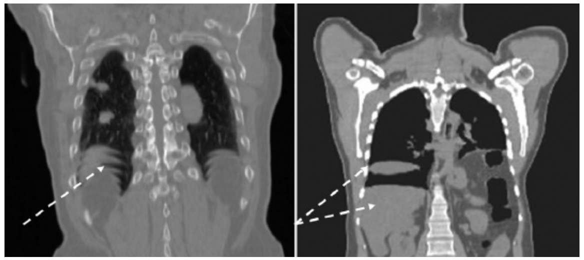
- A consistent set of rules or guidelines should be used to ensure both reproducibility and accuracy

The FDG uptake map does not contain all of the information needed to define the tumor volume and target volume in every case of lung cancer

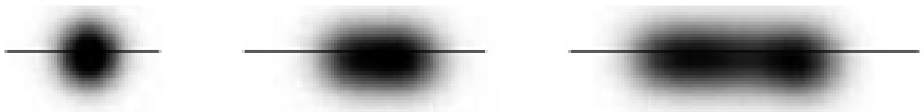
CT and PET/CT - site specific and practical issues

Imaging artifacts due to Respiratory Motion

Tumor movement in lung cancer is a particular problem, both for CT and PET delineation potentially leading to incorrect estimation and mislocalization of target volumes,

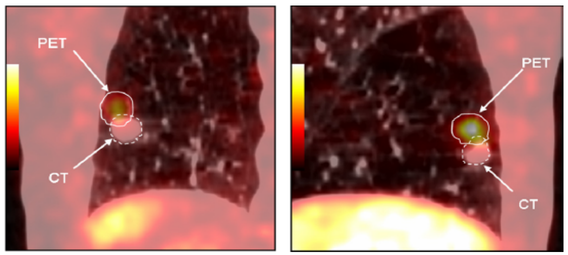


CT artifacts



static **1cm displacement** **2cm displacement**

PET artifacts



PET/CT artifacts

from Bettinardi 2012

CT and PET/CT – site specific and practical issues

Imaging artifacts due to Respiratory Motion

Motion management for radiation treatment planning can be achieved by 2 approaches:

1. Respiratory gating 4D-(PET)/CT acquisition techniques **(motion compensation)**

2. Breath-hold (BH) techniques, in which the patient is asked to hold his/her breath **(motion suppression)**

The correction for the respiratory motion effects has to be made all imaging modalities

from Bettinardi 2012


Insidious imaging…
CECI
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UN
LAPIN

Imaging to characterize the lung function

SPECT-guided RT plans

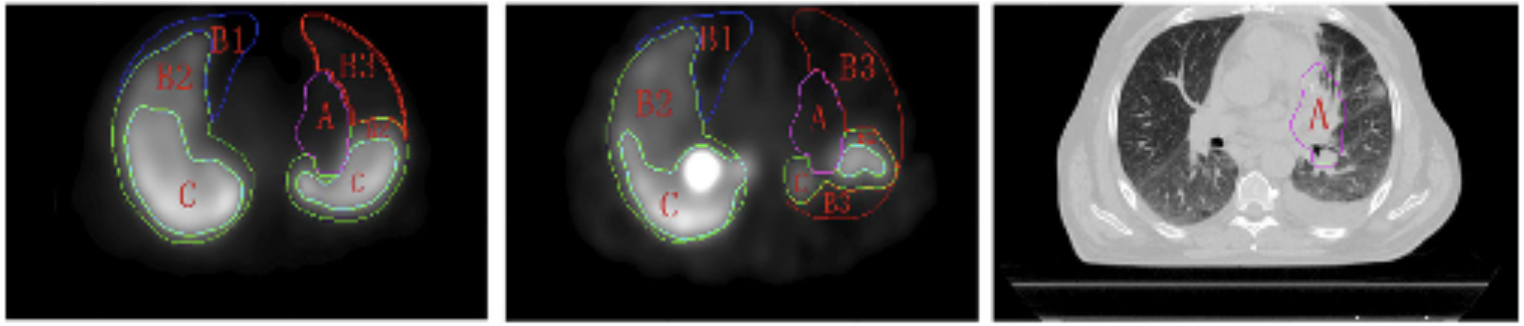
Lung V/Q SPECT scans obtained at baseline can be used to guide radiation planning for functional region avoidance

However, it is unknown whether local lung function actually changes during RT; on pre-RT SPECT may target functional regions as conditions change during the course of treatment

Changes in Global Function and Regional Ventilation and Perfusion on SPECT During the Course of Radiotherapy in Patients With Non-Small-Cell Lung Cancer

Shuanghu (Tiger) Yuan, M.D., Ph.D.[*,¶], Kirk A. Frey, M.D., Ph.D.[†], Milton D. Gross, M.D.[†], James A. Hayman, M.D.[*], Doug Arenberg, M.D.[‡], Xu-Wei Cai, M.D.[*], Nithya Ramnath, M.D.[‡], Khaled Hassan, M.D.[‡], Jean Moran, Ph.D.[*], Avraham Eisbruch, M.D.[*], Randall K. Ten Haken, Ph.D.[*], and Feng-Ming (Spring) Kong, M.D., Ph.D.[*,§]

Int J Radiat Oncol Biol Phys. 2012 March 15; 82(4): e631–e638.



Q SPECT pre-RT | V SPECT pre-RT | CT pre-RT

SPECT may provide an opportunity for RT plan optimization

- **type A**: occupied by tumor, must receive highest RT dose;
- **type B1**: unrecoverable nonfunctioning “bad” lung, can receive high-dose RT;
- **type B2**: unrecoverable low-functioning lung, may be given high doses (if no worse lung is available);
- **type B3**: temporarily dysfunctional lung caused by tumor-induced constriction and other potentially recoverable diseases, should be spared whenever possible; during RT the most remarkable changes were seen in this regions
- **type C**: normally functioning lung, the RT dose regions should be minimized

Conclusion

The collaboration with a radiologist and a nuclear medicine physician is recommended.

However, the potential of imaging to directly impact our practical decision requires enhanced training for the radiation oncologist

All the available information together with the **best clinical judgment** should be used to guide the delineation of the GTV

Review articles

- **Aristei C** et al. *PET and PET-CT in radiation treatment planning for lung cancer.* Expert Rev. Anticancer Ther. 10 (2010), 571-584

- **De Ruysscher D** et al. *PET scans in radiotherapy planning of lung cancer.* Radiother Oncol 96 (2010) 335-338

- **Greco C** et al. *Current status of PET/CT for tumour volume definition in radiotherapy treatment planning for non-small cell lung cancer (NSCLC).* Lung Cancer 57 (2007), 125-134

- **Lee P** et al. *Current concepts in F18 FDGPET/CT-based radiation therapy planning for lung cancer.* Frontiers in Oncology, july 2012

- **Nestle U** et al. *Practical integration of [18F]-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.* Radiother Oncol 81 (2006), 209-225

- **Mac Manus MP** et al. *The Role of Positron Emission Tomography/Computed Tomography in Radiation Therapy Planning for Patients with Lung Cancer.* Semin Nucl Med 42 (2012), 308-319

GRAZIE