29 novembre 2014

Congresso Inter-regionale

AIRO Lombardia e AIRO Piemonte-Liguria-Valle d'Aosta

L'INNOVAZIONE TECNOLOGICA IN RADIOTERAPIA: NUOVI STANDARD CLINICI E PROBLEMATICHE GESTIONALI

Imaging metabolico PET nella definizione dei volumi clinici: a che punto siamo?

Nadia Di Muzio

IRCCS Ospedale S. Raffaele - Milano

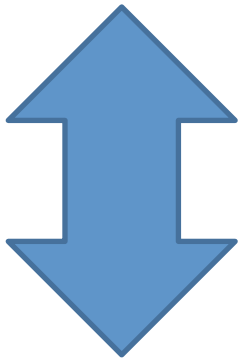
RADIOTHERAPY TODAY

Accurate target definition

Accurate target motion definition

Set-up verification

Imaging : IGRT



Highly conformal dose distribution

Planning and delivery : IMRT

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PET/CT IN ONCOLOGY

- **Established:** Diagnosis (SPN)
  Staging and Re-staging
- **Current:** Radiation Oncology
  - Staging
  - Target definition
  - Follow-up
  Treatment monitoring
- **Future:** Molecular diagnosis
  Custom treatments
  - Pharmacological
  - Radiation

PET → **Up to 20% of patients are excluded from radical RT treatment because of previously unsuspected metastases**

Lardinois et al. 2003

Schrevens et al 2004

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Target Definition

GTV → BTV

4D PET/CT

Adaptive Radiotherapy

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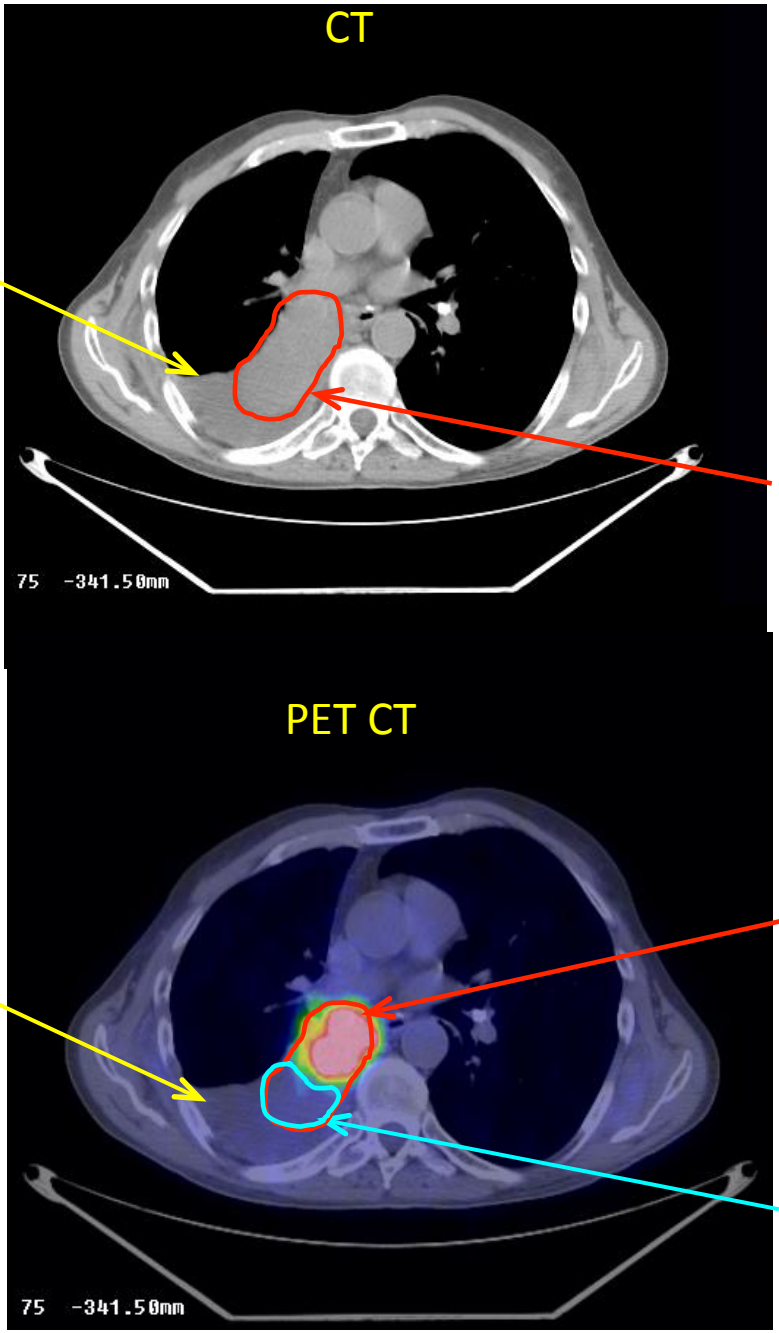
PET/CT: Primary tumor definition (GTV)



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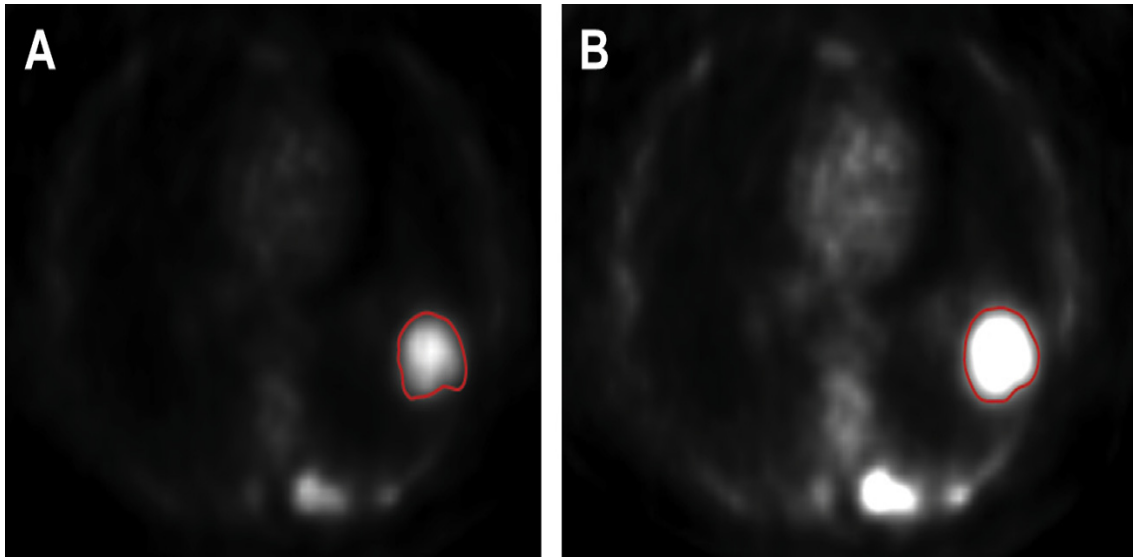
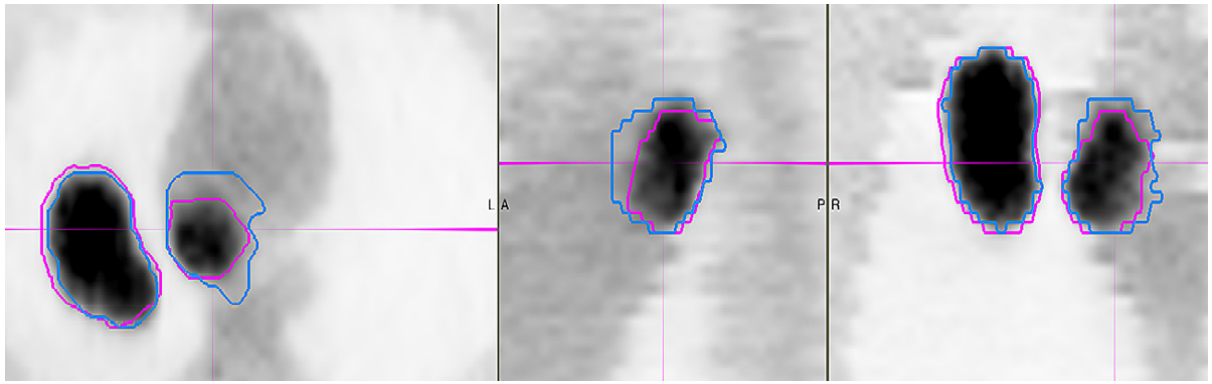


Manual segmentation
Automatic segmentation

Detectors inherent resolution
Blurring effect
"Bladder effect"
Time point image acquisition

The effect of windowing on PET-generated contours



comparisons for 45% THRESHOLD and GRADIENT methods

	Mean % error		Mean absolute % error	
	Diameter >20 mm	Diameter <20 mm	Diameter >20 mm	Diameter <20 mm
45% THRESHOLD (multiple cameras)	−1.64%	39.45%	3.94%	49.20%
GRADIENT (multiple cameras)	−0.69%	4.41%	4.19%	8.15%
p value	0.660	0.004	0.846	0.005
45% THRESHOLD (varied S/B* ratios)	16.7%	42.6%	18.2%	44.7%
GRADIENT (varied SBR)	0.09%	7.9%	3.49%	13.4
p value	.063	0.02	0.065	0.015

Abbreviation: SBR = source to background ratio.
Mean % error demonstrates bias and mean absolute % error demonstrates accuracy.

M. WERNER-WASIK *et al.*

I. J. Radiation Oncology ● Biology ● Physics Volume 82, Number 3, 2012

- Threshold %
- SUV
- Gradient of intensity fall off at the edge of the tumor

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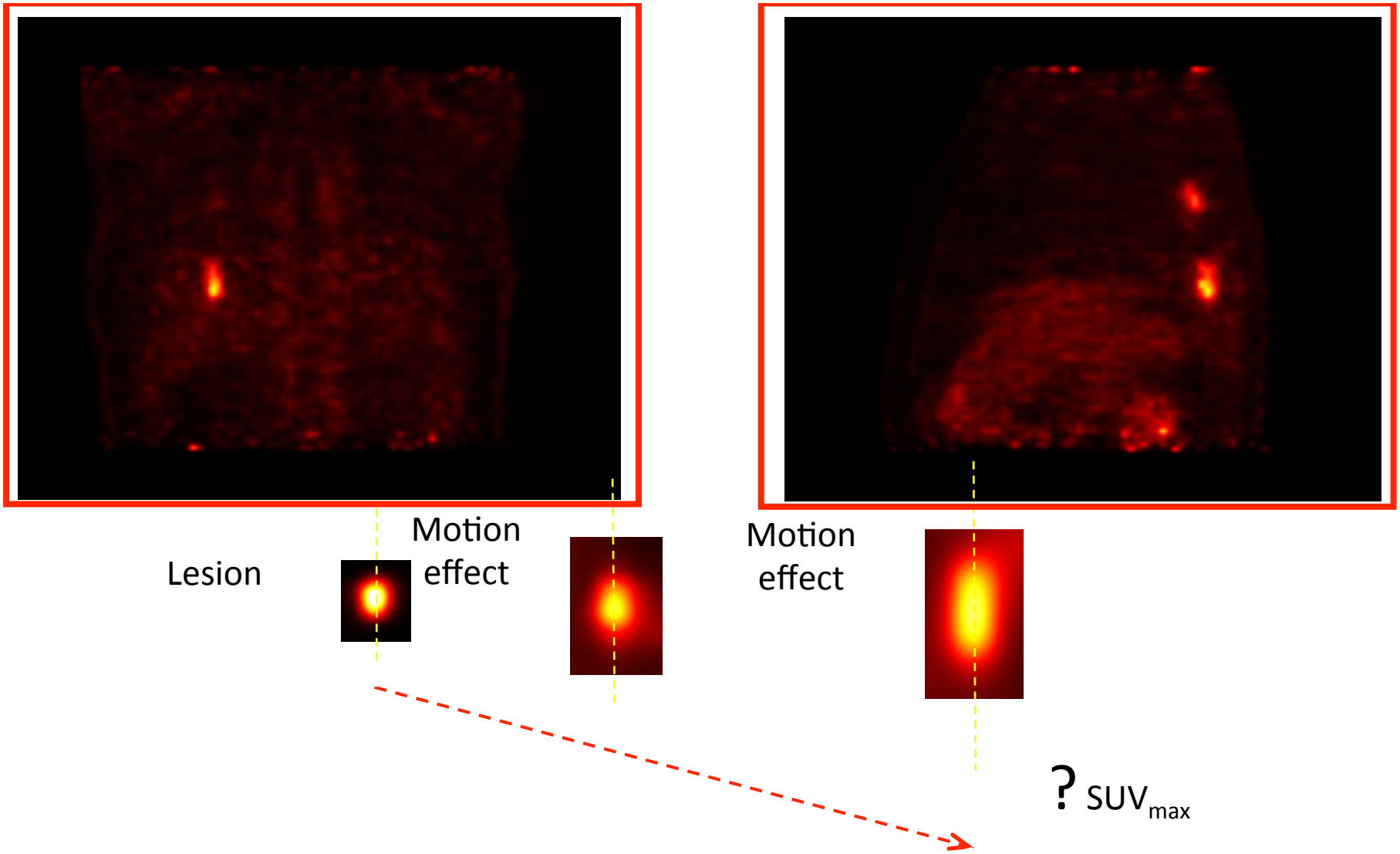

Organ and lesion motion cause:

- degradation of image quality
- reduction of the quantitative accuracy

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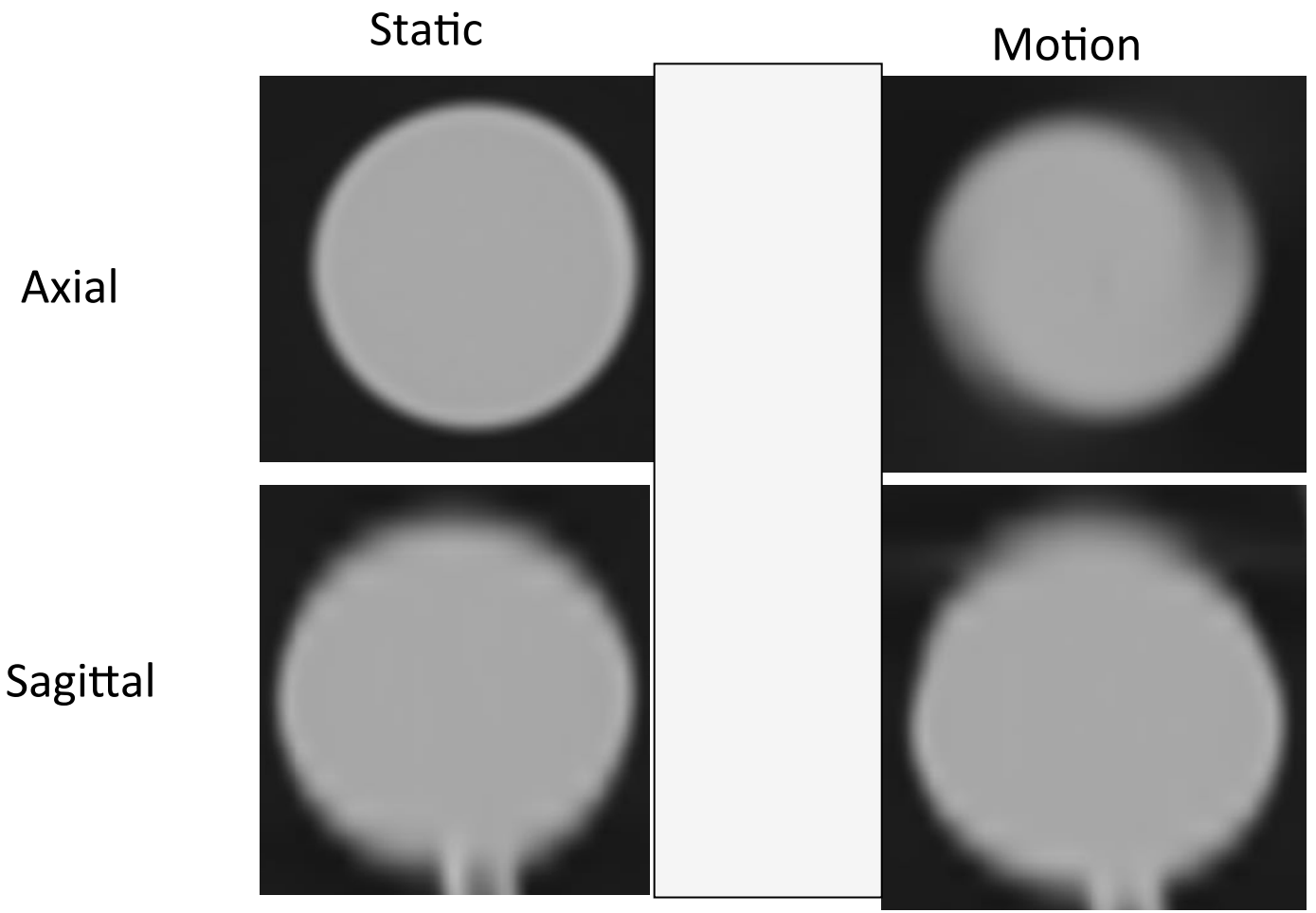
CT motion Issues



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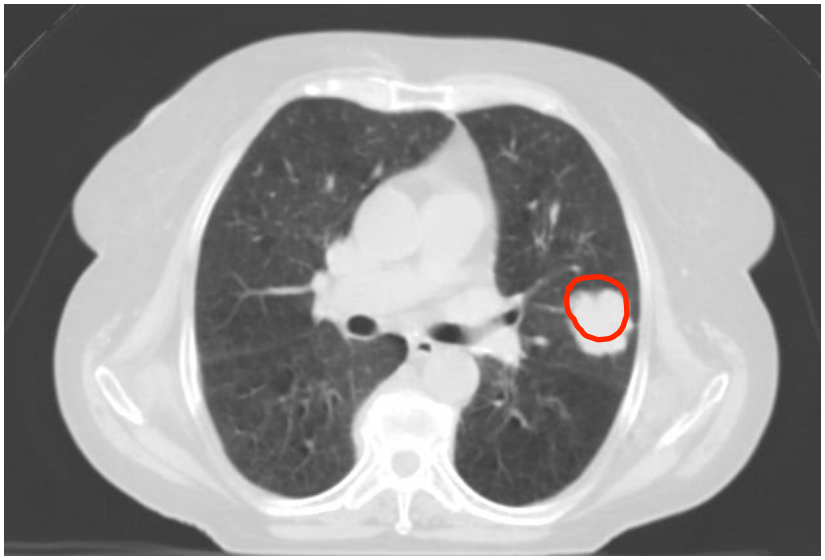
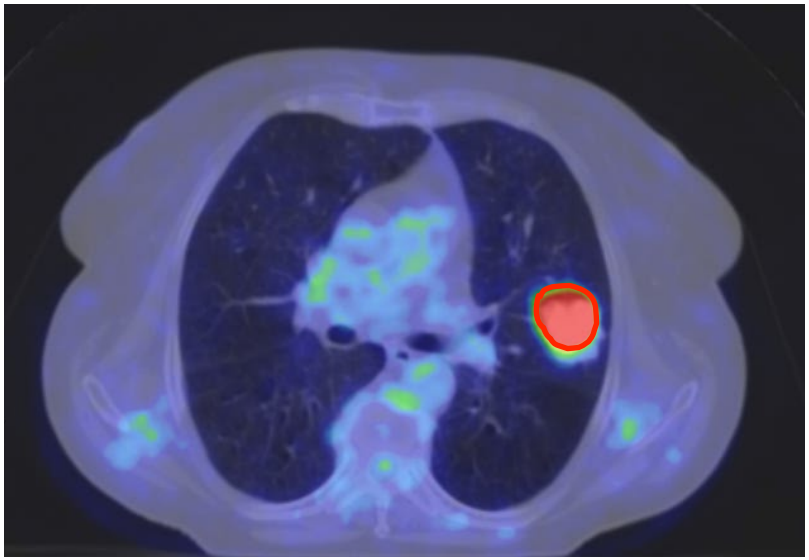
PET/CT CONTOURING AT HSR :

QUALITATIVE





PET ≠ TC : ?

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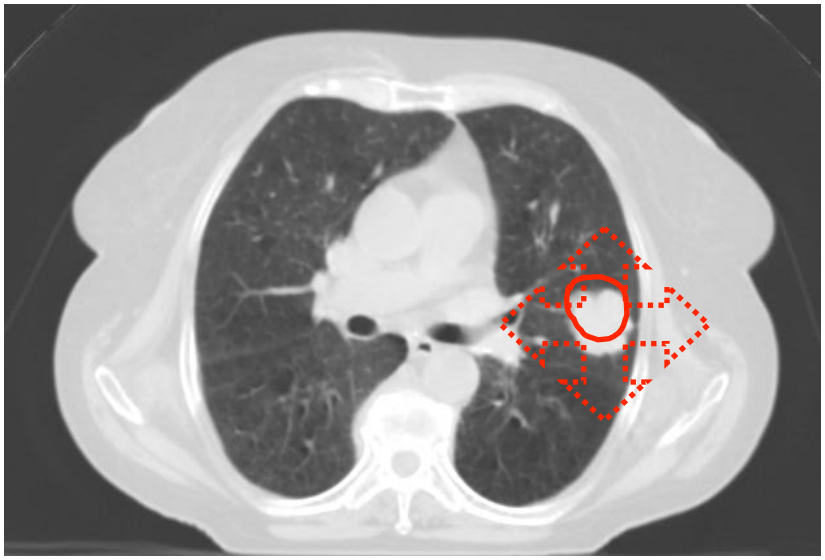
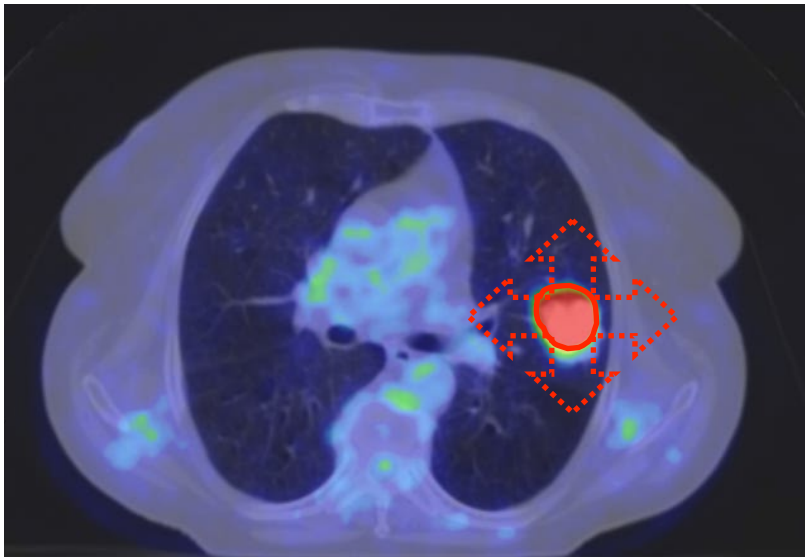
PET/CT CONTOURING AT HSR :

QUALITATIVE



PET ≠ TC : ?



ORGAN MOTION

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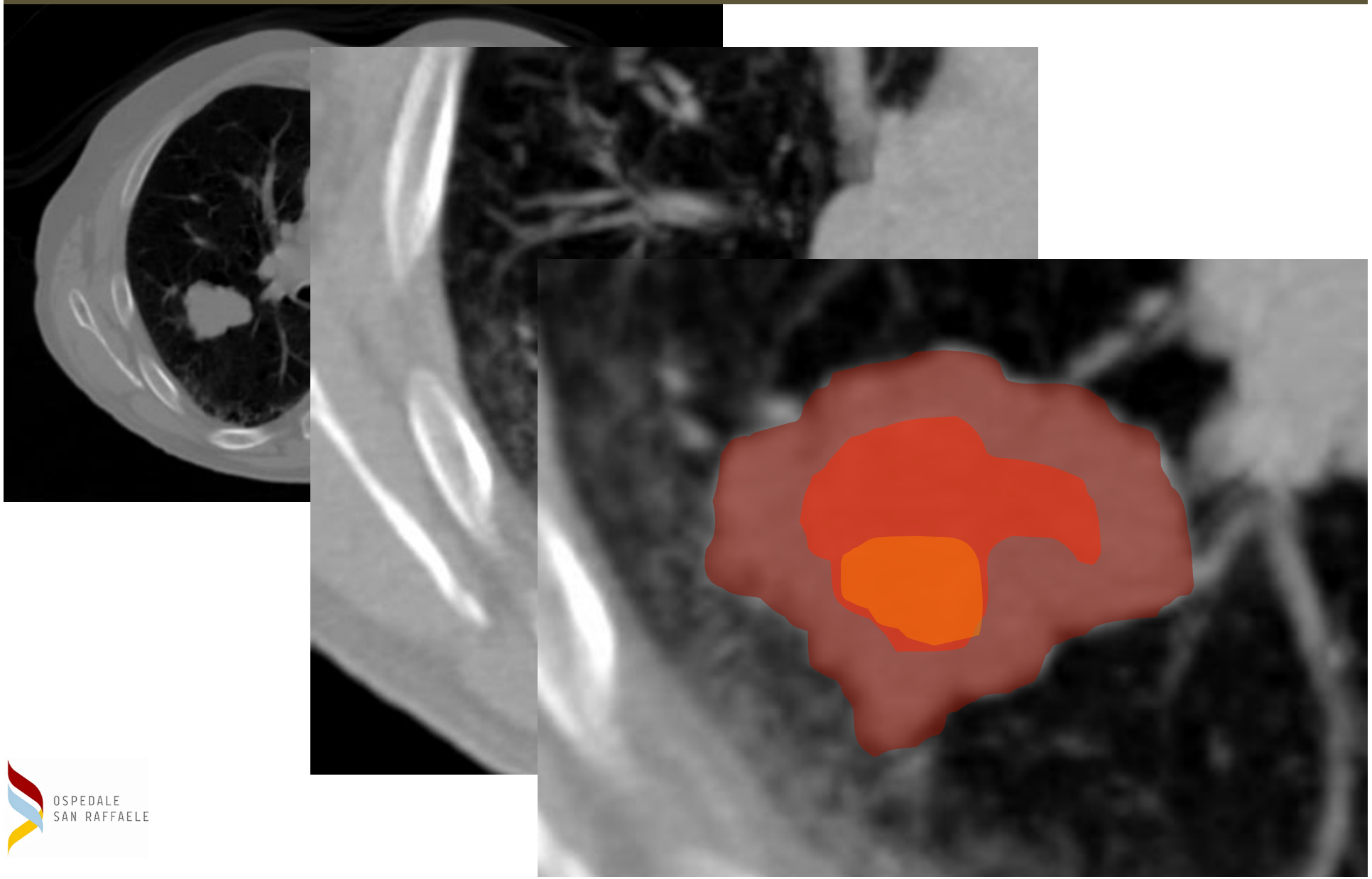
The notion of a tumour as a homogeneous volume of identical cells is replaced by that of a complex pattern with small regions (sub-volumes) needing a boost dose because of resistance or aggressive growth.



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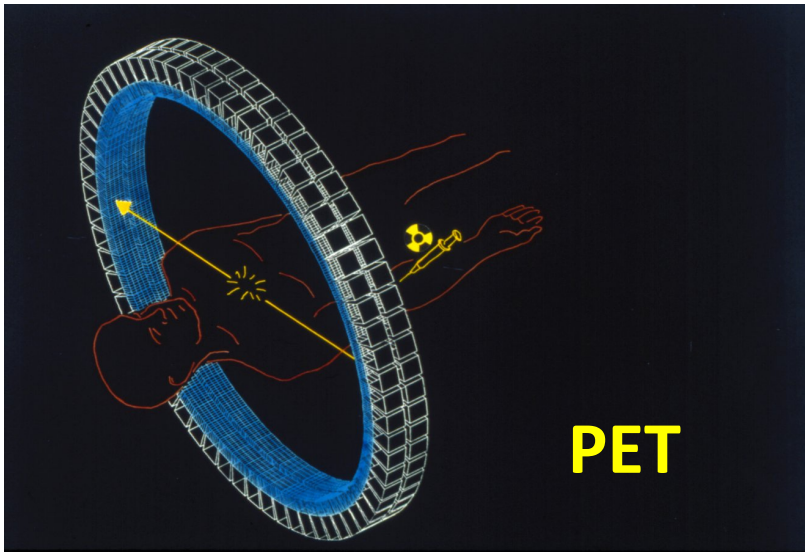
Molecular Imaging

The use of imaging techniques to identify regions in a tumour that might need a higher dose represents a step forward in biology



PET/CT: Oncological tracers

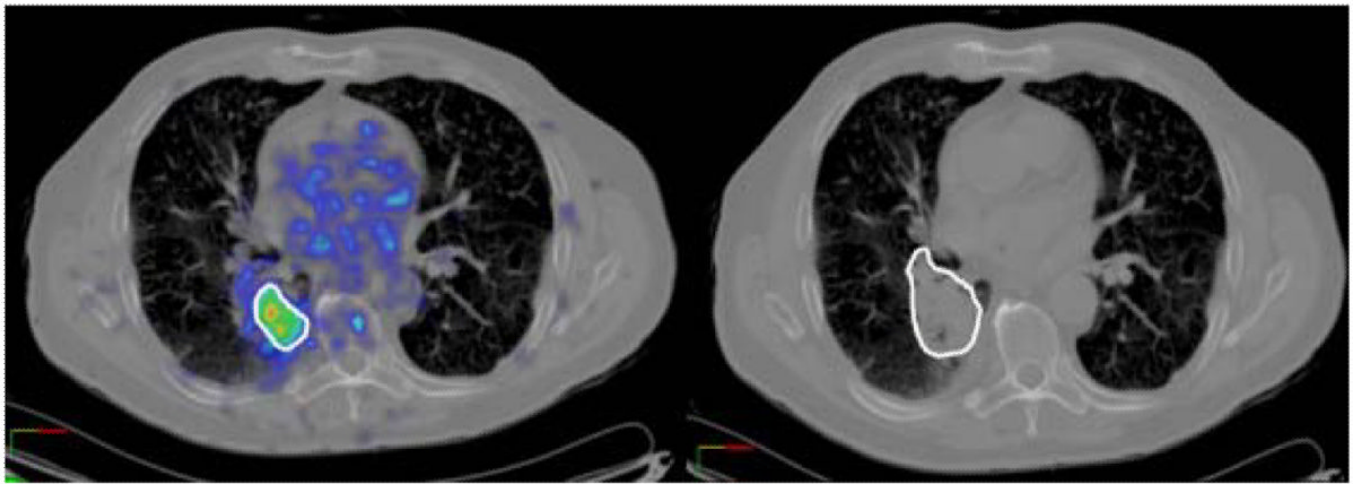
• Glucose metabolism	[^{18}F]FDG
• Membrane function	[^{11}C]Choline
• Amino acids metabolism	[^{18}F]FET / [^{11}C]MET
• Proliferation	[^{18}F]FLT
• Hypoxia	[^{18}F]FMISO [^{18}F]FAZA [^{64}Cu]ATSM
• Apoptosis	[^{18}F]Annexin V
• Angiogenesis	[^{18}F]RGD peptide

Such regions include: hypoxic regions, and those in which cells are refractive to being killed by x-rays, are dividing rapidly, are more malignant and aggressive, and express known characteristics of malignant disease.

Haubner R. et al Radiother Oncol. 2010

Lung cancers

Overall sensitivity, specificity and accuracy of FDG-PET for detection of lung cancers are very high for primary, residual and recurrent disease.
(Oyen WJ et al. Expert Rev Anticancer Ther. 2004)



•Reduction of interobserver variability
•safe decrease of radiotherapy volumes by better delineation of tumor

•enables radiation dose escalation
•allows definition of regions of tumor at greatest risk for recurrence(experimentally)
• permits redistribution of radiation doses within the tumor to focus on these regions
• useful tool for monitoring treatment response
•metabolic response correlated well with radiotherapy outcome.

PET/TC in Lung cancers

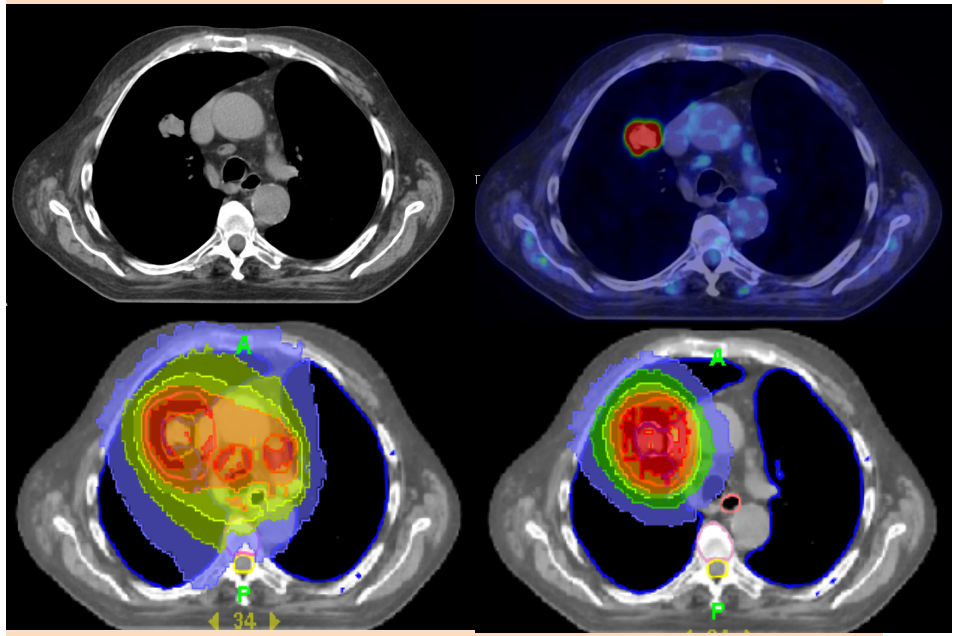
- Stage alteration of 20–50%
- Changes in the target volumes >20%

-atelectasis

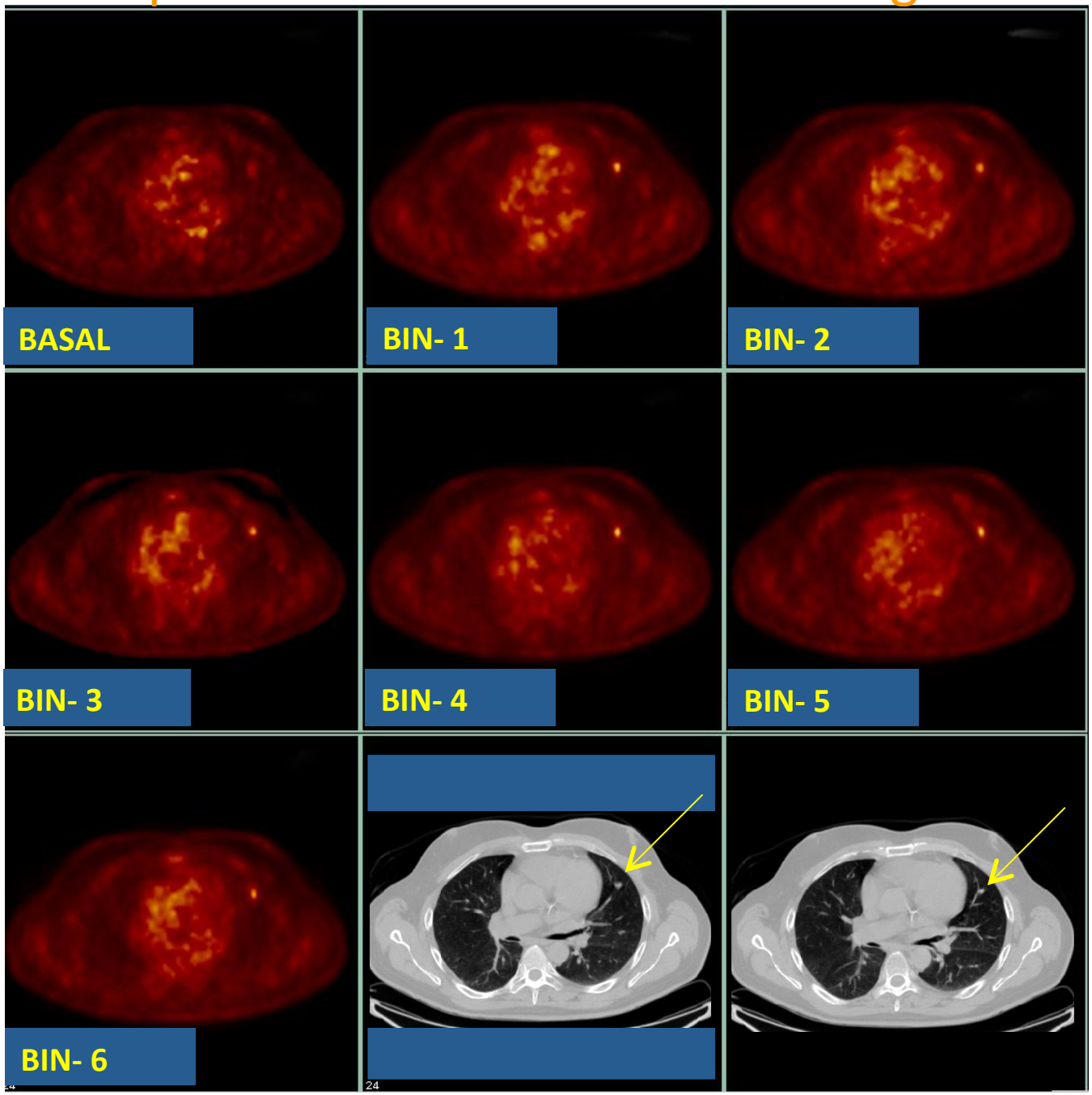
-additional nodal disease (Bradley J,et al; *IntJRadiatOncolBiolPhys 2004)*

- Pathological findings correlate better with FDG-PET than with CT alone in the delineation of nodal disease for NSCLC, (Faria et al; *IntJRadiatOncol BiolPhys 2008)*
- No consensus on how to best delineate gross tumor [Nestle U et al; *J NuclMed 2005)*
- An algorithm accounting for the source-to-background FDG- uptake ratio was found to be superior in the delineation of regional nodal disease (Nestle U,et al *EurJNuclMedMolImaging 2007)*
- Tumor volumes delineated on 4D-PET not only correlate better with that delineated on 4D CT, but also enhance the estimation of the true extent of tumor in the vicinity of similar density soft tissues, such as the diaphragm, chest wall and the heart (Lamb JM. Et al; *MedPhys 2011)*
- 4D-PET-based ITV shown to spare additional normal tissue
- Hypoxia imaging with PET has been explored in recent years (F-MISO, 18F-FAZA, or 18F-HX4) [Tachibana I et al; *J RadiatRes 2013)*

- PET-based planning may lead to at least equivalent clinical outcomes when compared with CT- based planning . (additional normal tissue sparing may aid dose escalation to the primary tumor, improving local control and potentially, patient survival (Aupérin A, et al; *J ClinOncol 2010)* .



Impact of the motion on PET images : Lung Study



PET SUV	
BASAL:	2.0
BIN1:	2.6
BIN2:	2.3
BIN3:	2.5
BIN4:	3.2
BIN5:	2.9
BIN6:	2.5

$SUV =: SUV_{bw}(g/ml)$

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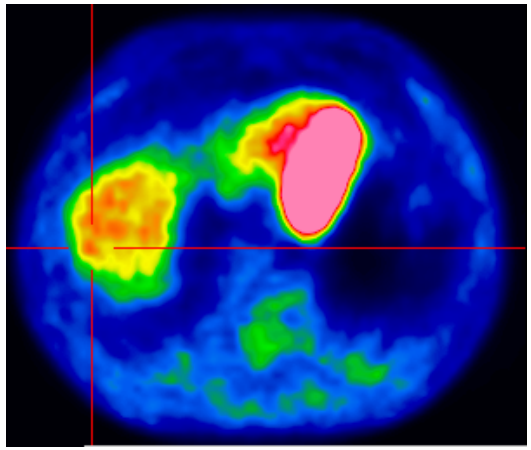
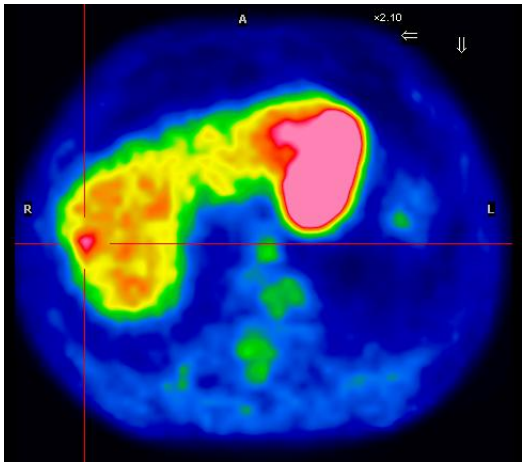
Impact of the motion on PET images: Liver Study

"Static" PET

SUV=1.8



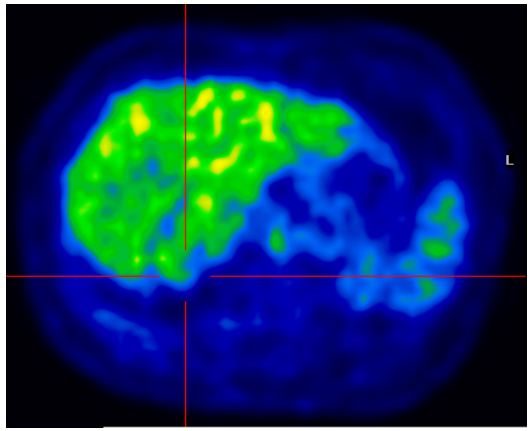


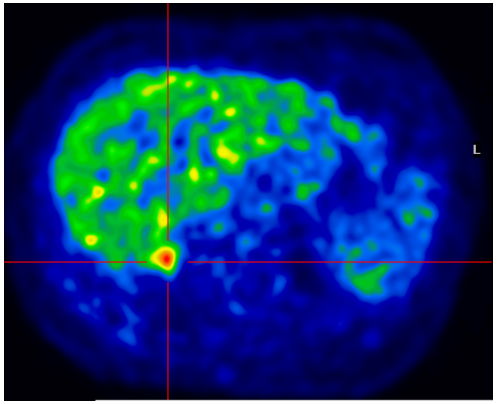
4D-PET

$SUV_{Phase\ 6}$=3.1

"Static" PET

SUV=1.6





4D-PET

$SUV_{Phase\ 1}$=2.9

SUV =: SUV_{bw}(g/ml)

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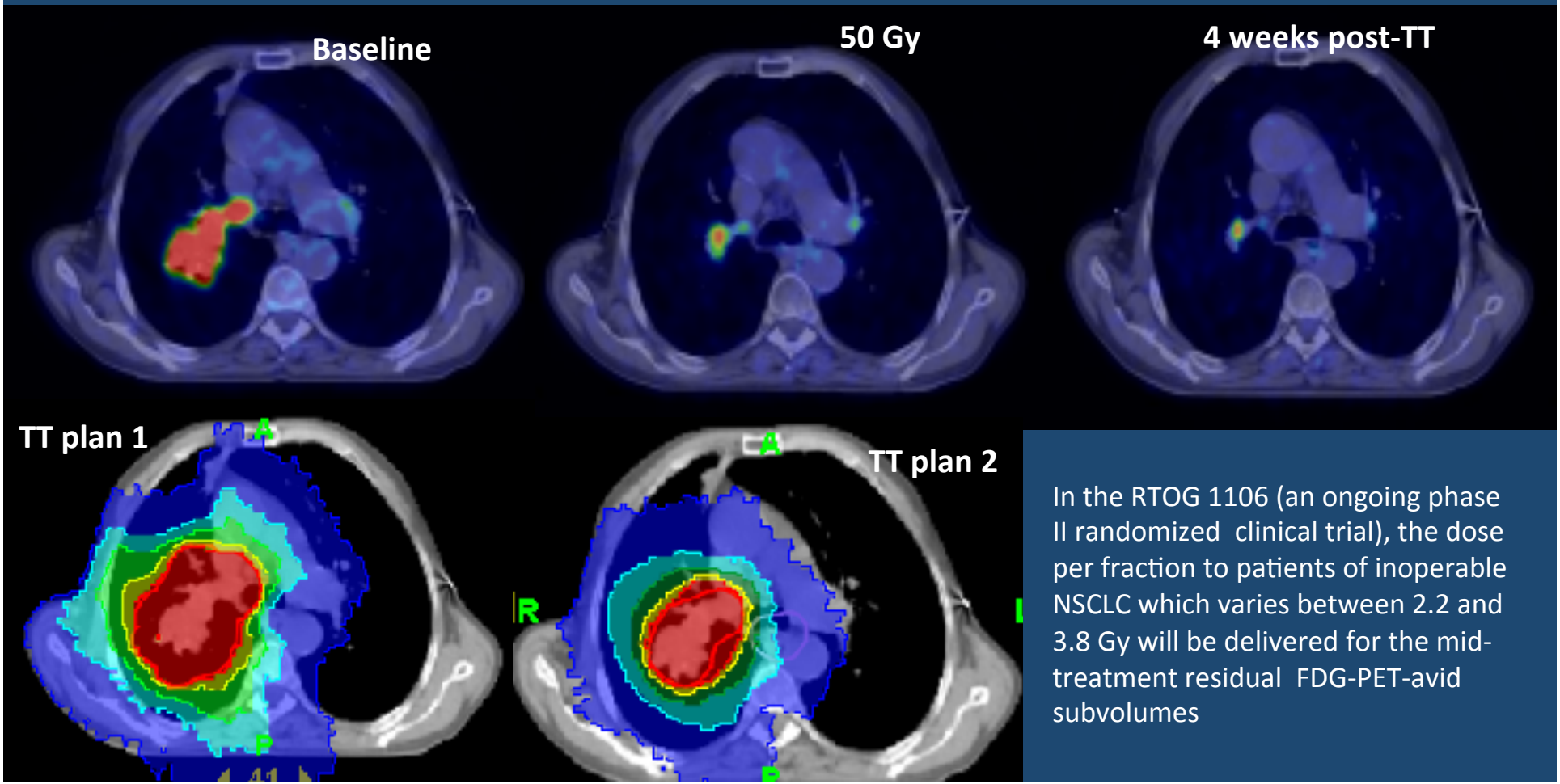
Lung cancers

- Lung cancer :
  - > 20% SHRINKAGE in 40% pts (Erridge SC et al;Siker et al)
- - average decrease in volume: 1.2% per day (range 0.6-2.3%) (Kupelian et al).



In the RTOG 1106 (an ongoing phase II randomized clinical trial), the dose per fraction to patients of inoperable NSCLC which varies between 2.2 and 3.8 Gy will be delivered for the mid-treatment residual FDG-PET-avid subvolumes

POTENTIAL ROLES OF 18F-FDG PET/CT IN HEAD AND NECK CANCER

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1 - Detection of Recurrent/Residual Disease

Isles et Al. Clinical Otolaryngol 2008

2- Delineation Of Radiotherapy Target Volume

Geets et Al. Radiother Oncol. 2007; Schinagl et Al. Int J Rad Oncol Biol Phy 2007

3- Staging (N, M and Synchronous Primary Tumor)

Rodrigues et Al. J Nucl Med 2009; Senft et Al. Radiot. Oncol 2008

Lonneux et Al. Journal of Clin Oncol 2010

4- Unknown Primary Carcinoma (CUP)

Dong et Al. Nuclear Medicine Comunications 2008

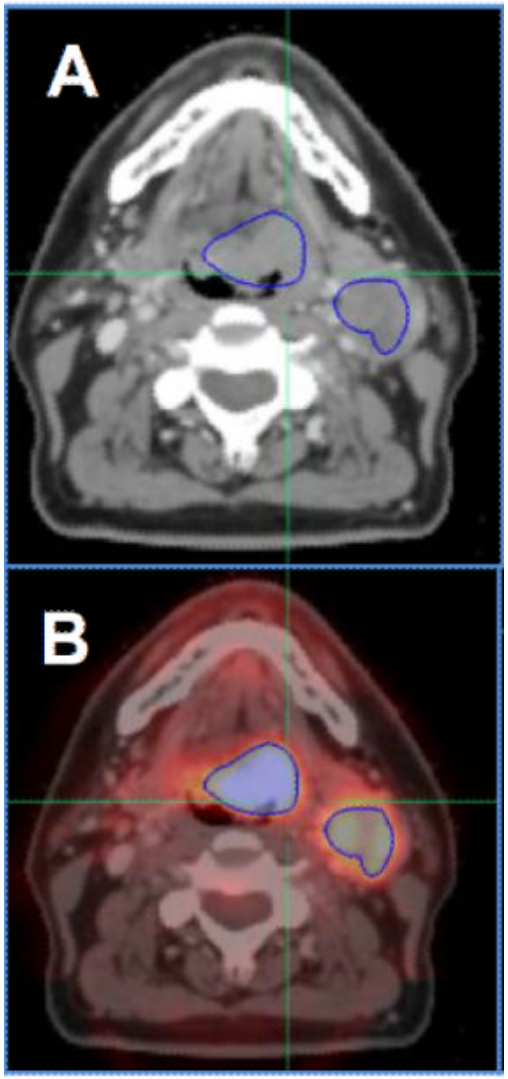
4- Prognostic Value

Moeller et Al. Int. J. Radiation Oncol Biol Phy 2010

PET nella definizione dei volumi clinici: Head and Neck

FDG-PET is widely accepted as a standard modality for evaluating SCCHN

- Good diagnostic performance in the overall pretreatment evaluation
- Limitations in detecting micrometastasis, due to low FDG uptake of small tumors without hypoxia *(Wong Rja et al, Jun 2008)*
- CT-based gross tumor volumes larger/ smaller than PET/CT-based GTVs (*P < 0.0001) (Newbold KL,et al Acta Oncol. 2008*; *Deantonio L, et al: Radiat Oncol. 2008)*
- Different threshold methods to delineate the target volume lead to variations in target volumes: SUVCO was more reliable to differentiate target volume from background than SUVmax *(Moule RN et al;R&O 2010)*
- Potentially, the GTV can be changed on the basis of PET information, facilitating sparing of nearby normal tissues and allowing dose escalation to relatively small subvolumes.
- 18F-FDG PET may identify areas of tumor spread not recognized by CT or MRI, potentially improving the accuracy of GTV definition.
- A comparison study of 11C-acetate (ACE) and FDG-PET indicated that ACEPET may be more sensitive than FDG-PET for the detection of primary tumors and metastases in patients with SCCHN *(Sun A, et al: IJROBP. 2011)*



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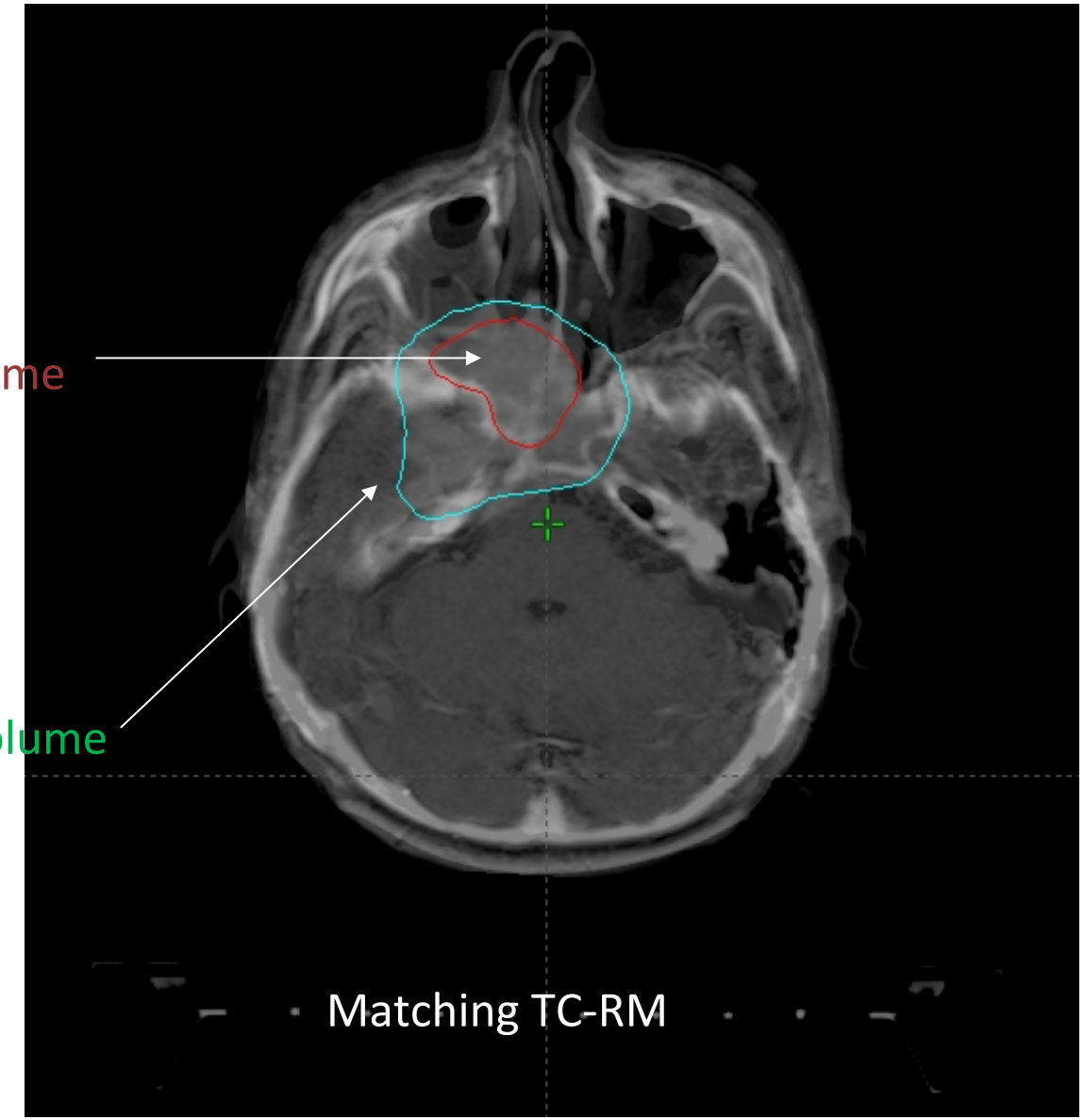
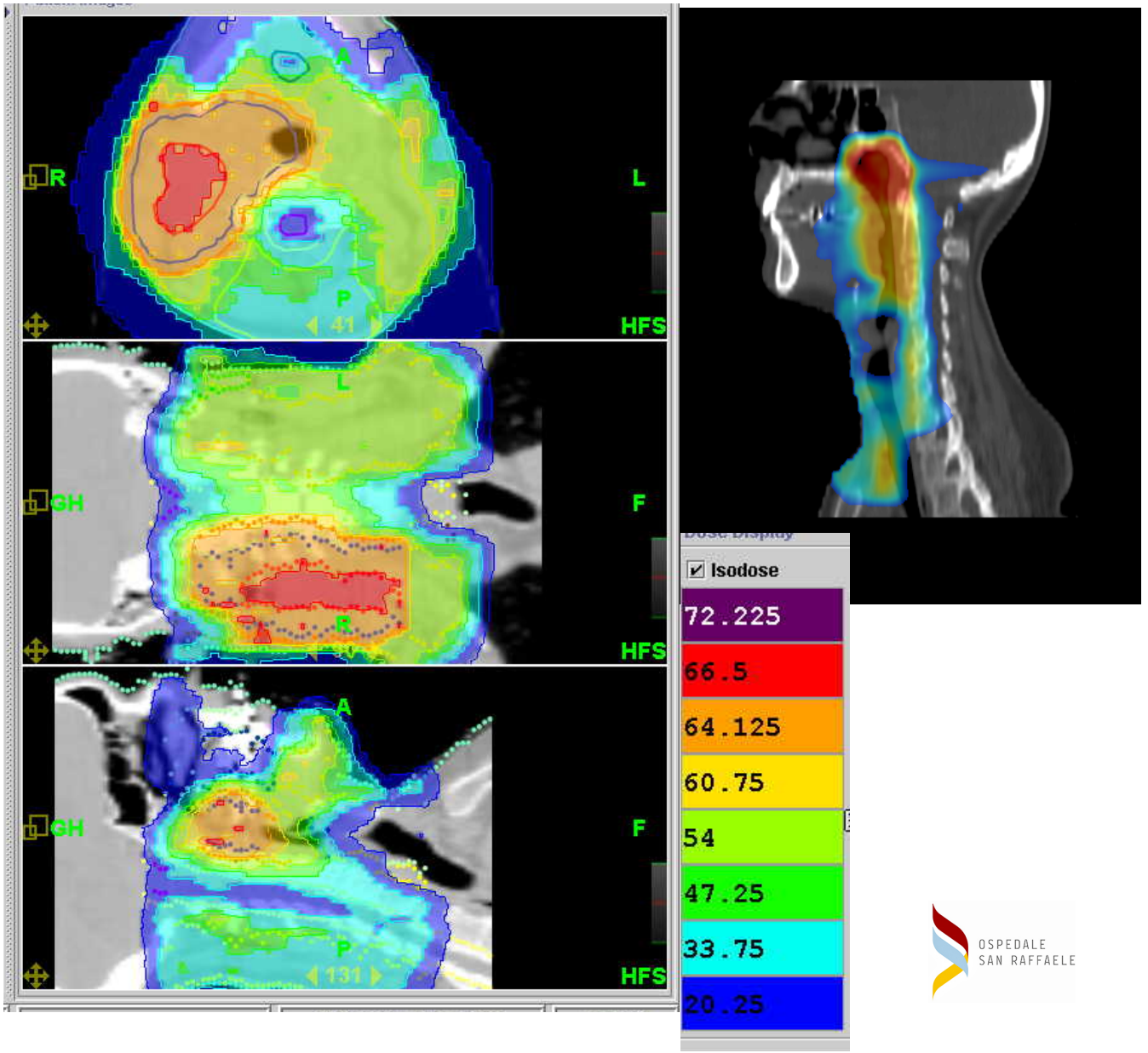
IMAGING MULTIMODALE



Dose escalation on GTV (PET+)

- SIB approach
- Dose escalated to metabolic subvolume
- Acute tox comparable to a similar group of patients without dose escalation on GTV



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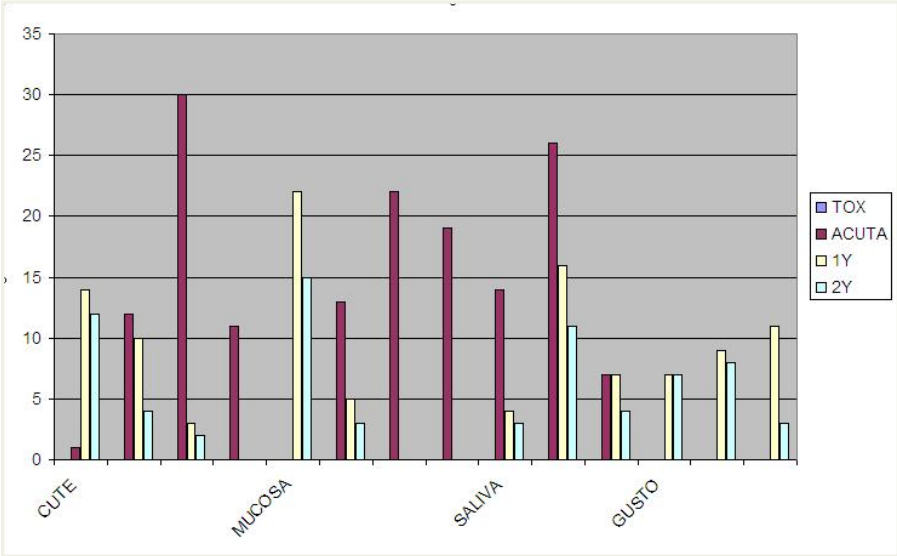
HEAD AND NECK CANCER TOXICITY

	Tossicità	Acuta	1 anno	2 anni
cute	0	1/54 (1.85%)	14/27 (51.85%)	12/18 (66.6%)
	1	12/54 (22.2%)	10/27 (37%)	4/18 (22.2%)
	2	30/54 (55.5%)	3/27 (11.1%)	2/18 (11.1%)
	3	11/54 (20.37%)		
mucosa	0		22/27 (81.5%)	15/18 (83.4%)
	1	13/54 (24%)	5/27 (18.5%)	3/18 (16.6%)
	2	22/54 (40.71%)		
	3	19/54 (35.2%)		
saliva	0	14/46 (30.4%)	4/27 (14.8%)	3/18 (16.6%)
	1	26/46 (56.5%)	16/27 (59.2%)	11/18 (61.1%)
	2	6/46 (13%)	7/27 (25.9%)	4/18 (22.2%)
gusto	0		7/27 (25.9%)	7/18 (38.8%)
	1		9/27 (33.3%)	8/18 (44.4%)
	2		11/27 (40.7%)	3/18 (16.6%)

Tabella 5.1: tabella riassuntiva delle tossicità dei pazienti



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HEAD AND NECK CANCER: LOCAL CONTROL

Pre-treatment FDG-PET is useful in predicting the response to treatment

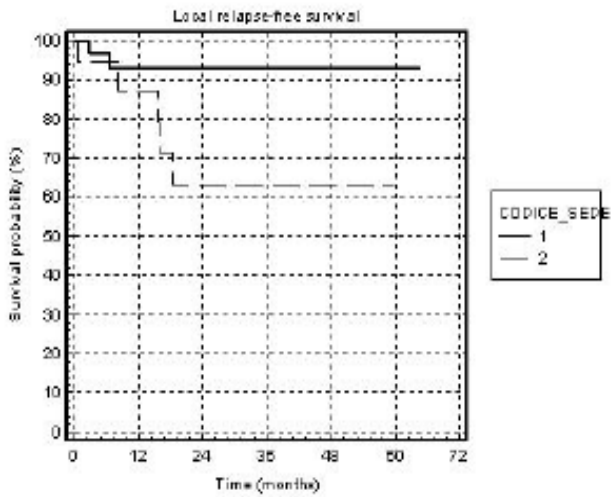
Local Control 94%

GTV PET (best cut off 24 cc) →(p=0.03)

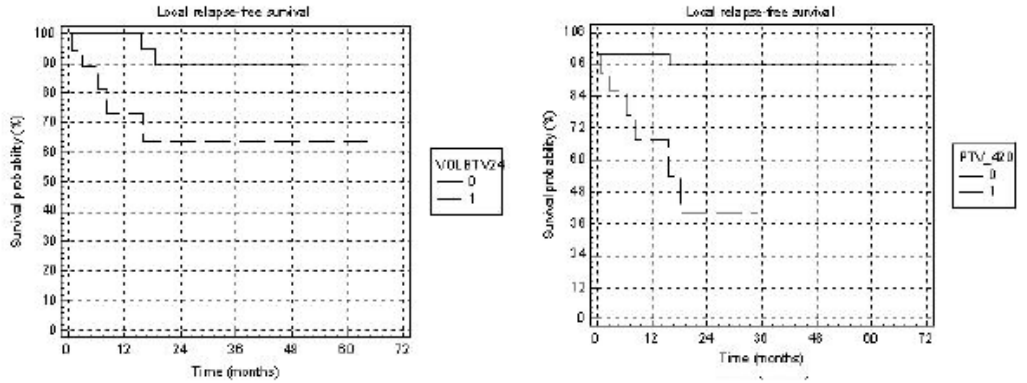
PTV 66 Gy (best cut off 420 cc)→(p=0.014)

Overall survival (OS) and disease-free survival (DFS) significantly different in good responders with a low SUVmax than poor responders with a high SUVmax (81 and 67% versus 50 and 40%, respectively),

[Farrag A, et al:Nucl Med Commun 2010]



(a)



(a) (b)

Figura 5.4: (a) Impatto GTV_{PET} >24cc, local relapse, p=0.02. (b) Impatto PTV_{66Gy}>420cc, local relapse, p<0.0001.

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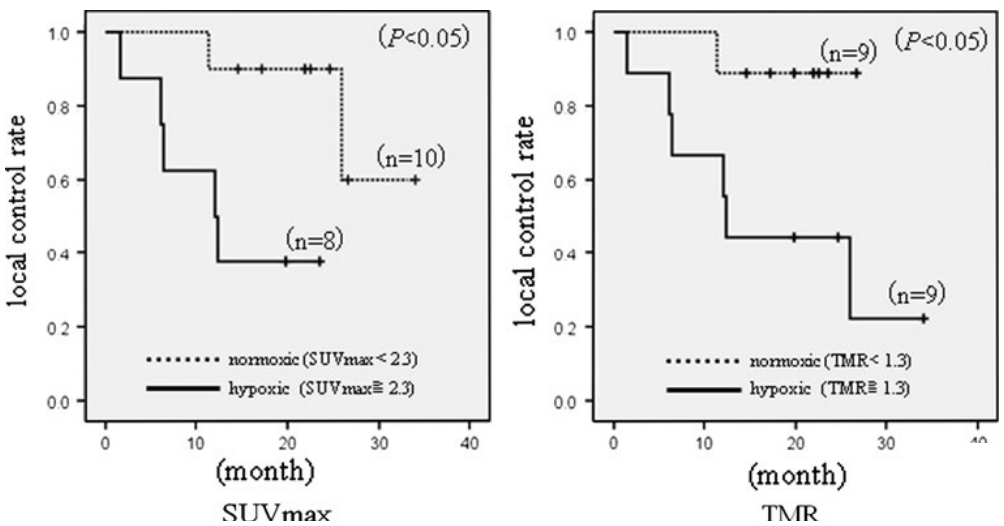
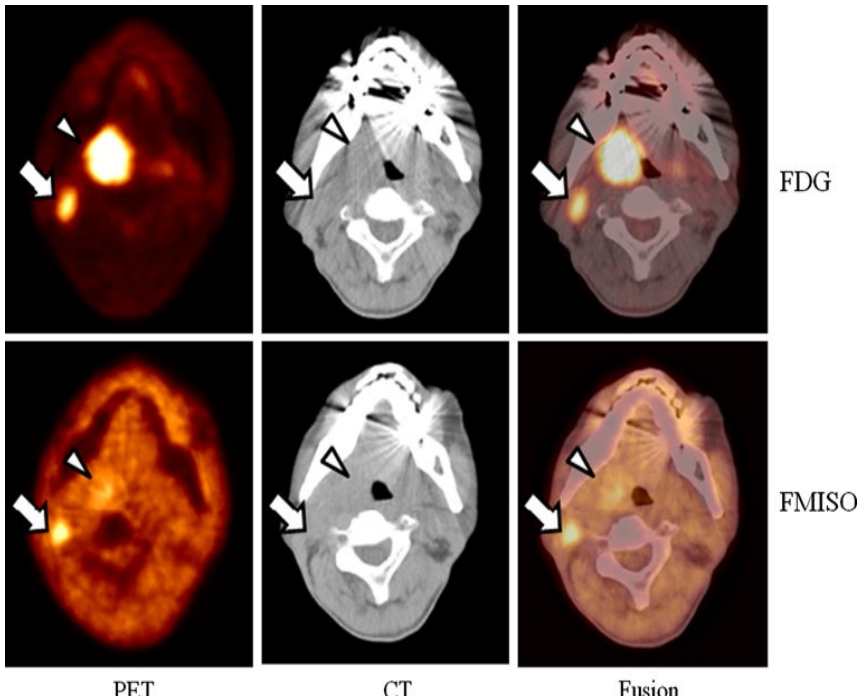
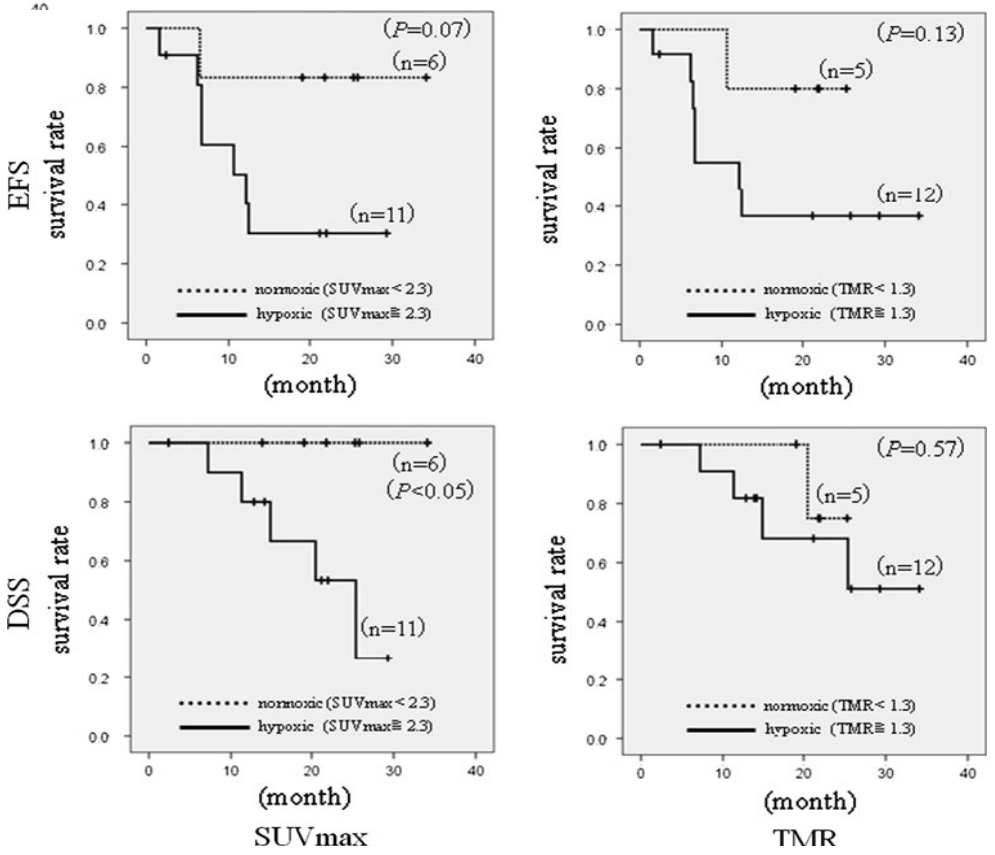
PROGNOSTIC VALUE OF 18F-FLUOROMISONIDAZOLO

SUV max /TMR)-
BOOST 15-20 GY







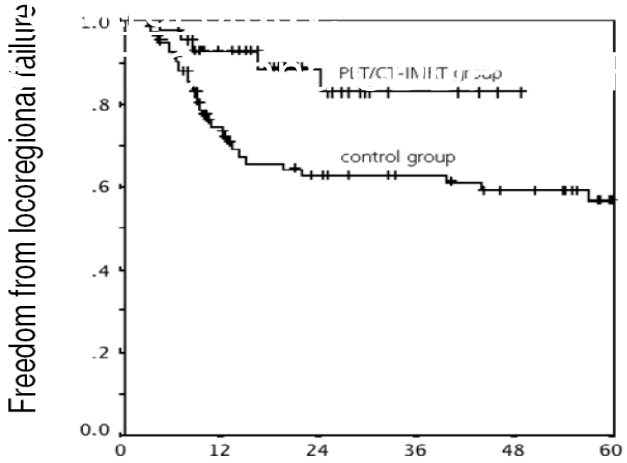
Masahiro Kikuki et Al: Ann Nucl Med 2011

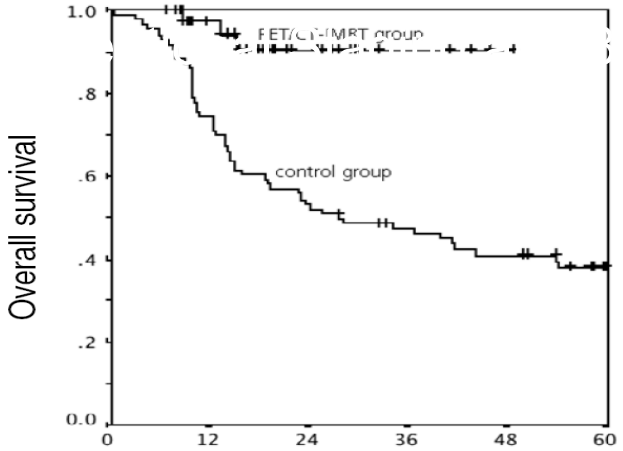
OSPEDALE SAN RAFFAELE

PET/CT Staging Followed by Intensity-Modulated Radiotherapy (IMRT) Improves Treatment Outcome of Locally Advanced Pharyngeal Carcinoma: a matched-pair comparison

Sacha Rothschild[1,2], Gabriela Studer[1], Burkhardt Seifert[3], Pia Huguenin[4], Christoph Glanzmann[1], J Bernard Davis[1], Urs M Lütolf[1], Thomas F Hany[5] and I Frank Ciernik*[6,7]

Radiation Oncology 2007





Event-free survival (p=0.005)
PET/CT+IMRT: 90% 1 yr, 80% 2 yrs
Control: 72% 1 yr, 56% 2yrs

Overall survival (p=0.002)
PET/CT+IMRT: 97% 1 yr, 91% 2 yrs
Control: 74% 1 yr, 54% 2 yrs

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In studies of locally-advanced head and neck cancers treated using PET/CT based IMRT planning: the gross target volume (GTV)-recurrent was completely encompassed by PTV (70 Gy) in70%-100% patients

Dose escalation and Dose redistribution: two strategies for the realization of dose escalation:

dose painting by contours (DPBC)

and dose painting by numbers (DPBN).

size of the subvolume is a vital factor in determining the level of the escalated dose, thus, the delineation method used for contouring is crucial

The optimal delineation method which could reproducibly and accurately identify the high recurrent-risk region needs further investigated.

The dose increases with the increasing intensity of the corresponding voxel, and thus forms a maximum dose

Currently most researches use bulk tumour characteristics measured by PET such as maximum or mean SUV or subvolumes contoured by a certain SUV-threshold. It does not give any information to verify the optimal dose which can result in a positive radioresponsiveness at the voxel level

the optimal dose prescription is not verified, the dose from the theoretical research and current clinical trials can only provide an estimation, the definite dose prescription with maximum therapeutic ratio can only be extracted from the sufficient data of clinical controlled trials.

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when the additional dose should be given??
PET/TC before the radiotherapy or after several fractions of radiotherapy??

In a prospective study, Aerts et al. Int. J. Radiat. Oncol. Biol. Phys. (2008) showed that the location of the low and high FDG uptake areas within the tumour for NSCLC remained stable during RT. The mean overlap fraction of FDG-avid area at Day 0 with Days 7 and 14 was 82.8%

Kong et al. demonstrated that the peak tumour FDG-activity decreased significantly after 45 Gy, and found a significant correlation in tumour metabolic response between during-RT scans and 3 months post-RT scans in patients with NSCLC

FMISO-PET/CT imaging, the temporal and spatial stability, such as the time window of complete reoxygenation and the conflict of whether the location of the hypoxic subvolumes varied during the treatment, has long been in concern

Does dose painting ultimately lead to higher cure rates?
The answer tends to be positive.....

Clinical progress of PET/CT guided dose painting.

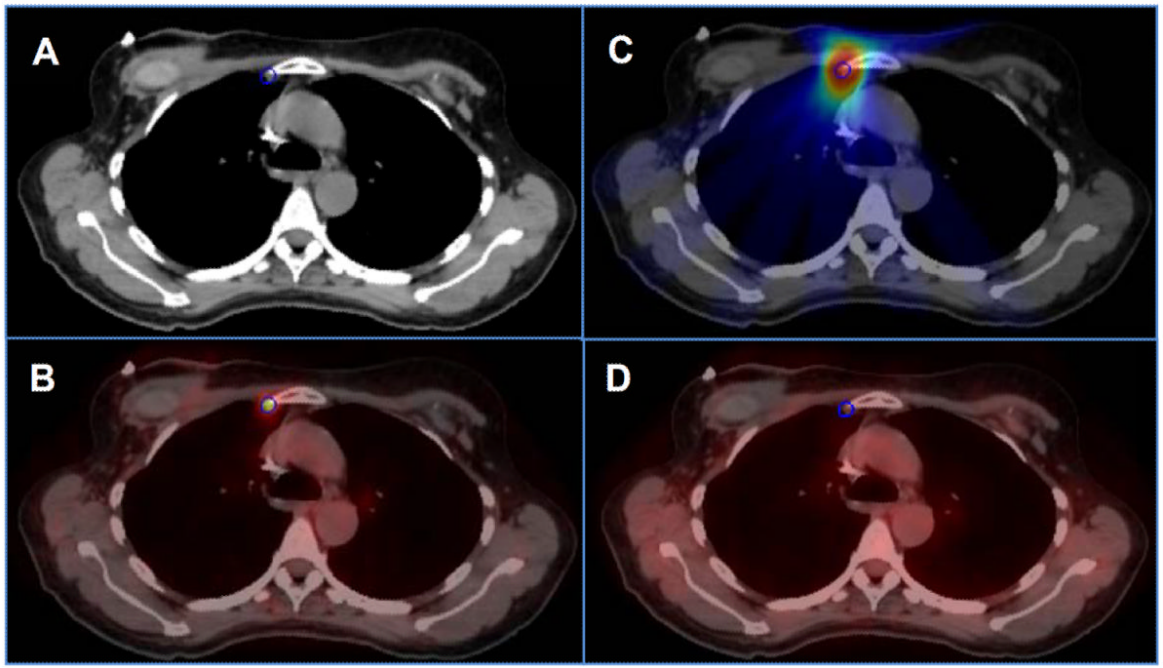
	Authors	Status	Phase	N.	Tumor type	Level of dose escalation	Conclusion
DPBC	Madani et al.2007 [12]	Completed	I	39	Head and neck cancer	72.5 and 77.5 Gy	Actuarial 1-year local control was 85% and 87%, and 1-year OS was 82% and 54% ($P = 0.06$)
	Fleckenstein et al. 2011 [61]	Completed	Pilot trial	32	Locally advanced NSCLC	Range of 66.6–73.8 Gy	The estimated median survival time was 19.3 months
	Kong et al. 2013 [33]	Completed	II	42	NSCLC	Median physical dose 84 Gy (BED108 Gy)	The 2-year rates of in-field LRC, overall LRC were 84% and 68%, the OS was51% (34%–65%)
	Heukelom et al. 2013 [62]	Ongoing	II	268	Head and neck cancer	Boost region 77 Gy, PTV outside the Boost region 67 Gy	It aimed to detect a 15% improvement in LRC with a power of 80% at a significance level of 0.05.
	Kong et al. (RTOG1106)	Ongoing	II	NR	NSCLC	Total dose of 80.4 Gy	NR
	van Elmpt et al. [34] (NCT01024829)	Ongoing	II	NR	NSCLC	Mean total dose 77.3 ± 7.9 Gy (arm A) and 77.5 ± 10.1 Gy (arm B). Boost region 86.9 ± 14.9 Gy	NR
DPBN	Berwouts et al. 2013 [24]	Completed	I	10	Head and neck cancer	A median prescription dose of GTV 70.2 Gy (68.7 ± 2.6, 80.7 ± 1.2)	Disease control in 9/10 patients at a median follow-up of 13 months
	Madani et al. 2011 [43]	Completed	I	21	Non-metastatic head and neck cancer	Median total dose of 80.9 and 85.9 Gy	An actuarial 2-year LRC and freedom from distant metastasis were 95%, 93% and 68%, respectively

Abbreviations: DPBC, dose painting by contours; DPBN, dose painting by numbers; N, numbers of patients; OS, overall survival; LRC, local-regional control; NSCLC, non-small cell lung cancer; NR, not reported.

X. Shi et al/Cancer Letters 355 (2014)

PET nella definizione dei volumi clinici Breast Cancer

- **FDG-PET has not shown significant utility in radiation planning after breast-conserving surgery**
- FDG-PET can contribute in significant ways to the clinical management and radiation planning of patients who have suspected locoregional recurrences (chest wall and supraclavicular nodes)
- FDG-PET is able to differentiate recurrences from post-surgical scars and is much more sensitive in detecting metastasis than CT and/or MRI.
- The role of FDG-PET is especially prominent in the management of oligometastatic disease

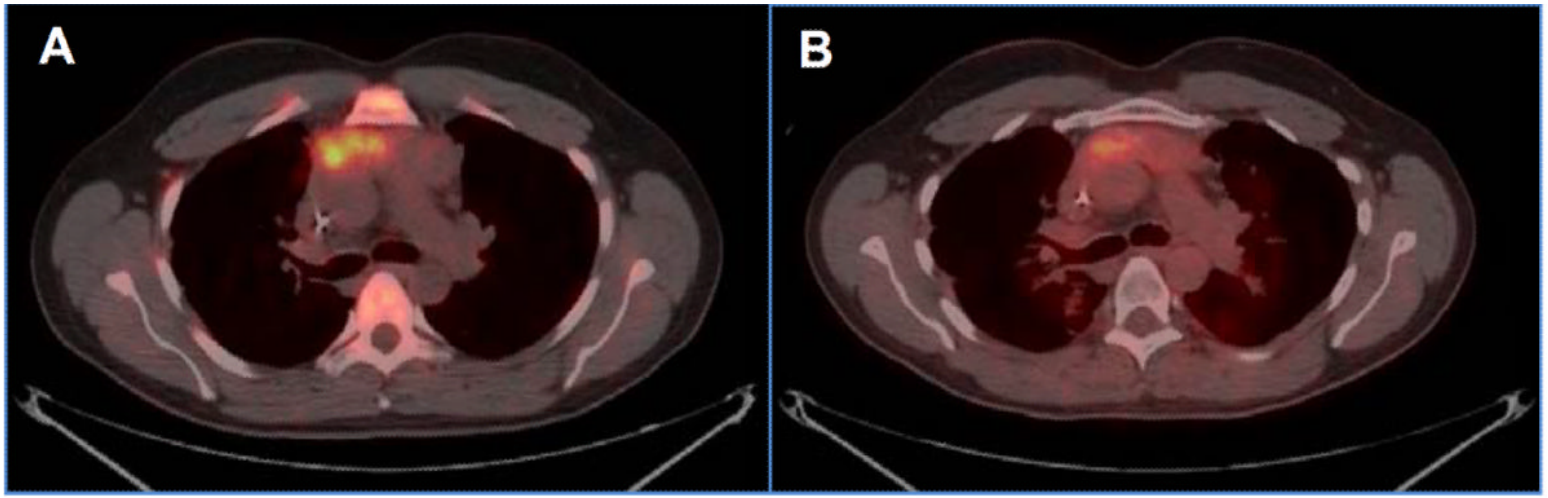


OSPEDALE
SAN RAFFAELE

PET nella definizione dei volumi clinici: Lymphoma

FDG-PET is more powerful than CT or MRI in evaluating both non-Hodgkin's and Hodgkin's lymphoma

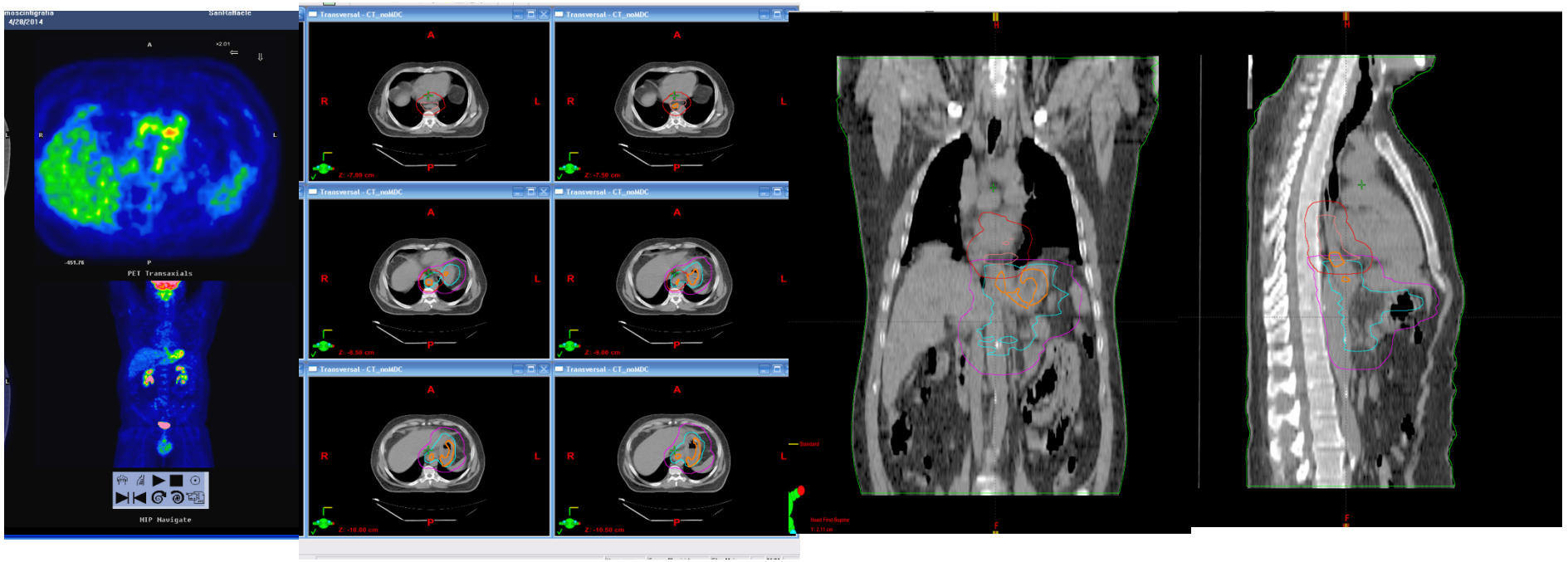
- FDG-PET/CT results in larger treatment volumes for radiotherapy planning
- The initial FDG-PET help the delineation of involved-field radiotherapy for the nodal regions at risk by the identification of lymph nodes that are undetected on CT in 36% of patients *(Girinsky T, et al R&O 2007)*
- *Asakura et al. 2010* published a series describing radiotherapy planning based on FDG-PET delineation, which resulted in good therapeutic outcome
- FDG-PET has significant value in monitoring response to therapy and predicting outcomes



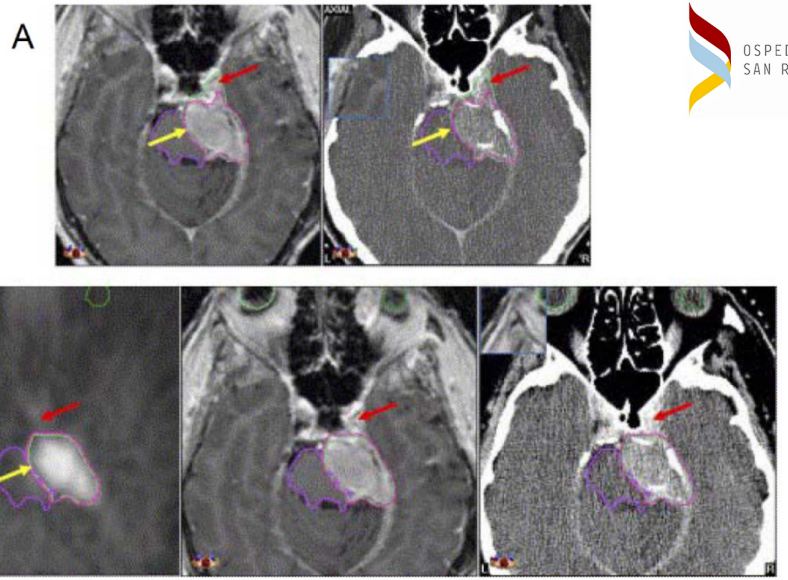
OSPEDALE
SAN RAFFAELE

PET nella definizione dei volumi clinici: Esophageal Cancer

- FDG-PET is not generally used for the initial diagnosis of esophageal cancer due to significant FDG uptake in infectious esophagitis,
- FDGPET plays a limited role in the evaluation of regional nodal disease
- High sensitivity for evaluation of local recurrence along with a high sensitivity and specificity for detection of distant disease occurring outside the initial surgical field. *(Zhong X, et al: IJROBP 2009).*
- FDG-PET/CT change target volumes contoured by radiation oncologists in a considerable proportion of patients (20–90%) with consequent changes in treatment planning (Moureau-Zabotto, at al Cancer Radiother. 2005*)*
- The tumor length evaluated by FDG-PET at an SUV cut off of 2.5 seemed most approximate to the pathological tumor length *(40, 41 Han D, et al: IJROBP; 2010)*
- The inter- and intra-observer variability of GTV contours based on FDG-PET is less that of CT-based planning *(Schreurs et al : Dis Esophagus. 2010)*



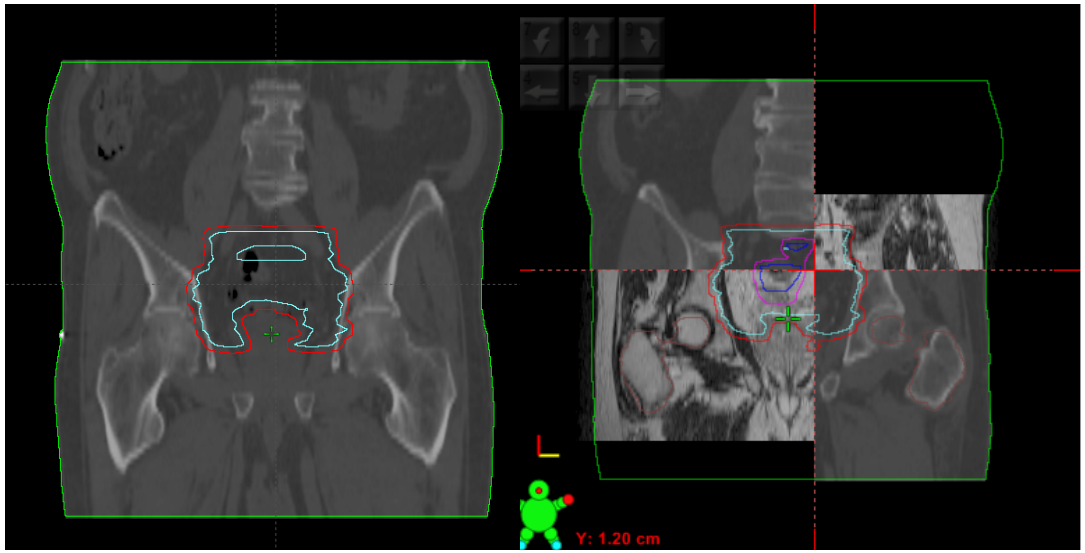
PET nella definizione dei volumi clinici:
BRAIN TUMORS

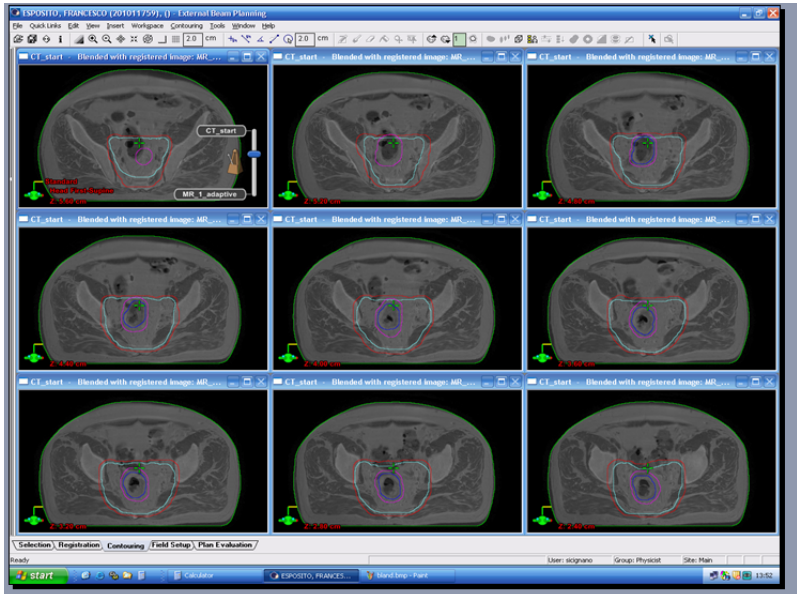


- MET-PET shows promising results in the detection and delineation of viable tumor, especially in low-grade glioma
- MET-PET is reported to be superior to CT alone, FDG-PET and 18F-labeled fluorothymidine (FLT)-PET in delineating low grade gliomas (*Jacobs AH,et al: J Nucl Med. Dec; 2005).*
- In high grade gliomas,the use of the 11C-MET tracer results in PET images that increased the size of the GTV obtained by more standard approaches (*Kaschten B, et al :J Nucl Med 2010*)
- Treatment planning using MET-PET-based tumor delineation versus CT/MRI images was associated with an improvement in survival *(Grosu AL, et al IJROBPj 2010).*
- In tumor delineation of meningiomas, MET-PET also led to a significant increase in the size of the GTV (*Shoup TM, et al:J Nucl Med. 1999)*
- Some tumors not seen with CT/MRI, are visible with PET imaging
- 11C-labeled tyrosine (TYR) was reported to monitor protein synthesis rate in pituitary adenoma pre- and post-radiotherapy and showed great decrease in TYR accumulation after radiotherapy *(van den Bergh et al: Radiother Oncol. 2011*)
- 18F-labeled 1-amino-3-fluomcyclobutane-1-carboxylic acid (FACBC), an unnatural amino acid, is in the clinical trial stage for brain tumor imaging.

PET nella definizione dei volumi clinici: Colorectal cancer

- FDG PET/CT sensitivity and accuracy in detecting both intrahepatic and extrahepatic metastases 95% and 97%.
- FDG PET/CT fail the detection of extrahepatic disease in 11% pts versus 33% of CT (Selzner et al. *Ann*
- *Surg 2004)*
- Positive impact of PET/CT on tumor delineation for radiation planning in rectal cancer [8, 42–45].
- Studies of GTV delineation by MRI compared with PET/CT have shown that MRI tends to overestimate GTV
- The PET-derived GTV is strongly correlated with the CT-derived GTV *and with the volume determined* by subsequent anatomic-pathologic analysis (Braendengen M,et al *Int J Radiat Oncol Biol Phys 2011)*
- PET/CT has been found to be effective both in assessing early response and in monitoring for relapse after RT (Kitajima K, et al *Eur J Nucl Med Mol Imaging 2009)*
- PET metabolic responders show a statistically significant higher 5-year relapse-free survival compared with the nonresponders (86% vs 55%, respectively; *p* =0.014) [Avallone et al. *Eur J Nucl Med Mol Imaging 2012]*





PET nella definizione dei volumi clinici: Colorectal cancer

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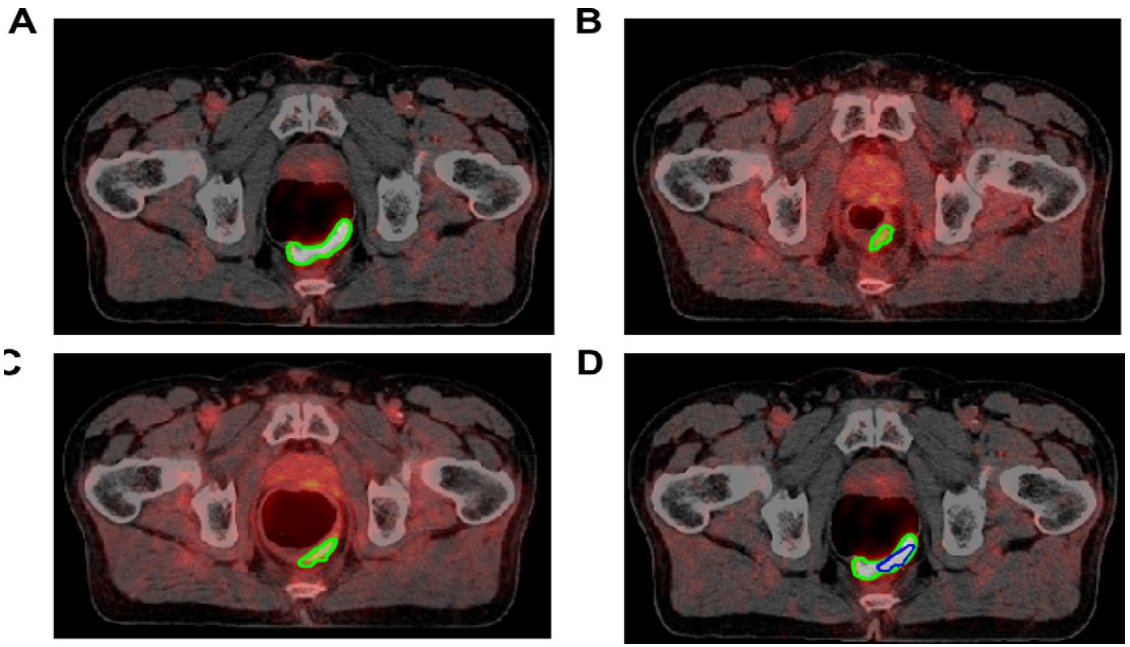
Rectal cancer

Residual metabolic tumor activity after chemo-radiotherapy is mainly located in initially high FDG uptake areas in rectal cancer

Jørgen van den Bogaard [a,1], Marco H.M. Janssen [a,*,1], G. Janssens [b], Jeroen Buijsen [a], Brigitte Reniers [a], Philippe Lambin [a], Guido Lammering [a,1], Michel C. Öllers [a,1]

[a] Department of Radiation Oncology (MAASTRO), GROW Research Institute, Maastricht, The Netherlands; [b] Center for Molecular Imaging and Experimental Radiotherapy (IMRE), Université Catholique de Louvain, Brussels, Belgium

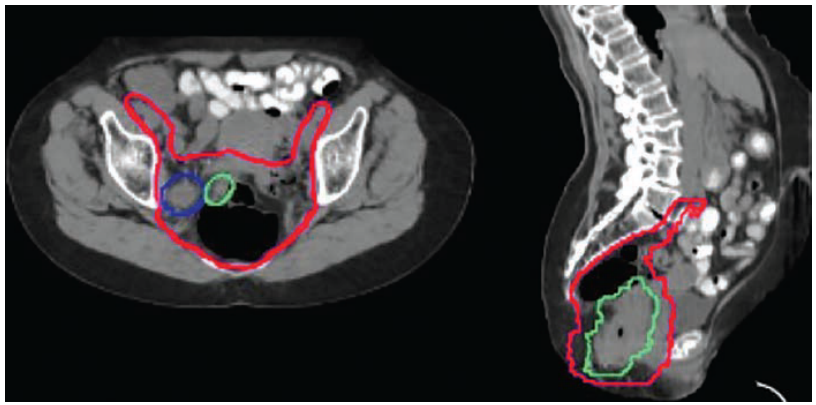
For the voxels with a pre-treatment FDG uptake of >50% of SUVmax, 70.6 ± 5.6% of the voxels were still metabolic active in the residual tumor, whereas for voxels with an FDG uptake of <50% of SUVmax only 51.1 ± 6.7% were present in the metabolic active residual tumor.

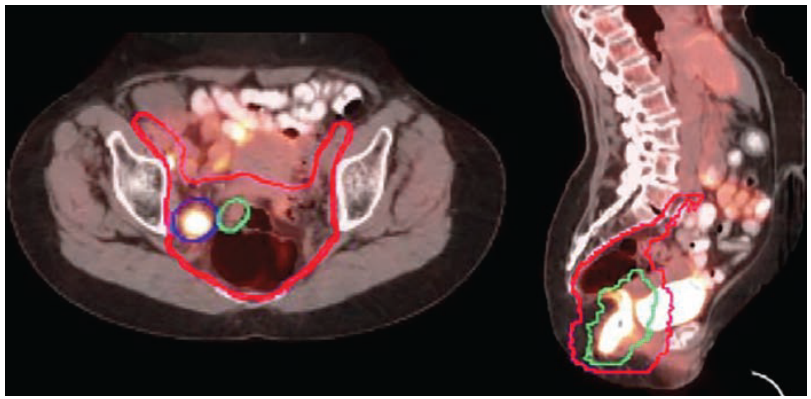


OSPEDALE SAN RAFFAELE

PET nella definizione dei volumi clinici: Anal cancer

- studies suggest that PET/CT has a sensitivity of between 89% and 100% for the detection of primary tumor, whereas CT has a sensitivity of 58–75% [Saboo SS, et al :*Abdom Imaging 2013]*
- PET/CT is also more sensitive for the detection of regional lymph node and distant metastases than conventional imaging. (Krengli M,et al *Radiat Oncol 2010)*
- Krengly et al reported that PET/CT, GTV and CTV contours changed in 55.6% and 37.0% of patients, respectively.
- PET/CT is recommended by the NCCN guidelines for radiation therapy planning in patients with anal cancer since 2012 [*Frankel TL et* al:*J Gastrointest Oncol 2012*]
- Day FL, et al (*Br J Cancer* 2011) , reported the 2-year PFS was found to be 95% for patients with a complete metabolic response, 71% for those with partial metabolic response, and 0% for those with no response ($p < 0.0001$)
- High sensitivity and specificity of PET/CT for the detection of persistent or recurrent disease [93% and 81%] (Vercellino L, et al ; *Int J Colorectal Dis* 2011)



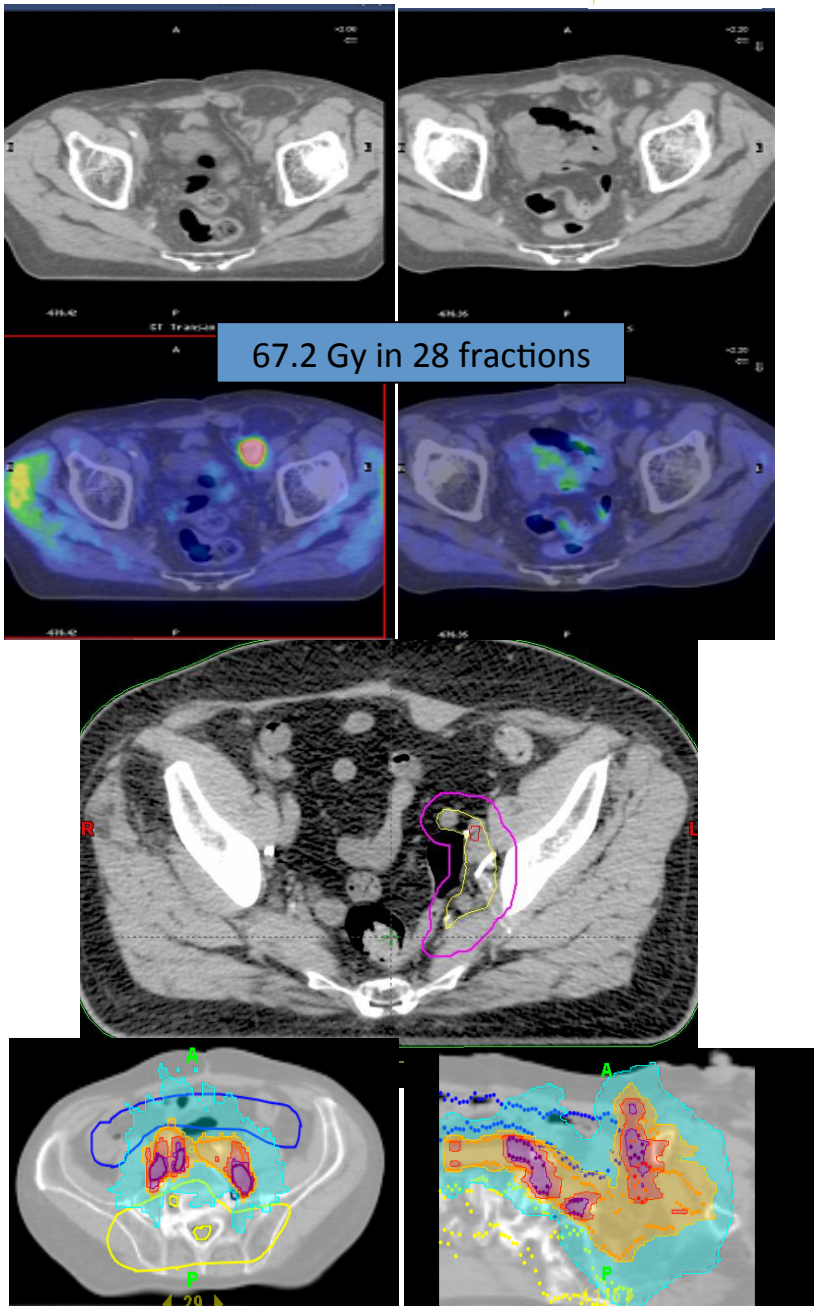


OSPEDALE SAN RAFFAELE

PET nella definizione dei volumi clinici: Prostate cancer

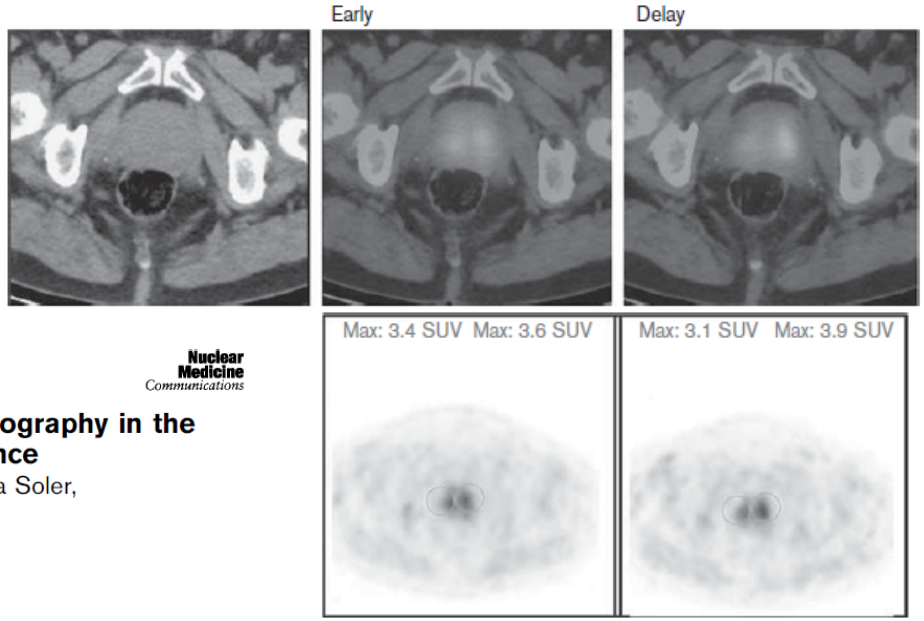
OSPEDALE SAN RAFFAELE

- 11C-choline-PET/CT is not suitable for the initial diagnosis (multiple foci that may be smaller than PET spatial resolution)
- Low 11C-choline-PET/CT accuracy in lymph nodal staging of prostate cancer makes it inappropriate to plan target volumes in the lymph nodes *(Schiavina R. et al; Eur Urol 2008)*
- 11C-choline-PET/CT presents high values of sensitivity and specificity in detecting distant recurrent sites of the disease, especially at the level of lymph nodes *(Fuccio C, et al; Ann Nucl Med 2010)*
- In radiotherapy planning, 11C-choline-PET/CT may be considered to select and delineate target volumes at recurrent sites in lymph nodes.
- The role of 11C-acetate in image guidance for radiotherapy planning has been evaluated in patients with intra-capsular prostate carcinoma with promising results *(Seppala J et al; Radiother Oncol. 2009)*
- 18F-choline has been used to delineate gross tumor volume and to generate the planning target volume in patients with intra-prostatic lesions (overall sensitivity of 86% in detecting local recurrent disease) *[Husarik DB et al; Eur J Nucl Med Mol Imaging. 2008]* . However, data to establish the role of 18F-choline in radiotherapy planning are still limited *(Weber DC, et al ; Radiat Oncol.2009)*
- Radiolabeled amino acid analog anti-1- amino-3-18F-fluorocyclobutyl-1-carboxylic acid (anti-18F-FACBC) has shown promising results in diagnosing primary and recurrent prostate cancers *(Schuster DM,et al; Radiology 2011)*
- Preliminary clinical reports with 18F-FACBC showed an improvement in the detection rate of 20-40% in comparison with 11C-Choline (*Nanni C, et al; Eur J Nucl Med Mol Imaging 2013)*



PET nella definizione dei volumi clinici: Prostate cancer

In the malignant lesions, the tracer uptake remained stable or increased, whereas it decreased in the benign lesions, using the dual-phase technique. In the benign lesions, choline is dephosphorylated, probably by prostatic acid phosphatase, an enzyme specific to prostate tissues.

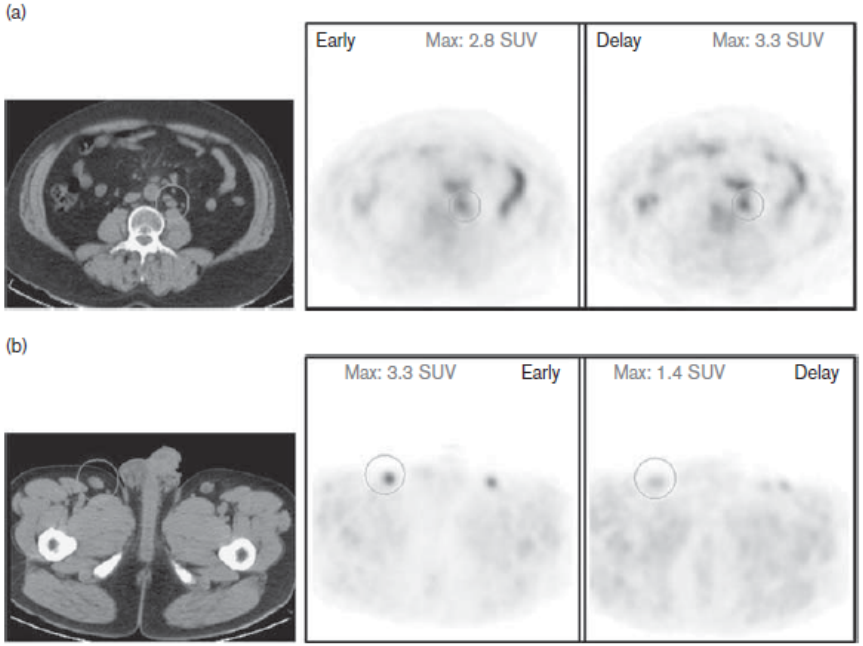


Original article

Nuclear Medicine Communications

Dual-phase ^{11}C-choline PET/computed tomography in the early evaluation of prostate cancer recurrence

Jose R. Garcia, Gemma Cuberas, Eduard Riera, Marina Soler, Merce Moragas and Francisco Lomeña



In patients initially treated with radiotherapy, the study showed how the metabolic dynamics between the two studies enable differentiation between benign lesions and recurrence .

In patients treated with surgery, all the foci of 11C-choline were accumulative in relation to local recurrence because the absence of prostatic tissue makes uptake by benign processes impossible

OSPEDALE SAN RAFFAELE

CONCLUSIONS 1

- Lung cancer: (NSCLC) FDG-PET has led to the safe decrease of radiotherapy volumes, enabling radiation dose escalation and, experimentally, redistribution of radiation doses within the tumor, along with playing a significant role in monitoring radiotherapy response

- Head and neck cancer: FDG-PET can provide important complementary information for radiotherapy planning

significant role in monitoring radiotherapy response

- Breast cancer: FDG-PET detection and definition of the extent of recurrent or metastatic disease

- Esophageal cancer: FDG-PET detection of unrecognized lymph node metastases.

significant role in monitoring radiotherapy response

- Lymphoma: FDG-PET is essential for involved nodal irradiation and leads to decreased irradiation volumes while also decreasing geographic misses

significant role in monitoring radiotherapy response

- Brain tumors: 11C-MET may play an increasingly important role in radiation planning

- Colorectal cancer : FDG-PET has value in the detection of hepatic and extrahepatic metastases during disease staging and often leads to a change in management. It is also useful for CRC radiation therapy planning and is the modality of choice for identifying recurrence, especially in patients with rising CEA levels + significant role in monitoring radiotherapy response

- Anal cancer: FDG PET/CT is playing an increasing role in initial staging, radiation therapy planning, and therapy assessment. Since April 2012, PET/CT has been recommended by the NCCN guidelines for radiation therapy planning in patients with anal cancer + a significant role in monitoring radiotherapy response

- Prostate cancer: 11C-choline may have a potential role for recurrent prostate cancer radiotherapy planning. The role of anti-18F-FACBC in the radiotherapy management of prostate cancer may emerge in the near future.

OSPEDALE
SAN RAFFAELE

Conclusions 2

Currently, besides for staging/restaging purposes, PET/CT is only playing a complementary role to other modalities such as CT and MRI for target volume delineation in radiotherapy.

The inter- and intra-observer variability of GTV contours based on FDG-PET is less than that of CT-based planning

Standardized protocols should be established to better define what role PET and/or PET/CT scans should play in radiotherapy planning

Assessment of cost effectiveness of this new combined RT of (multiple) re-imaging, re-delineation and re-planning that is urgently needed.

More randomized controlled trials are expected to be presented to provide more robust evidence of the effectiveness of dose painting in disease control and the toxicity rates against standard RT strategy.

The application is not ready for routine clinical practice for now.

OSPEDALE SAN RAFFAELE

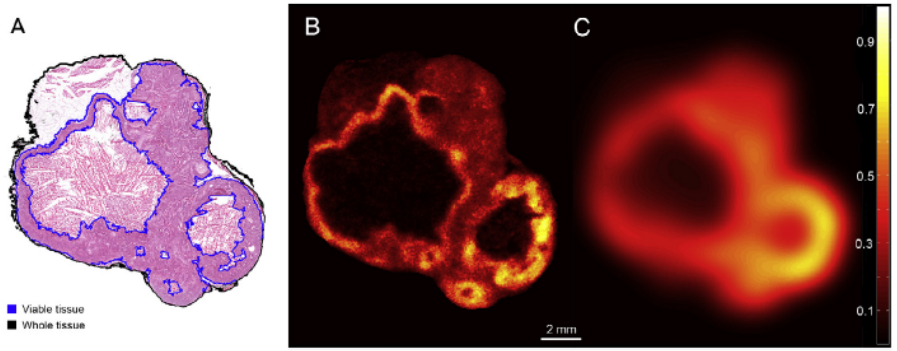


Fig. 3. (A) Microscopy image of haematoxylin and eosin staining. Image was acquired at 20× using Olympus BX61 microscope equipped with a motorised stage. (B) Autoradiography image. (C) Simulated PET image slice at the same location. Both B and C images were normalised to the maximum activity value in the whole tumour. All images are shown on the same scale. All images were obtained at the same tumour location. Microscopy image was obtained from tissue section adjacent to the one used for autoradiography.

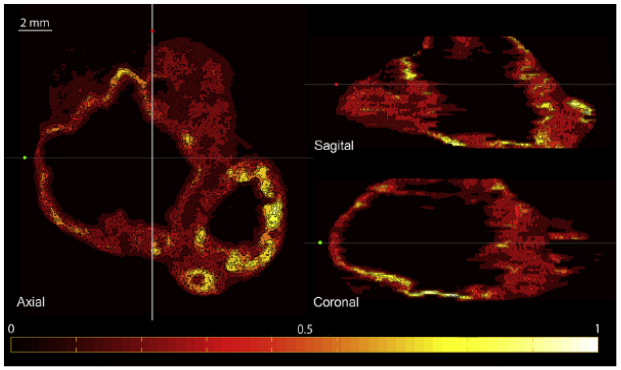


Fig. 4. Orthogonal slices through the reconstructed 3D FDG autoradiography image set for one of the tumours. All images are normalised to the maximum tumour activity registered in the aligned autoradiography stack. Colour bar is linear and it indicates [0, 1] range. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

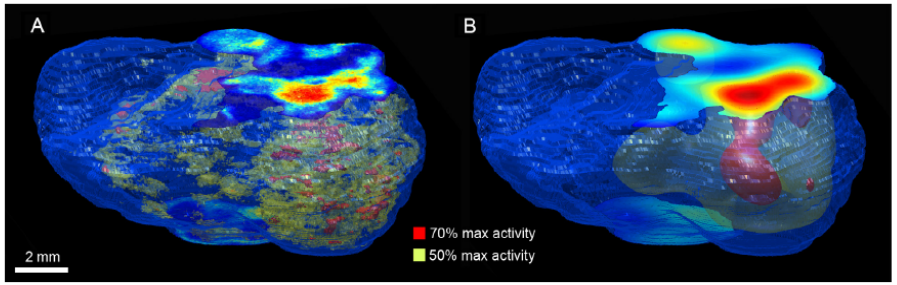


Fig. 5. Rendered tissue outline with volumes segmented from the FDG images: (A) 3D reconstructed autoradiography; (B) sPET. Threshold values represent % of maximum intensity.

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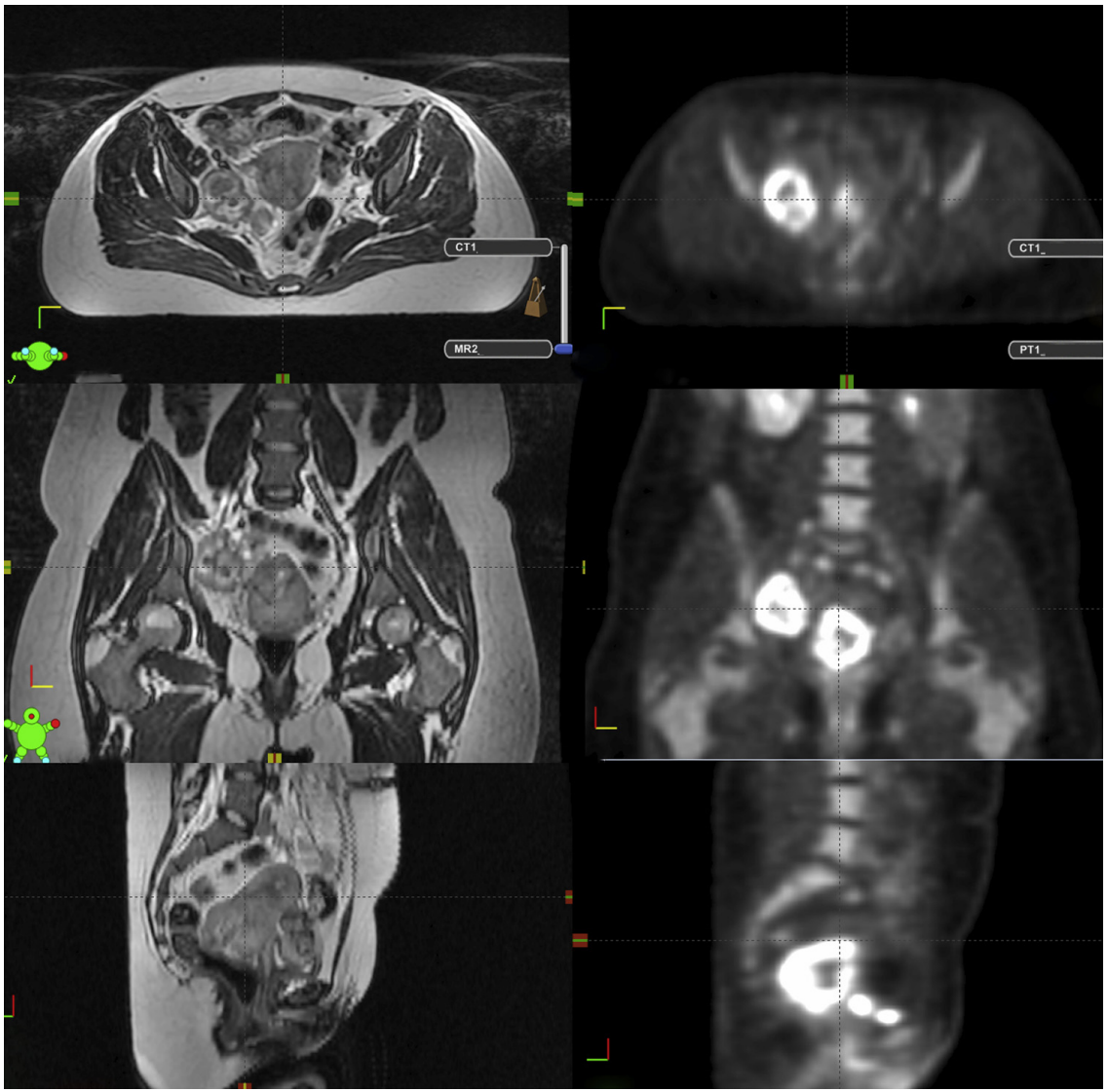

Pet/RMN

KEY POINTS

- Positron emission tomography (PET) has proved to be an indispensable tool in the staging of many malignancies, as well as in discriminating responses to therapy.

- Technological advances in radiation therapy planning and delivery have made highly conformal and accurate treatments a reality.

- Integration of PET into radiation treatment planning increases the accuracy of target definition at the start as well as during the treatment in an adaptive approach.

- Future research should be focused on determining the potential benefits of such adaptations in a prospective manner, as well as exploring new tracers that may improve existing results.

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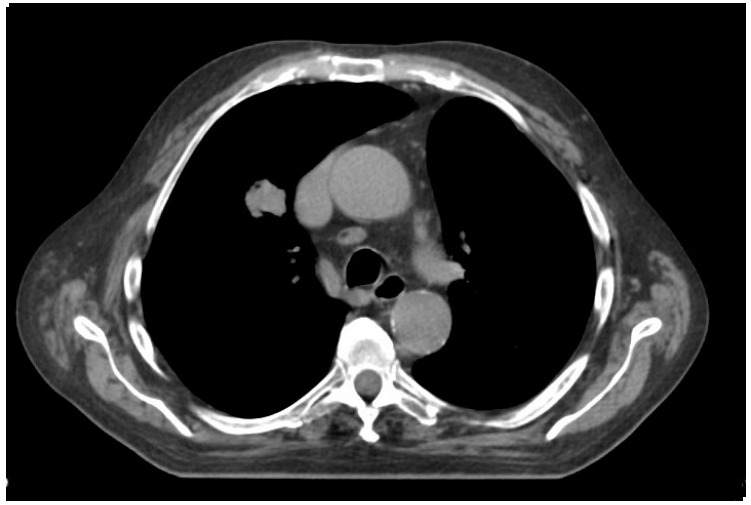
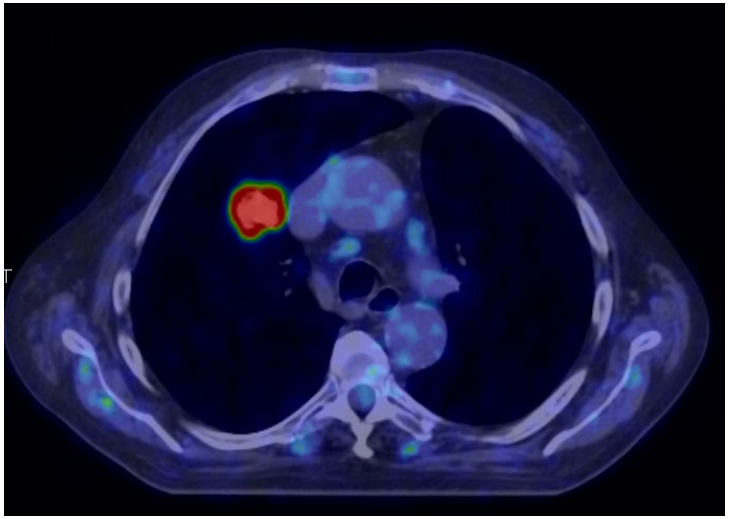
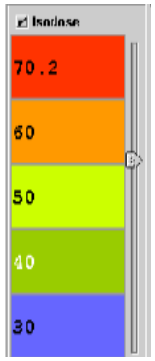
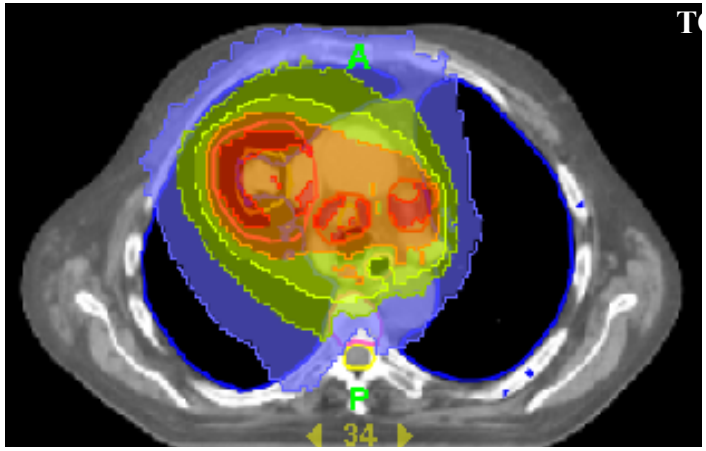
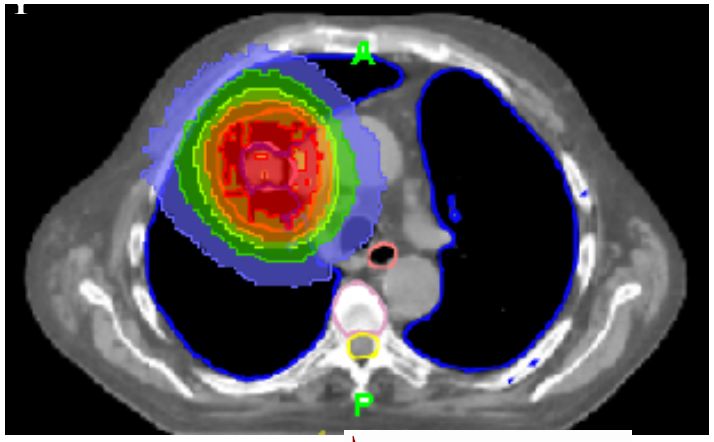
GTV (CT-based) vs BTV (PET/CT-based)











OSPEDALE
SAN RAFFAELE

Table 2 | Methods of GTV delineation on PET in correlation with surgical specimens.

	Patient no.	Method of GTV delineation on PET	Correlation between CT, PET, PET/CT, and pathological tumor size
Lin et al. (22)	37	Halo for tumor observed in fused PET-CT images	Stronger correlation between GTV and pathological tumor dimensions were observed with PET/CT Mean SUV of the external margin of halo was 2.41 ± 0.73 T stage and histology significantly influenced SUV at the edge of the halo
Yu et al. (23)	52	SUV of 2.5	FDG-PET/CT has significantly better correlation with surgical specimens than CT or PET alone, especially in the presence of atelectasis
Yu et al. (24)	15		Best correlation between PET GTV and the actual tumor was found at the SUV threshold of $31 \pm 11\%$, and absolute SUV cut-off of 3.0 ± 1.6
Wu et al. (25)	31	Thresholding with 20–55% of SUV_{max}	Maximal primary tumor dimension was more accurately predicted by CT at the window-level of 1,600 and −300 HU than PET GTVs (best correlation with pathological tumor volume at 50% SUV_{max})
Schaefer et al. (27)	15	Tumor threshold = A*mean $SUV_{70\%}$ + B*background	Pathological tumor volume: 39 ± 51 mL PET tumor volume: 48 ± 62 mL CT tumor volume: 60.6 ± 86.3 mL Both CT and PET volumes are highly correlated with pathological volumes ($p < 0.001$). Increased variation between PET and pathological tumor volumes were observed in lower lobes
van Baardwijk et al. (28)	33	Source-to-background ratio auto-segmentation	Maximal tumor diameter of the PET GTV is highly correlated with that in surgical specimens (CC = 0.90). Auto-segmented GTVs are smaller than manually contoured GTVs on PET/CT
Wanet et al. (31)	10	Gradient-based method Fixed threshold at 40 and 50% of the SUV_{max}. Adaptive thresholding based on the source-to-background ratio	Comparison of both CT and PET GTV Gradient-based method led to the best estimation of the GTV PET GTVs were smaller than CT GTVs in general
Cheebsumon et al. (32)	19	Absolute SUV cut-off (2.5) Fixed threshold at 50% and 70% SUV_{max} Adaptive thresholding 41–70% SUV_{max} Contrast-oriented algorithm Source-to-background ratio Gradient-based method	Adaptive 50% and gradient-based methods generated the most consistent maximal tumor dimension, which had a fair correlation with the pathological tumor size

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