Associazione Italiana Radioterapia Oncologica
Lazio Abruzzo Molise

Incontro scientifico regionale di aggiornamento dell' AIRO

Martedì 26 Giugno 2012 Ore 17.00
Sede:Università La Sapienza di Roma, Policlinico Umberto I. Istituto Radiologia

Target veri o presunti: le neoplasie polmonari

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PRINCIPLES OF RADIATION THERAPY (8 of 10)

Table 4. Commonly Used Doses for Conventionally Fractionated and Palliative RT

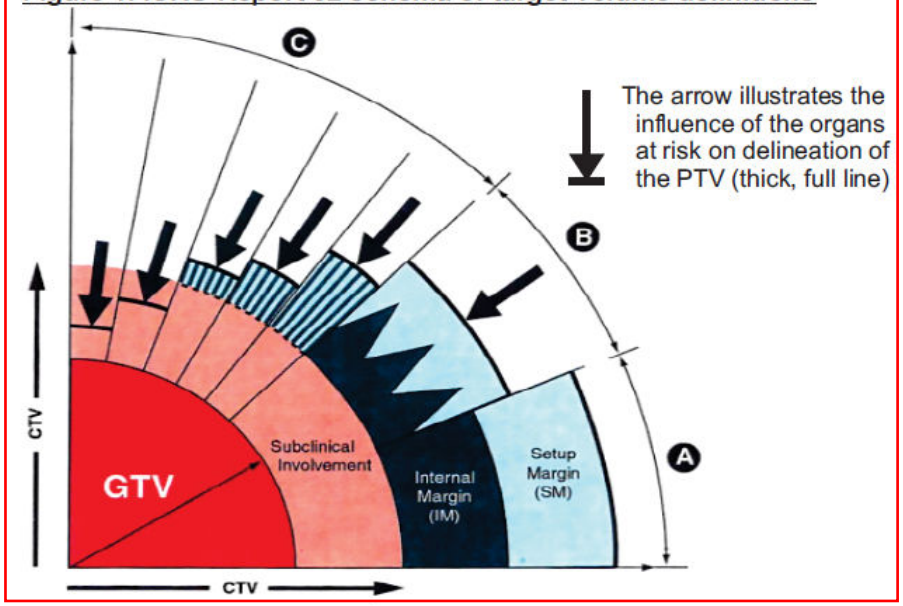
Treatment type	Total dose	Fraction size	Treatment duration
Definitive RT with or without chemotherapy	60-74 Gy	2 Gy	6-7.5 weeks
Preoperative RT	45-50 Gy	1.8-2 Gy	5 weeks
Postoperative RT			
• Negative margins	50-54 Gy	1.8-2 Gy	5-6 weeks
• Extracapsular nodal extension or microscopic positive margins	54-60 Gy	1.8-2 Gy	6 weeks
• Gross residual tumor	60-70 Gy	2 Gy	6-7 weeks
Palliative RT			
• Obstructive disease (SVC syndrome or obstructive pneumonia)	30-45 Gy	3 Gy	2-3 weeks
• Bone metastases with soft tissue mass	20-30 Gy	4-3 Gy	1-2 weeks
• Bone metastases without soft tissue mass	8-30 Gy	8-3 Gy	1 day-2 weeks
• Brain metastases	CNS GLs	CNS GLs	CNS GLs
• Symptomatic chest disease in patients with poor PS	17 Gy	8.5 Gy	1-2 weeks
• Any metastasis in patients with poor PS	8-20 Gy	8-4 Gy	1 day-1 week

Table 5. Normal Tissue Dose-Volume Constraints for Conventionally Fractionated RT

OAR	Constraints in 30-35 Fractions
Spinal cord	Max ≤ 50 Gy
Lung	V20 ≤ 30-35%; V5 ≤ 70%; MLD ≤ 20 Gy
Heart	V40 ≤ 80 %; V45 ≤ 60%; V60 ≤ 30%; Mean ≤ 35 Gy
Esophagus	Mean ≤ 34 Gy; Max ≤ 105% of prescription dose
Brachial plexus	Max ≤ 66 Gy

Vxx = % of the whole OAR receiving ≥ xx Gy.

Figure 1. ICRU Report 62 schema of target volume definitions



NCCN Guidelines Version 3.2012 Staging
Non-Small Cell Lung Cancer

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Table 6. Definitions for T, N, M*

T	Primary Tumor
TX	Primary tumor cannot be assessed, or tumor proven by the presence of malignant cells in sputum or bronchial washings but not visualized by imaging or bronchoscopy
T0	No evidence of primary tumor
Tis	Carcinoma in situ
T1	Tumor ≤ 3 cm in greatest dimension, surrounded by lung or visceral pleura, without bronchoscopic evidence of invasion more proximal than the lobar bronchus (i.e., not in the main bronchus)[a]
T1a	Tumor ≤ 2 cm in greatest dimension
T1b	Tumor > 2 cm but ≤ 3 cm in greatest dimension
T2	Tumor > 3 cm but ≤ 7 cm or tumor with any of the following features:[b] Involves main bronchus, ≥ 2 cm distal to the carina Invades visceral pleura Associated with atelectasis or obstructive pneumonitis that extends to the hilar region but does not involve the entire lung
T2a	Tumor > 3 cm but ≤ 5 cm in greatest dimension
T2b	Tumor > 5 cm but ≤ 7 cm in greatest dimension
T3	Tumor > 7 cm or one that directly invades any of the following: chest wall (including superior sulcus tumors), diaphragm, phrenic nerve, mediastinal pleura, parietal pericardium; or tumor in the main bronchus < 2 cm distal to the carina[a] but without involvement of the carina; or associated atelectasis or obstructive pneumonitis of the entire lung or separate tumor nodule(s) in the same lobe
T4	Tumor of any size that invades any of the following: mediastinum, heart, great vessels, trachea, recurrent laryngeal nerve, esophagus, vertebral body, carina; separate tumor nodule(s) in a different ipsilateral lobe

N	Regional Lymph Nodes
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in ipsilateral peribronchial and/or ipsilateral hilar lymph nodes and intrapulmonary nodes, including involvement by direct extension
N2	Metastasis in ipsilateral mediastinal and/or subcarinal lymph node(s)
N3	Metastasis in contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene, or supraclavicular lymph node(s)

M	Distant Metastasis
MX	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis
M1a	Separate tumor nodule(s) in a contralateral lobe; tumor with pleural nodules or malignant pleural (or pericardial) effusion[c]
M1b	Distant metastasis

[a] The uncommon superficial spreading tumor of any size with its invasive component limited to the bronchial wall, which may extend proximally to the main bronchus, is also classified as T1.

[b] T2 tumors with these features are classified T2a if ≤ 5 cm or if size cannot be determined, and T2b if > 5 cm but ≤ 7 cm

[c] Most pleural (and pericardial) effusions with lung cancer are due to tumor. In a few patients, however, multiple cytopathologic examinations of pleural (pericardial) fluid are negative for tumor, and the fluid is nonbloody and is not an exudate. Where these elements and clinical judgment dictate that the effusion is not related to the tumor, the effusion should be excluded as a staging element and the patient should be classified as T1, T2, T3, or T4.

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Table 7. Descriptors, T and M Categories, and Stage Grouping*

Sixth Edition T/M Descriptor	7th Edition T/M	N0	N1	N2	N3
T1 (less than or equal to 2 cm)	T1a	IA	IIA	IIIA	IIIB
T1 (>2–3 cm)	T1b	IA	IIA	IIIA	IIIB
T2 (less than or equal to 5 cm)	T2a	IB	**IIA**	IIIA	IIIB
T2 (>5–7 cm)	T2b	**IIA**	IIB	IIIA	IIIB
T2 (> 7 cm)	T3	**IIB**	**IIIA**	IIIA	IIIB
T3 invasion		IIB	IIIA	IIIA	IIIB
T4 (same lobe nodules)		**IIB**	**IIIA**	**IIIA**	IIIB
T4 (extension)	T4	**IIIA**	**IIIA**	IIIB	IIIB
M1 (ipsilateral lung)		**IIIA**	**IIIA**	**IIIB**	**IIIB**
T4 (pleural effusion)	M1a	**IV**	**IV**	**IV**	**IV**
M1 (contralateral lung)		IV	IV	IV	IV
M1 (distant)	M1b	IV	IV	IV	IV

Cells in bold indicate a change from the sixth edition for a particular TNM category.

Polmone: anatomia topografica

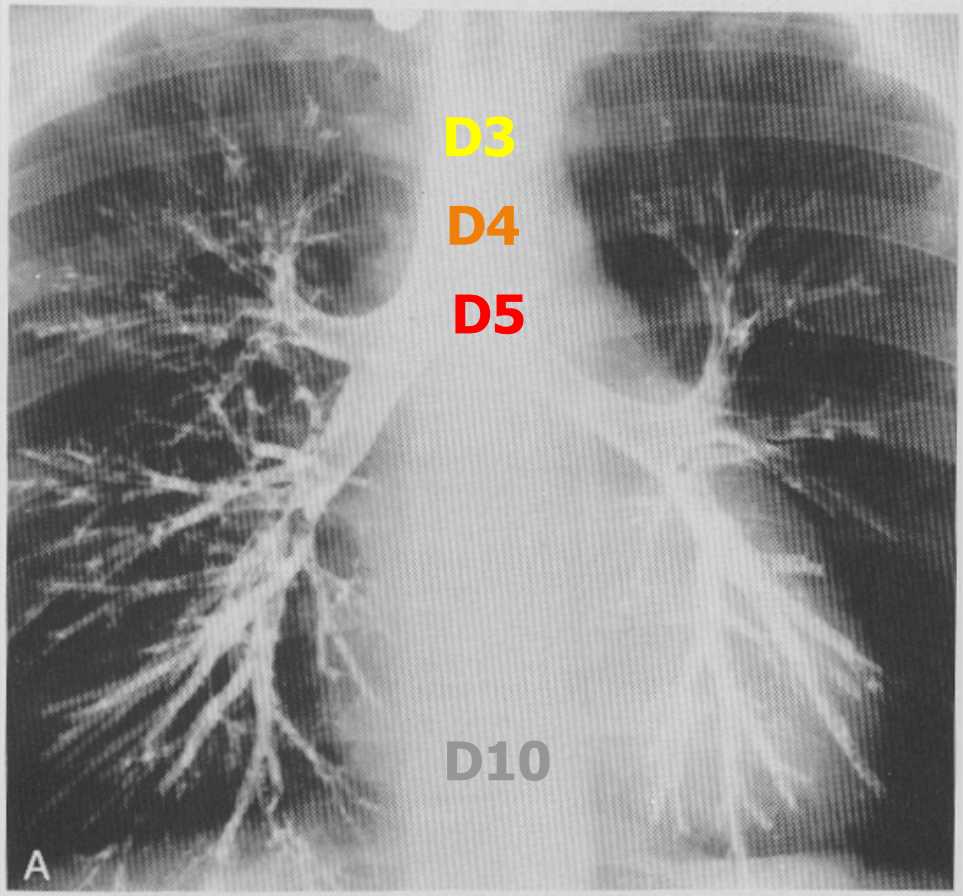
RIFERIMENTI 2D

Mediastino: D3-D10

Giugulo: D3

Arco aortico: D4

Carena: D5



Polmone: stazioni linfonodali

12. Lobari

13. Segmentari

14. Subsegmentari

11. Interlobari

10R-10L. Ilari

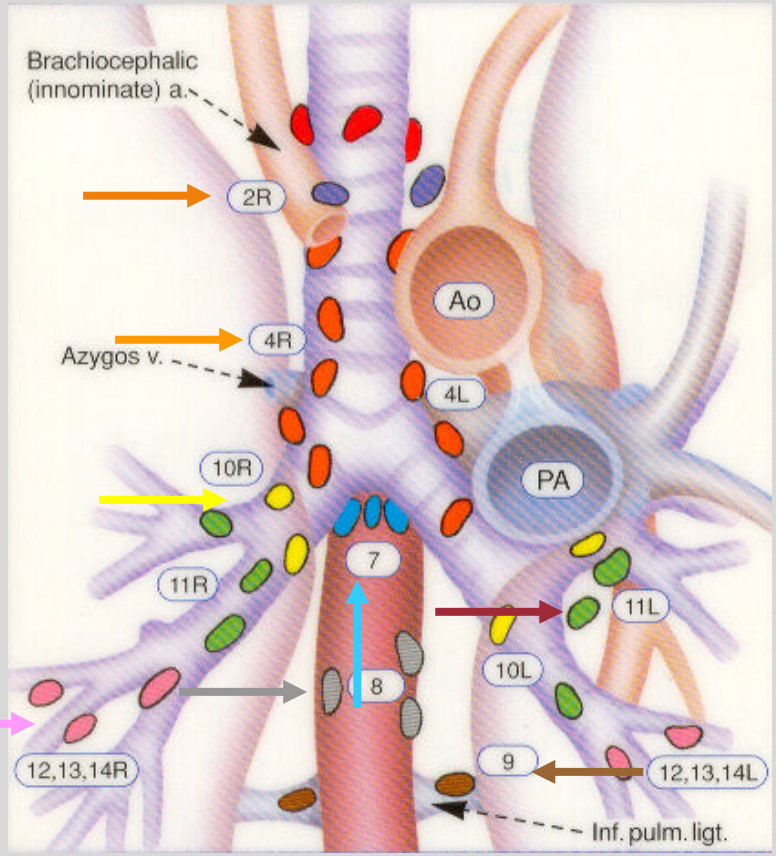
2R-2L. Paratracheali superiori

4R-4L. Paratracheali inferiori

7. Sottocarenali

8. Paraesofagei

9. Legamento polmonare



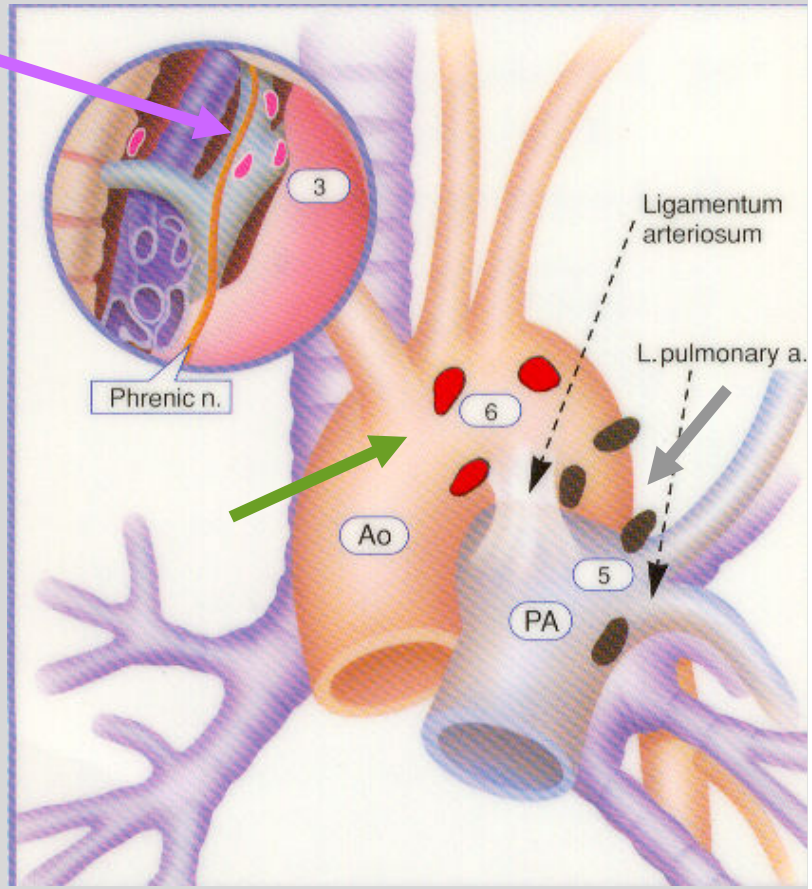
Classificazione linfonodale di Mountain e Dresler

Polmone: stazioni linfonodali

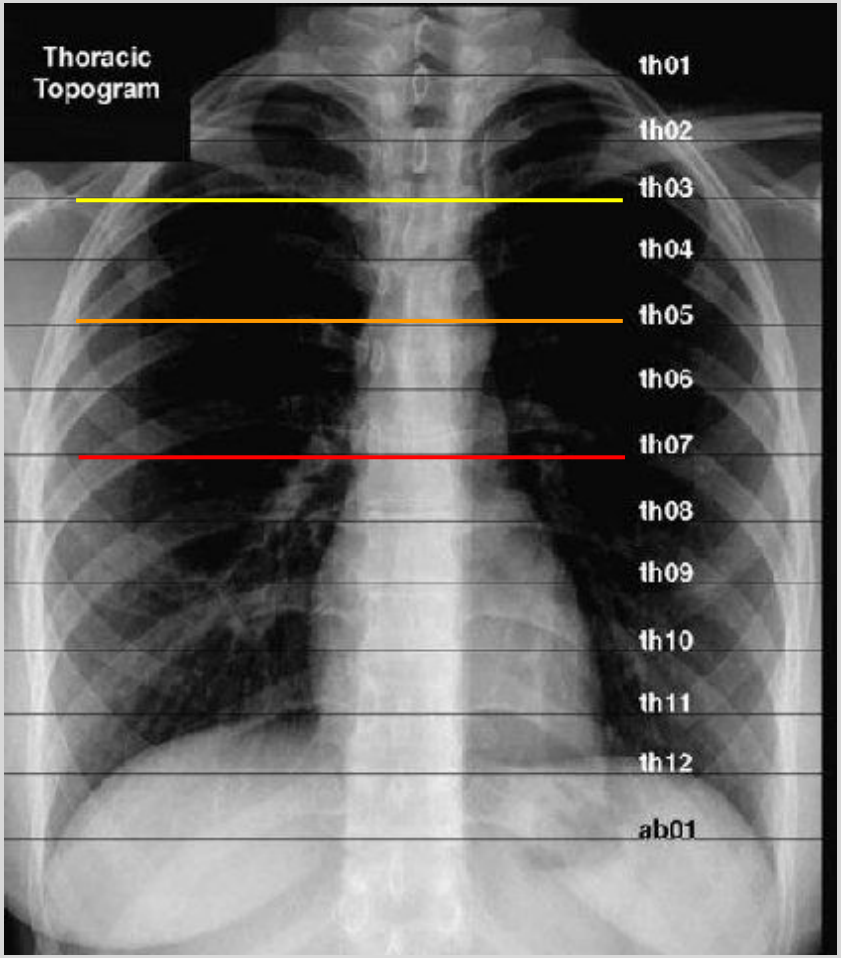
3. Prevascolari e retrotracheali

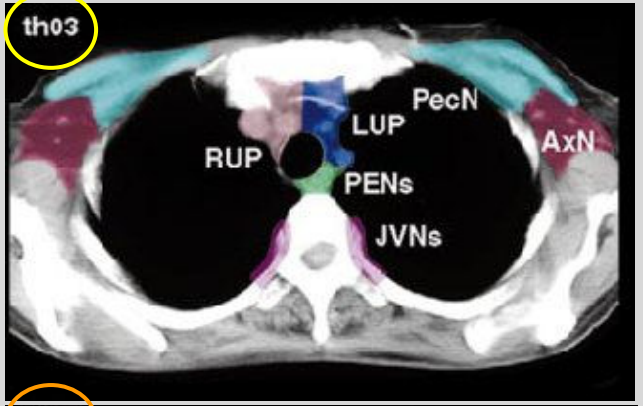
5. Finestra Aorto-Polmonare

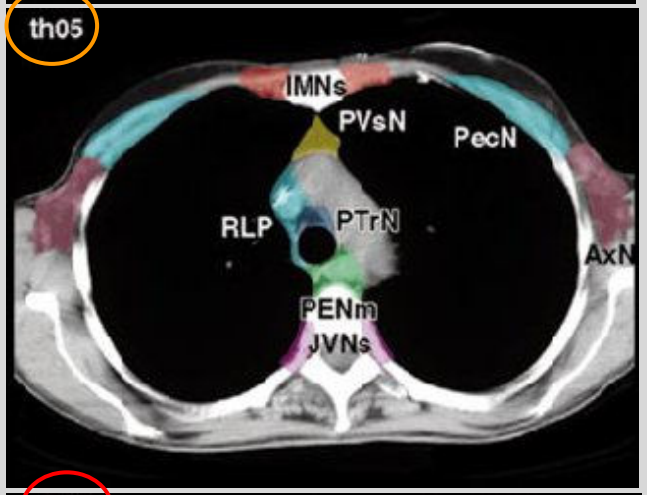
6. Para-aortici o frenici

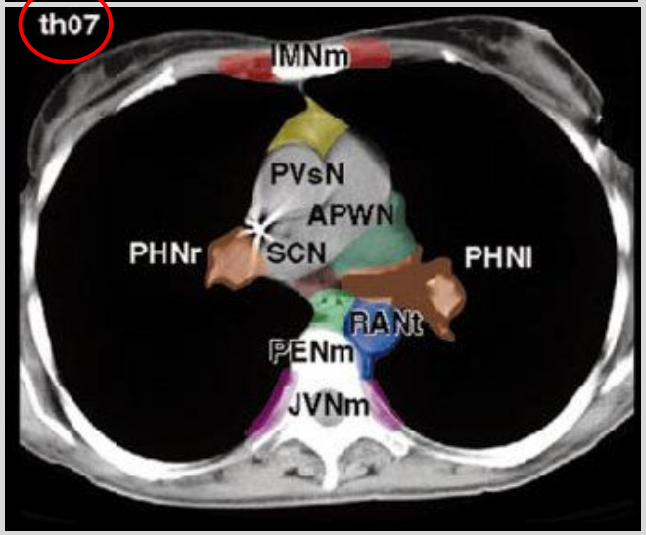


Classificazione linfonodale di Mountain e Dresler


Thoracic
Topogram
th01
th02
th03
th04
th05
th06
th07
th08
th09
th10
th11
th12
ab01


th03
PecN
LUP
AxN
RUP
PENs
JVNs


th05
IMNs
PVsN
PecN
RLP
PTrN
AxN
PENm
JVNs


th07
IMNm
PVsN
APWN
PHNr
SCN
PHNl
RANt
PENm
JVNm

Riduzione di volume polmonare irradiato

- Migliore definizione di GTV – CTV
  sulla base della estensione infraclinica microscopica
  carcinomi squamocellulari: margini 6 mm
  adenocarcinomi: margini 8 mm

Giraud P, Int J Radiat Oncol Biol Phys, 2000

- Migliore riproducibilità del set-up del paziente
- Riduzione della mobilità degli organi interni

↓

Riduzione volumetrica del PTV T e PTV N

In termini di controllo locale, “involved field” equivalente alla tecnica tradizionale “extended field”

Programmi di dose escalation

Criticità nella contornazione dei volumi polmonari

- Difficoltà di differenziare aree di consolidamento (atelettasia, ritenzione di secrezioni) dal tumore
- Effetti di volume parziale (normale anatomia di vasi versus tumore)
- Corretta interpretazione di manifestazioni pleuriche (effusione reattiva versus infiltrazione)
- Manifestazioni della parete toracica (infiltrazione o meno)
- Quadri clinici degli apici polmonari (definizione dell'estensione di un tumore di Pancoast)
- Fisiologica motilità del volume bersaglio

Grado di mobilità e sede tumorale

- Maggiore mobilità di tumori localizzati in prossimità del diaframma
- Minore mobilità di tumori localizzati agli apici

Margini personalizzati (“patient-based”)

Riduzione dell'internal margin in fase di trattamento: metodiche

- Compressione addominale
- DIBH: deep inspiration breath holding
- ABC: active breathing coordinator
- Target tracking
- Gated radiotherapy

- Impiego di specifiche finestre contrastografiche modulabili in ciascuno scenario anatomo - radiologico
- Training interdisciplinare radioterapista-radiologo
- Acquisizione volumetrica TC in regime di respiro controllato

Cancer Imaging (2006) **6**, 116–123
DOI: 10.1102/1470-7330.2006.0019

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REVIEW

Volume definition in radiotherapy planning for lung cancer: how the radiologist can help

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Date accepted for publication 30 May 2006

Abstract

Effective treatment for carcinoma of the lung remains one of the biggest challenges in oncology. Radical radiotherapy may be a curative option for patients who are unsuitable for radical surgery either because of disease stage or because of co-morbidity. Long-term disease control with radical radiotherapy is disappointing with only about 6% of patients treated being alive at 5 years[1]. Technological advances involved in the planning and delivery of radiotherapy may improve this. The advent of conformal radiotherapy, utilizing computed tomography and three-dimensional planning systems, allows much more accurate shaping of the radiation fields. This greater accuracy of target volume definition facilitates a reduction in the radiation dose to normal tissues, allowing for dose escalation to the tumour. Delineation of the target volume can be problematic. Conventional CT has limitations in term of distinguishing between benign and malignant tissues, e.g. the size criteria for involved lymph nodes. The oncologist uses a combination of radiological and clinical information when defining the target volume but their radiological interpretation of imaging is inferior to that of a radiologist.

The Royal College of Radiologists (RCR) issued guidance in 2004 on the optimal imaging strategies for common cancers. These guidelines address issues regarding the localisation and staging of cancers and treatment planning, and also reporting and training. They recommend the development of closer links between radiologists and oncologists to optimise the interpretation of imaging and target volume definition.

This article aims to briefly explain the planning process involved in irradiating lung cancers, highlight problematic areas and suggest ways in which co-operation with radiologists may improve the delivery of radiotherapy and therefore the treatment outcomes for this group of patients.

Definizione dei volumi dopo chemioterapia di induzione

- Contornazione delle sedi di malattia (GTVs e CTVs) basata sul quadro di malattia all'esordio (pre-chemioterapia) o sul nuovo quadro di malattia alla ristadiazione post-chemioterapia?

- Progressivo orientamento nei confronti di una prescrizione dei volumi bersaglio post-chemioterapici

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0360-3016/07/$–see front matter

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CLINICAL INVESTIGATION **Lung**

SHRINKAGE OF LOCALLY ADVANCED NON–SMALL-CELL LUNG CANCERS IN RESPONSE TO INDUCTION CHEMOTHERAPY: IMPLICATIONS FOR RADIOTHERAPY TREATMENT PLANNING

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Purpose: To quantify the impact that changes in tumor volume after induction chemotherapy have on radiotherapy treatment planning for locally advanced non–small-cell lung cancer.

Methods and Materials: An analysis of coregistered pre- and postchemotherapy tumor volumes in a Phase II study of induction chemotherapy delivered before radical radiotherapy.

Results: Using the Response Evaluation Criteria In Solid Tumors measurement, 35% of patients had a partial response and 62% had stable disease after chemotherapy. Conversely, volumetric decreases in tumor size were seen in 95% of patients. Mean decreases in gross tumor volume and planning target volume were 37% and 26%, respectively. Using the smaller postchemotherapy tumor volume to plan radiotherapy treatment leads to a mean decrease in volume of lung receiving 20 Gy or greater of 3% ($p < 0.005$). Targeting the postchemotherapy volume also results in the delivery of a significant, although inhomogeneous, incidental dose of radiation to the rind of tissue formed around the shrinking tumor. Disease shrinkage is anisotropic, with greater displacements observed along anterior, posterior, and lateral margins. After chemotherapy, there is measurable blurring of the tumor's radiologic edge.

Conclusions: Modest decreases in tumor volume that are not reflected by the Response Evaluation Criteria In Solid Tumors measurement occur in most patients. Although targeting the postchemotherapy tumor may decrease lung toxicity, the magnitude of the benefit is small. Because this strategy runs the risk of increasing the marginal recurrence rate, it should be used with caution. Quantification of tumor shrinkage and margin blurring permits more accurate reconstruction of the prechemotherapy target volume.

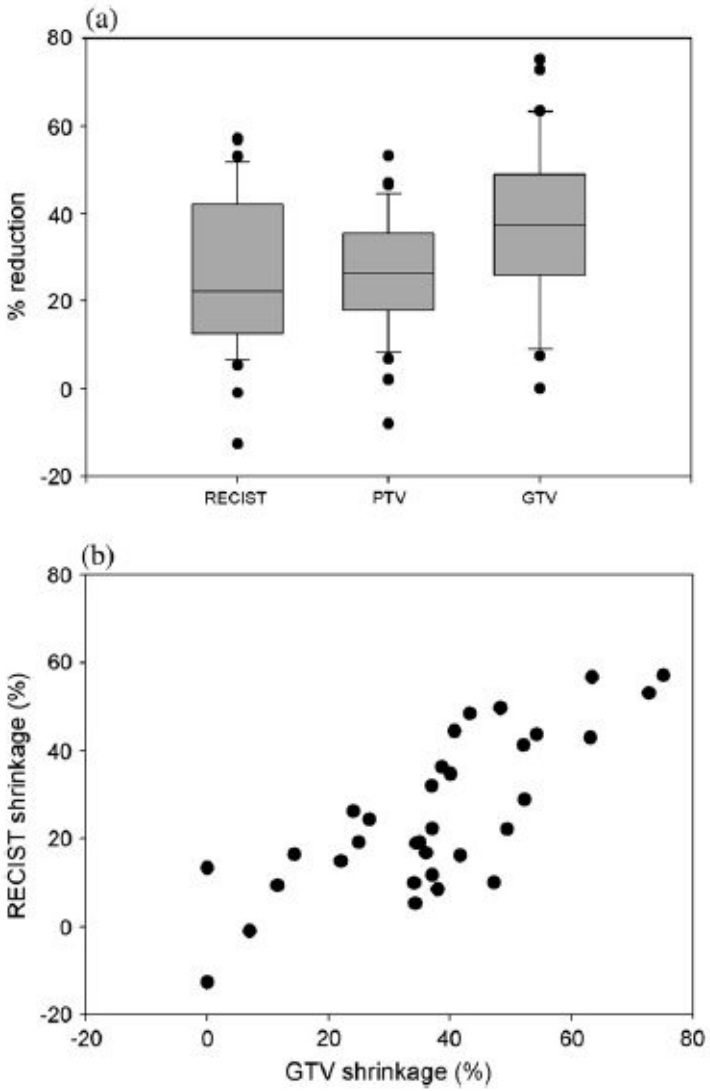


Fig. 1. (a) The magnitude of tumor shrinkage quantified using the Response Evaluation Criteria In Solid Tumors (RECIST) measurement or volumetric decrease in planning target volume (PTV) or gross tumor volume (GTV; $n = 33$). Four patients who had lobar or segmental collapse and 1 patient who developed distant progression were omitted. (b) Correlation between tumor shrinkage measured volumetrically and using RECIST.

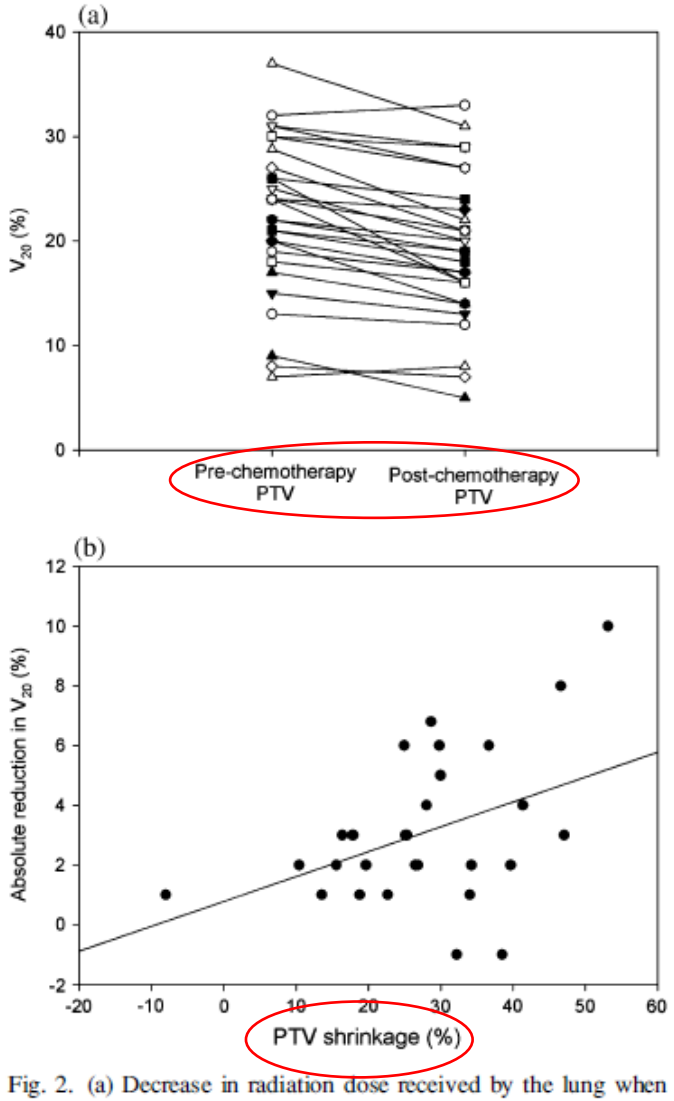


Fig. 2. (a) Decrease in radiation dose received by the lung when postchemotherapy rather than prechemotherapy tumor volume is used to target radiotherapy ($n = 30$). The fractional volume of lung receiving 20 Gy or greater (V_{20}) was defined for the entire lung after subtracting the planning target volume (PTV). Data from 4 patients with lobar or segmental collapse, 1 patient who developed distant progression, and 3 patients with poor registration accuracy were omitted. (b) Correlation between absolute decrease in V_{20} and shrinkage of the PTV ($r = 0.4$).

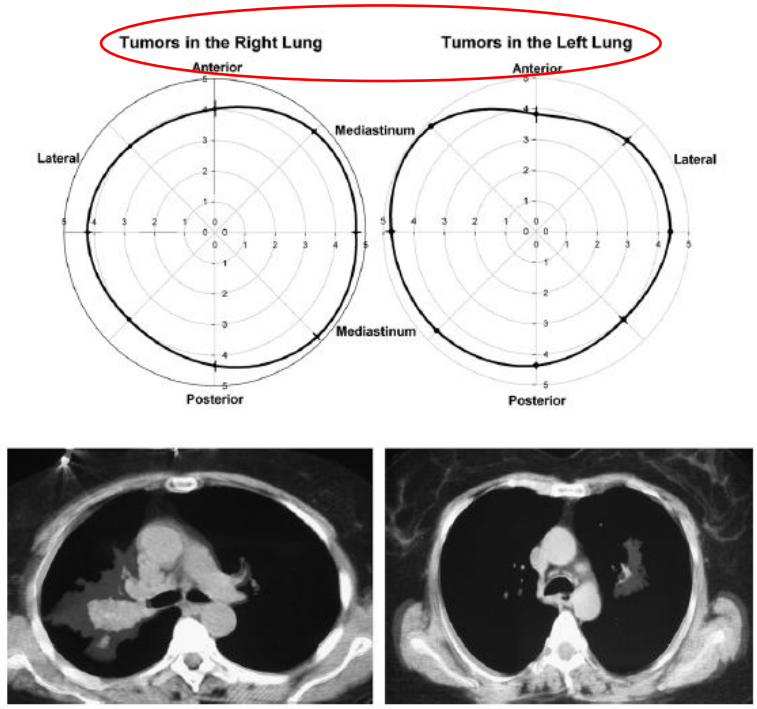
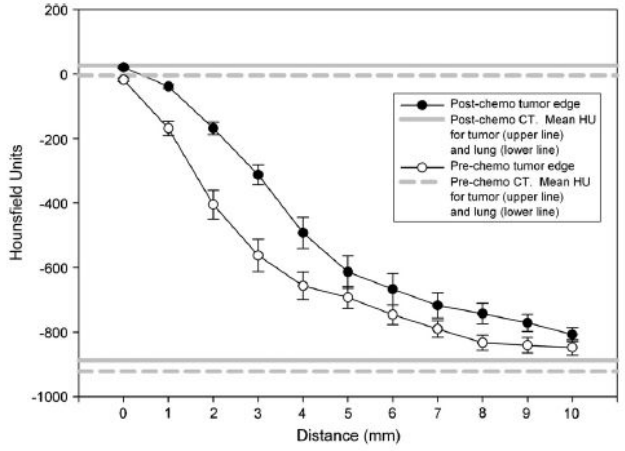


Fig. 3. The pattern of tumor shrinkage with chemotherapy. (Top panel) Prechemotherapy tumor volumes were normalized arbitrarily to a 5-cm diameter circle. Mean displacements and standard errors of the tumor edge are plotted for 20 tumors in the right and 10 in the left lung. (Bottom panel) Overlaid images illustrate the anisotropic nature of tumor shrinkage.



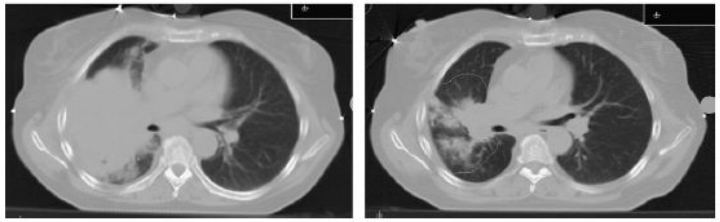


Fig. 4. The effect of chemotherapy on the tumor margin. (Top panel) Computed tomographic (CT) numbers (Hounsfield units [HU]) were recorded for 10 adjacent voxels along 20 lines perpendicular to the edge of the tumor. Mean values and standard errors are plotted for one patient. (Bottom panel) Pre- (left) and postchemotherapy (right) CT scans. Despite considerable shrinkage, the true edge of the tumor is more difficult to determine on the postchemotherapy scan because of blurring.

Definizione dei volumi nella radioterapia post-operatoria

Irradiazione di tutti i potenziali siti di malattia microscopica endotoracici

- Moncone bronchiale
- Eventuali siti di residuo micro-macroscopico di malattia
- Regione ilare omolaterale
- Intero mediastino

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doi:10.1016/j.ijrobp.2009.02.072

CLINICAL INVESTIGATION **Lung**

VARIATIONS IN TARGET VOLUME DEFINITION FOR POSTOPERATIVE RADIOTHERAPY IN STAGE III NON–SMALL-CELL LUNG CANCER: ANALYSIS OF AN INTERNATIONAL CONTOURING STUDY

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Purpose: Postoperative radiotherapy (PORT) in patients with completely resected non–small-cell lung cancer with mediastinal involvement is controversial because of the failure of earlier trials to demonstrate a survival benefit. Improved techniques may reduce toxicity, but the treatment fields used in routine practice have not been well studied. We studied routine target volumes used by international experts and evaluated the impact of a contouring protocol developed for a new prospective study, the Lung Adjuvant Radiotherapy Trial (Lung ART).

Methods and Materials: Seventeen thoracic radiation oncologists were invited to contour their routine clinical target volumes (CTV) for 2 representative patients using a validated CD-ROM–based contouring program. Subsequently, the Lung ART study protocol was provided, and both cases were contoured again. Variations in target volumes and their dosimetric impact were analyzed.

Results: Routine CTVs were received for each case from 10 clinicians, whereas six provided both routine and protocol CTVs for each case. Routine CTVs varied up to threefold between clinicians, but use of the Lung ART protocol significantly decreased variations. Routine CTVs in a postlobectomy patient resulted in V_{20} values ranging from 12.7% to 54.0%, and Lung ART protocol CTVs resulted in values of 20.6% to 29.2%. Similar results were seen for other toxicity parameters and in the postpneumectomy patient. With the exception of upper paratracheal nodes, protocol contouring improved coverage of the required nodal stations.

Conclusion: Even among experts, significant interclinician variations are observed in PORT fields. Inasmuch as contouring variations can confound the interpretation of PORT results, mandatory quality assurance procedures have been incorporated into the current Lung ART study.

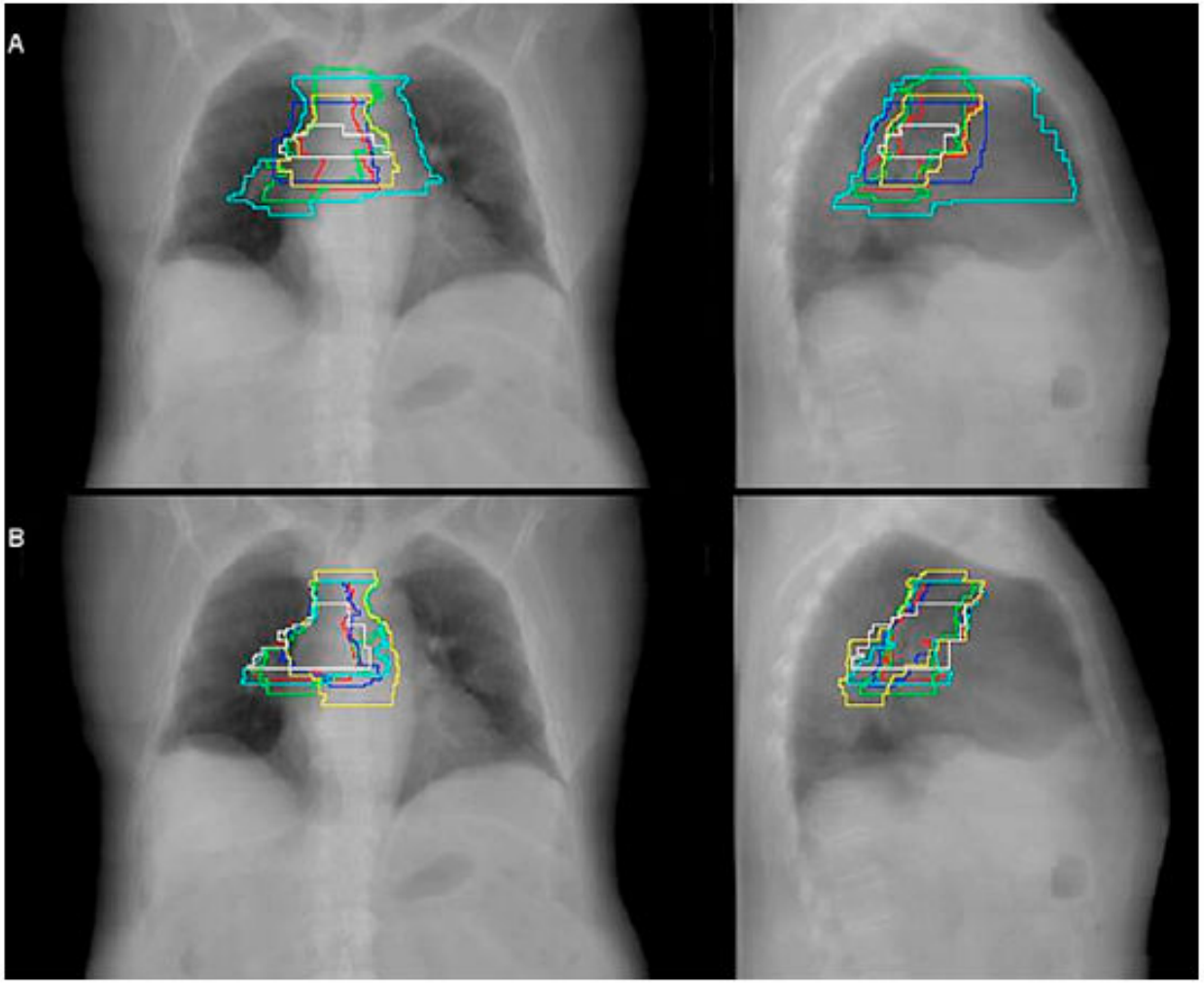

Fig. 1. Routine clinical target volumes (CTVs) (upper panel) and protocol CTVs (lower panel) from six observers projected on a digital reconstruction of a computed tomography dataset from the postlobectomy patient.

Strategia adaptive per ridurre il volume di trattamento in corso di radioterapia radicale

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0360-3016/$–see front matter

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doi:10.1016/j.ijrobp.2010.04.002

CLINICAL INVESTIGATION **Lung**

DAILY MEGAVOLTAGE COMPUTED TOMOGRAPHY IN LUNG CANCER RADIOTHERAPY: CORRELATION BETWEEN VOLUMETRIC CHANGES AND LOCAL OUTCOME

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Purpose: To assess the predictive or comparative value of volumetric changes, measured on daily megavoltage computed tomography during radiotherapy for lung cancer.

Patients and Methods: We included 80 patients with locally advanced non–small-cell lung cancer treated with image-guided intensity-modulated radiotherapy. The radiotherapy was combined with concurrent chemotherapy, combined with induction chemotherapy, or given as primary treatment. Patients entered two parallel studies with moderately hypofractionated radiotherapy. Tumor volume contouring was done on the daily acquired images. A regression coefficient was derived from the volumetric changes on megavoltage computed tomography, and its predictive value was validated. Logarithmic or polynomial fits were applied to the intratreatment changes to compare the different treatment schedules radiobiologically.

Results: Regardless of the treatment type, a high regression coefficient during radiotherapy predicted for a significantly prolonged cause-specific local progression free-survival ($p = 0.05$). Significant differences were found in the response during radiotherapy. The significant difference in volumetric treatment response between radiotherapy with concurrent chemotherapy and radiotherapy plus induction chemotherapy translated to a superior long-term local progression-free survival for concurrent chemotherapy ($p = 0.03$). An enhancement ratio of 1.3 was measured for the used platinum/taxane doublet in comparison with radiotherapy alone.

Conclusion: Contouring on daily megavoltage computed tomography images during radiotherapy enabled us to predict the efficacy of a given treatment. The significant differences in volumetric response between treatment strategies makes it a possible tool for future schedule comparison. © 2011 Elsevier Inc.

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doi:10.1016/j.ijrobp.2010.04.050

PHYSICS CONTRIBUTION

POTENTIAL OF ADAPTIVE RADIOTHERAPY TO ESCALATE THE RADIATION DOSE IN COMBINED RADIOCHEMOTHERAPY FOR LOCALLY ADVANCED NON–SMALL CELL LUNG CANCER

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Purpose: To evaluate the potential of adaptive radiotherapy (ART) for advanced-stage non–small cell lung cancer (NSCLC) in terms of lung sparing and dose escalation.

Methods and Materials: In 13 patients with locally advanced NSCLC, weekly CT images were acquired during radio- ($n = 1$) or radiochemotherapy ($n = 12$) for simulation of ART. Three-dimensional (3D) conformal treatment plans were generated: conventionally fractionated doses of 66 Gy were prescribed to the planning target volume without elective lymph node irradiation (Plan_3D). Using a surface-based algorithm of deformable image registration, accumulated doses were calculated in the CT images acquired during the treatment course (Plan_4D). Field sizes were adapted to tumor shrinkage once in week 3 or 5 and twice in weeks 3 and 5.

Results: A continuous tumor regression of 1.2% per day resulted in a residual gross tumor volume (GTV) of 49% ± 15% after six weeks of treatment. No systematic differences between Plan_3D and Plan_4D were observed regarding doses to the GTV, lung, and spinal cord. Plan adaptation to tumor shrinkage resulted in significantly decreased lung doses without compromising GTV coverage: single-plan adaptation in Week 3 or 5 and twice-plan adaptation in Weeks 3 and 5 reduced the mean lung dose by 5.0% ± 4.4%, 5.6% ± 2.9% and 7.9% ± 4.8%, respectively. This lung sparing with twice ART allowed an iso–mean lung dose escalation of the GTV dose from 66.8 Gy ± 0.8 Gy to 73.6 Gy ± 3.8 Gy.

Conclusions: Adaptation of radiotherapy to continuous tumor shrinkage during the treatment course reduced doses to the lung, allowed significant dose escalation and has the potential of increased local control.

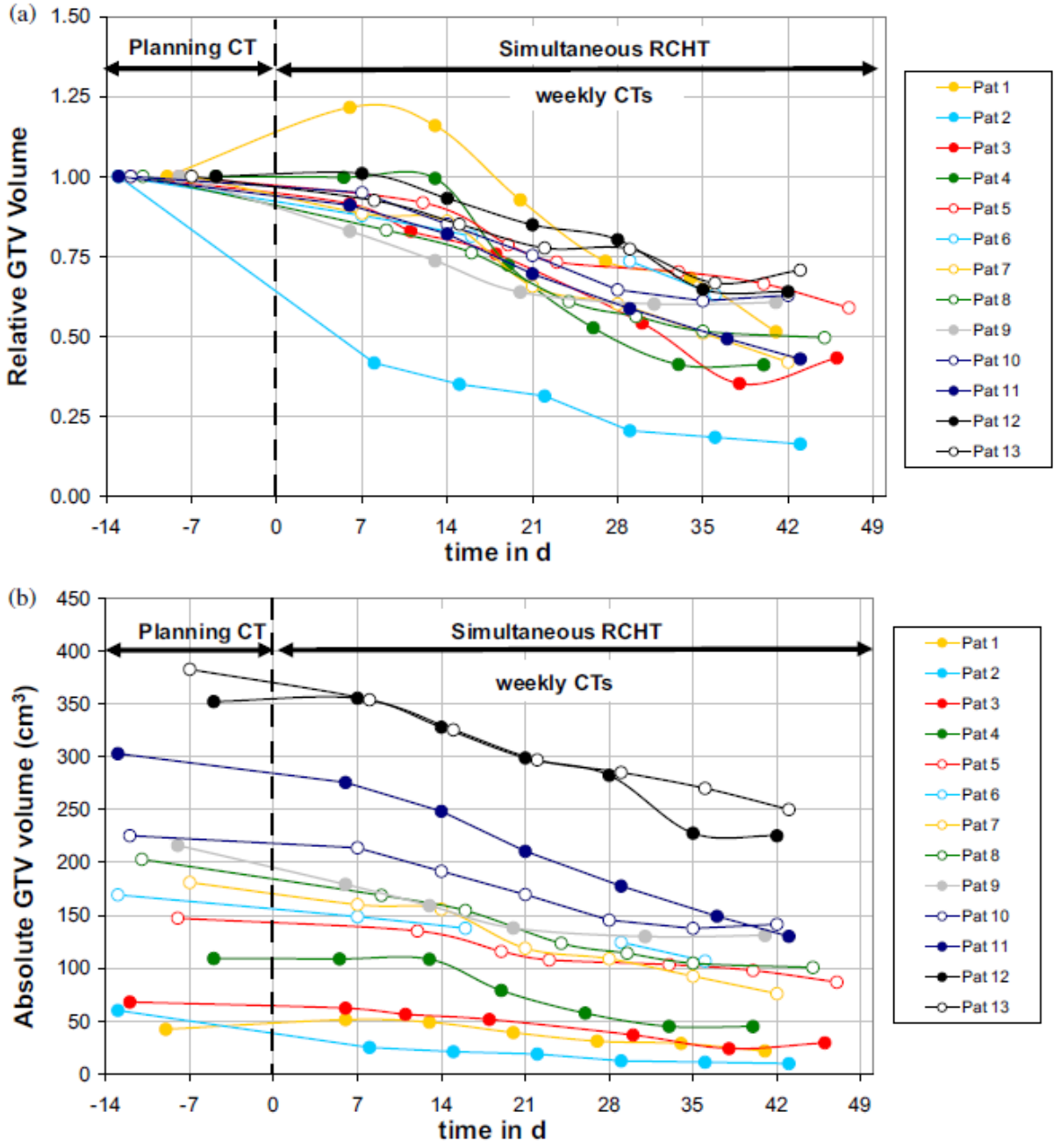

Fig. 1. Relative (a) and absolute (b) gross tumor volumes (GTV) during radio- and radiochemotherapy (RCHT) individually for all 13 patients.

Table 3. Comparison of doses to the GTV, lung, and spinal cord for Plan_3D, Plan_4D, Plan_4D-Adapt3, Plan_4D-Adapt5, and Plan_4D-Adapt3&5.

	Plan_3D	Plan_4D	Plan_4D-Adapt3	Plan_4D-Adapt5	Plan_4D-Adapt3&5
	Average ± SD (Gy)	Average ± SD (Gy)	Average ± SD (Gy)	Average ± SD (Gy)	Average ± SD (Gy)
GTV					
Mean dose	66.6 ± 0.3	66.8 ± 0.8	66.8 ± 1.0	66.9 ± 0.4	66.7 ± 0.9
D99	64.2 ± 0.7	64.4 ± 0.9	64.6 ± 1.0	64.0 ± 2.4	63.8 ± 3.0
D95	64.8 ± 0.6	65.1 ± 0.7	65.2 ± 0.9	65.0 ± 1.3	64.8 ± 1.8
D5	68.7 ± 0.6	68.6 ± 1.2	68.4 ± 1.3	68.6 ± 0.5	68.3 ± 0.9
Lungs – GTV					
MLD	17.7 ± 3.9	17.9 ± 4.1	17.0 ± 3.9	16.9 ± 3.9	16.5 ± 3.8
Spinal cord					
$D1cm^3$	41.7 ± 4.7	42.5 ± 5.0	41.7 ± 4.8	41.6 ± 5.1	41.1 ± 5.0

Abbreviations: $D1cm^3$ = dose to 1 cm^3 of the spinal cord; Dx = minimum dose to x% of the reference volume); GTV = gross tumor volume; MLD = mean lung dose.

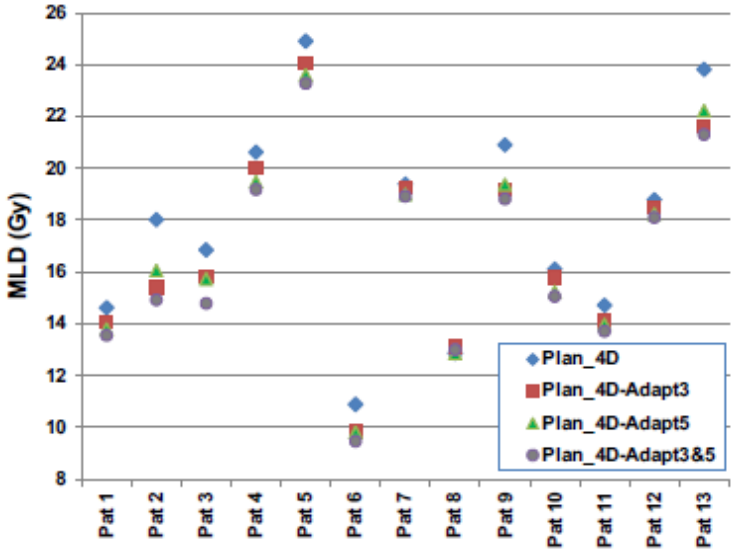

Fig. 2. Patient individual values of the mean lung dose (MLD) without and with adaptive radiotherapy.

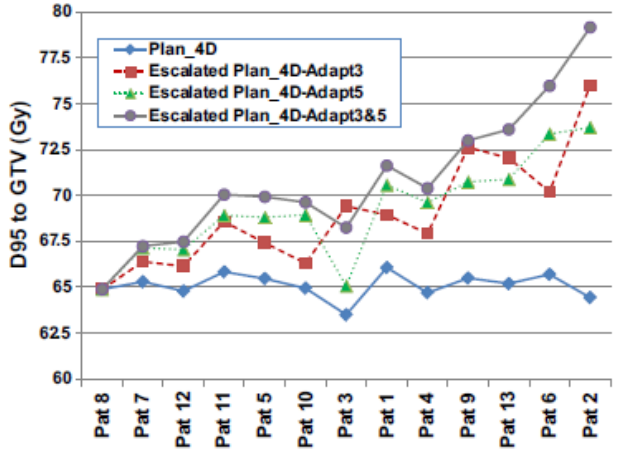

Fig. 4. Individual patient data of D95 (minimum dose to 95% of the reference volume) to the gross tumor volumes (GTV) for plans without adaptive radiotherapy (Plan_4D) and plans with iso-MLD (mean lung dose) dose escalation using adaptive radiotherapy. Note that the order of patients (Pat) has been adjusted according to increasing benefit of ART.

Ruolo della PET nella pianificazione del trattamento

Table 1 Impact of (staging-) PET scan on radiotherapy treatment

	Changes in staging	Effect on radiotherapy
T-stage	Larger extension of primary tumour (upstaging)	Enlargement of radiotherapy fields to avoid geographical miss Change of radiotherapy indication from curative to palliative
	Less extension of primary tumour (downstaging)	Decrease in radiotherapy fields and hence decrease in radiation exposure of normal tissues, and thus possible allowing dose escalation Change of radiotherapy indication from palliative to curative
N-stage	Detection of new site of lymph node involvement (upstaging)	Enlargement of radiotherapy fields to avoid geographical miss Change of radiotherapy indication from curative to palliative
	Omission of enlarged lymph nodes, diagnosed as malignant on CT or MRI (down staging)	Change of radiotherapy indication from palliative to curative Decrease in radiotherapy fields and hence decrease in radiation exposure of normal tissues, and thus possible allowing dose escalation
M-stage	Detection of distant metastases	Change of radiotherapy indication from curative to palliative

- Migliore definizione del tumore rispetto ad aree atelettasiche o fibrotiche o reazioni pleuriche infiammatorie
- Inclusione di linfonodi captanti ma con morfologia e dimensioni normali alla TC
- Maggiori informazioni quantitative (morfologiche) e qualitative (funzionali)
- Riduzione delle variabilità inter e intra-osservatore

Definizione del Biological Target Volume (BTV)

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Special commentary

Positron emission tomography for target volume definition in the treatment of non-small cell lung cancer

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Abstract

The additional benefit of positron emission tomography (PET) in the initial staging of non-small cell lung cancer (NSCLC) has generated interest in ^{18}F-fluorodeoxyglucose (FDG) PET as a means of defining the extent of primary lung tumour for radiotherapy treatment planning (RTP). A review of published data suggests that PET results in a reduction in the CT-derived GTV for NSCLC primary target volume in 15% of the patients. This is principally due to the ability of PET to distinguish tumour from atelectasis. However, the difficulty of tumour edge definition, limited spatial resolution and tumour motion during image acquisition currently limits the accuracy of PET in target volume delineation in NSCLC without adjacent lung consolidation. This is compounded by the lack of data correlating PET with spatial pathology at the primary tumour site. With the current technical limitations, it is not established that PET can add accuracy to the CT-defined primary target delineation in RTP of NSCLC. It is hoped that advances in PET and combined PET/CT imaging may overcome some of the technical limitations. Future use of PET for primary tumour delineation in NSCLC will also be critically dependent on the detailed studies of imaging-pathology correlation.

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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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Abstract

The value of positron emission tomography using [^{18}F]-fluoro-deoxy-glucose (FDG-PET) for pretherapeutic evaluation of patients with non-small cell lung cancer (NSCLC) is beyond doubt. Due to the increasing availability of PET and PET-CT scanners the method is now widely available, and its technical integration has become possible for radiotherapy planning systems. Due to the depiction of malignant tissue with high diagnostic accuracy, the use of FDG-PET in radiotherapy planning of NSCLC is very promising. However, by uncritical application, PET could impair rather than improve the prognosis of patients. Therefore, in the present paper we give an overview of technical factors influencing PET and PET-CT data, and their consequences for radiotherapy planning. We further review the relevant literature concerning the diagnostic value of FDG-PET and on the integration of FDG-PET data in RT planning for NSCLC. We point out the possible impact in gross tumor volume (GTV) definition and describe methods of target volume contouring of the primary tumor, as well as concepts for the integration of diagnostic information on lymph node involvement into the clinical target volume (CTV), and the possible implications of PET data on the definition of the planning target volume (PTV). Finally, we give an idea of the possible future use of tracers other than [^{18}F]-FDG in lung cancer.

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REVIEW

Current status of PET/CT for tumour volume definition in radiotherapy treatment planning for non-small cell lung cancer (NSCLC)

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KEYWORDS
PET/CT scanners;
Functional imaging;
Non-small cell lung cancer;
Dose escalation;
Conformal radiotherapy;
Treatment planning;
Inter-observer variability;
Segmentation

Summary Target volume delineation of lung cancer is well known to be prone to large inter-observer variability. The advent of PET/CT devices, with co-registered functional and anatomical data, has opened new exciting possibilities for target volume definition in radiation oncology. PET/CT imaging is rapidly being embraced by the radiation oncology community as a tool to improve the accuracy of target volume delineation for treatment optimization in NSCLC. Several studies have dealt with the feasibility of incorporating FDG-PET information into contour delineation with the aim to improve overall accuracy and to reduce inter-observer variation. A significant impact of PET-derived contours on treatment planning has been shown in 30–60% of the plans with respect to the CT-only target volume. The most prominent changes in the gross tumour volume (GTV) have been reported in cases with atelectasis and following the incorporation of PET-positive nodes in otherwise CT-insignificant nodal areas. Although inter-observer variability is still present following target volume delineation with PET/CT, it is greatly reduced compared to conventional CT-only contouring. PET/CT may also provide improved therapeutic ratio compared to conventional CT planning. Increased target coverage and often reduced target volumes may potentially result in PET/CT-based planning to yield better tumour control probability through dose escalation, while still complying with dose/volume constrains for normal tissues. Despite these exciting results, more clinical studies need to be performed to better define the role of combined PET/CT in treatment planning for NSCLC.

Table 1 Studies assessing effect of FDG-PET target volume delineation in NSCLC

Author	Patients	Fusion method	Method of contour	Overall changes in GTV (%)	GTV increase (%)	GTV decrease (%)	Influence of PET on GTV: conclusions
Kiffer et al. [25]	15	Visual (graphical co-registration)	Visual	4/15 (27)	4/15 (27)	–	Increase in volume due to PET positive lymph-nodes
Munley et al. [26]	35	Visual (manual registration)	Visual	12/35 (34%)	12/35 (34)	–	Increase in beam aperture
Nestle et al. [12]	34	Visual	Visual	12/34 (35)	3/34 (9)	9/34 (26)	Significant reduction in portal field size in patients with atelectasis
Vanuytsel et al. [27]	73	Visual/Software	Visual	45/73 (62)	16/63 (22)	29/63 (40)	Patients with a reduction in with PET-CT-GTV had a significantly smaller PTV than if planned with CT-only ($p = 0.002$) allowing dose intensification
Mac Manus et al. [3]	102	Visual	Visual	38/102 (37)	22/102 (21)	16/102 (16)	30% of potential radical treatments were converted to palliative because of PET-detected distant metastases
Erdi et al. [11]	11	Software	42% of maximum level	11/11 (100)	7/11 (64)	4/11 (36)	Improvement of target delineation by including PET-positive lymph-nodes
Mah et al. [2]	30	Software	50% intensity level	5/23 (22)	5/23 (22)	–	GTV changes involved PET-positive nodes which were not localized on CT
Ciernik et al. [31]	6	Hardware		5/6 (83)	1/6 (17)	4/6 (66)	Mean change in PTV volume was 26%
Bradley et al. [9]	26	Software	≥2.5 SUV	14/24 (58)	11/24 (46)	3/24 (12)	Improvement in GTV coverage in > 50% of patients
Deniaud-Alexandre et al. [13]	101	Software	Visual	45/92 (49)	24/92 (26)	21/92 (23)	Atelectasis was the single independent factor to result in a significant effect in the size of the GTV (with atelectasis vs. without $p = 0.0001$)
Van der Wel et al. [29]	21	Visual	Visual	14/21 (67)	3/21 (14)	11/21 (52)	In N2–N3 patients, reduced PTV with fulfilment of normal tissue constraints allows significant dose escalation
Messa et al. [28]	18	Software	Visual (~40–50% maximum intensity)	10/18 (55)	7/18 (39)	3/18 (17)	GTV changes ≥25% mainly due to inclusion or exclusion of lymph-nodes
Ashamalla et al. [16]	19	Hardware	Halo phenomenon	10/19 (52%)	5/19 (26)	5/19 (26)	Improved GTV delineation accuracy and reduced inter-observer variability.
Grills et al. [34]	21	Hardware	Mean SUV regressive function	18/21 (86%)	10/20 (50)	7/21 (33%)	Although quantitatively often similar, CT- and PET-based volumes differed qualitatively, leading to underdosage of the target when planning done without PET data.
Gondi et al. [33]	14	Hardware	Standardization to background liver activity	–	12/14 (86)	2/14 (14%)	Target volume differences quantified in three-dimensional using a conformality index

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CLINICAL INVESTIGATION **Lung**

^{18}F-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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Purpose: ^{18}F-Fluorodeoxyglucose positron emission tomography/computed tomography (PET/CT) has benefits in target volume (TV) definition in radiotherapy treatment planning (RTP) for non–small-cell lung cancer (NSCLC); however, an optimal protocol for TV delineation has not been determined. We investigate volumetric and positional variation in gross tumor volume (GTV) delineation using a planning PET/CT among three radiation oncologists and a PET radiologist.

Methods and Materials: RTP PET/CT scans were performed on 28 NSCLC patients (Stage IA–IIIB) of which 14 patients received prior induction chemotherapy. Three radiation oncologists and one PET radiologist working with a fourth radiation oncologist independently delineated the GTV on CT alone (GTV_{CT}) and on fused PET/CT images (GTV_{PETCT}). The mean percentage volume change (PVC) between GTV_{CT} and GTV_{PETCT} for the radiation oncologists and the PVC between GTV_{CT} and GTV_{PETCT} for the PET radiologist were compared using the Wilcoxon signed-rank test. Concordance index (CI) was used to assess both positional and volume change between GTV_{CT} and GTV_{PETCT} in a single measurement.

Results: For all patients, a significant difference in PVC from GTV_{CT} to GTV_{PETCT} exists between the radiation oncologist (median, 5.9%), and the PET radiologist (median, -0.4%, $p = 0.001$). However, no significant difference in median concordance index (comparing GTV_{CT} and GTV_{FUSED} for individual cases) was observed (PET radiologist = 0.73; radiation oncologists = 0.66; $p = 0.088$).

Conclusions: Percentage volume changes from GTV_{CT} to GTV_{PETCT} were lower for the PET radiologist than for the radiation oncologists, suggesting a lower impact of PET/CT in TV delineation for the PET radiologist than for the oncologists. Guidelines are needed to standardize the use of PET/CT for TV delineation in RTP.

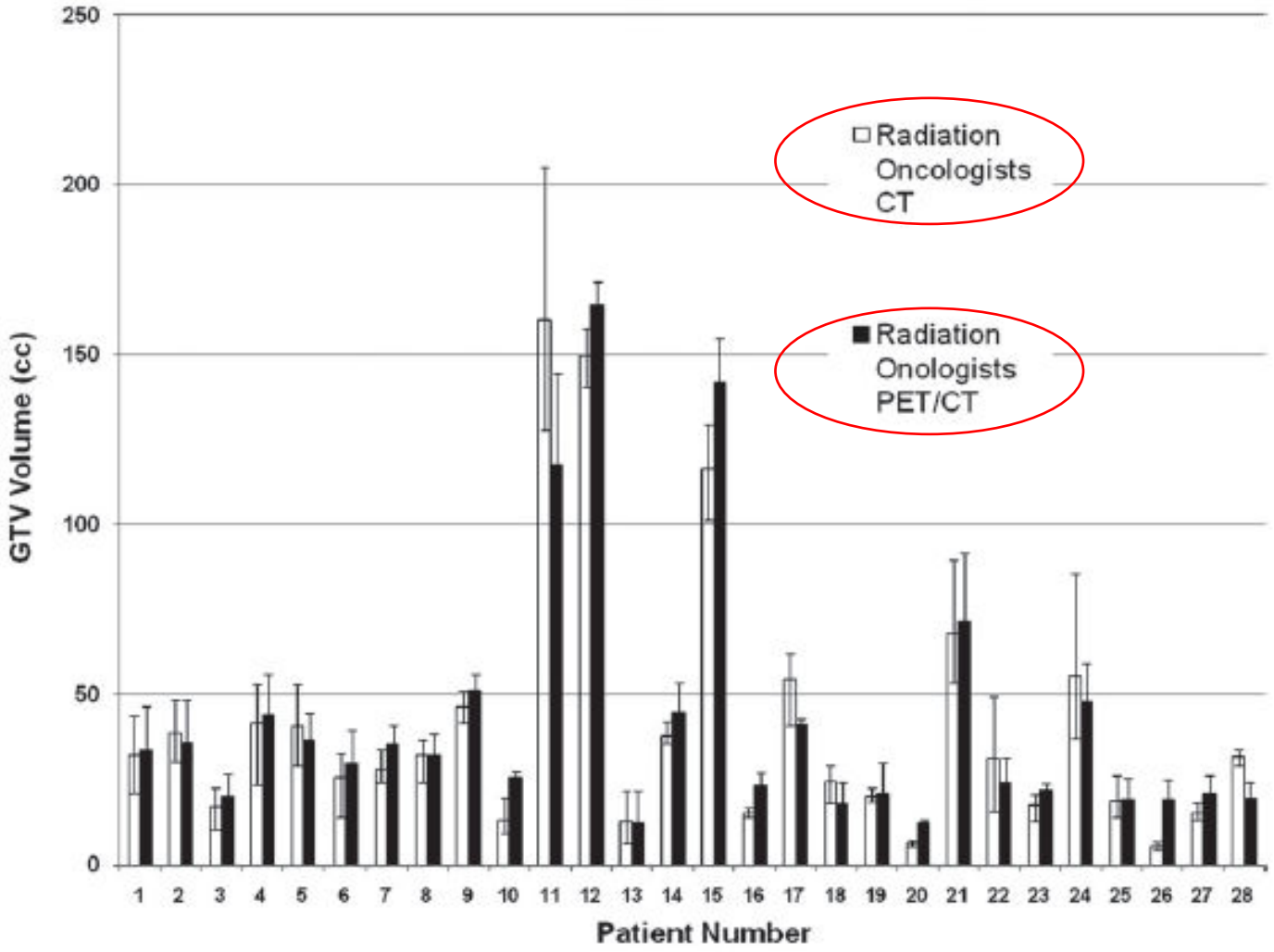

Fig. 1. Quantitative relationship between the mean gross tumor volume (GTV) as delineated by the three radiation oncologists on computed tomography (CT) alone and on then on positron emission tomography (PET/CT). The error bars represent the range of values obtained.

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CLINICAL INVESTIGATION **Lung**

^{18}F-FDG PET-CT SIMULATION FOR NON–SMALL-CELL LUNG CANCER: EFFECT IN PATIENTS ALREADY STAGED BY PET-CT

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Purpose: Positron emission tomography (PET), in addition to computed tomography (CT), has an effect in target volume definition for radical radiotherapy (RT) for non–small-cell lung cancer (NSCLC). In previously PET-CT staged patients with NSCLC, we assessed the effect of using an additional planning PET-CT scan for gross tumor volume (GTV) definition.

Methods and Materials: A total of 28 patients with Stage IA-IIIB NSCLC were enrolled. All patients had undergone staging PET-CT to ensure suitability for radical RT. Of the 28 patients, 14 received induction chemotherapy. In place of a RT planning CT scan, patients underwent scanning on a PET-CT scanner. In a virtual planning study, four oncologists independently delineated the GTV on the CT scan alone and then on the PET-CT scan. Intraobserver and interobserver variability were assessed using the concordance index (CI), and the results were compared using the Wilcoxon signed ranks test.

Results: PET-CT improved the CI between observers when defining the GTV using the PET-CT images compared with using CT alone for matched cases (median CI, 0.57 for CT and 0.64 for PET-CT, $p = .032$). The median of the mean percentage of volume change from GTV_{CT} to GTV_{FUSED} was −5.21% for the induction chemotherapy group and 18.88% for the RT-alone group. Using the Mann-Whitney U test, this was significantly different ($p = .001$).

Conclusion: PET-CT RT planning scan, in addition to a staging PET-CT scan, reduces interobserver variability in GTV definition for NSCLC. The GTV size with PET-CT compared with CT in the RT-alone group increased and was reduced in the induction chemotherapy group.

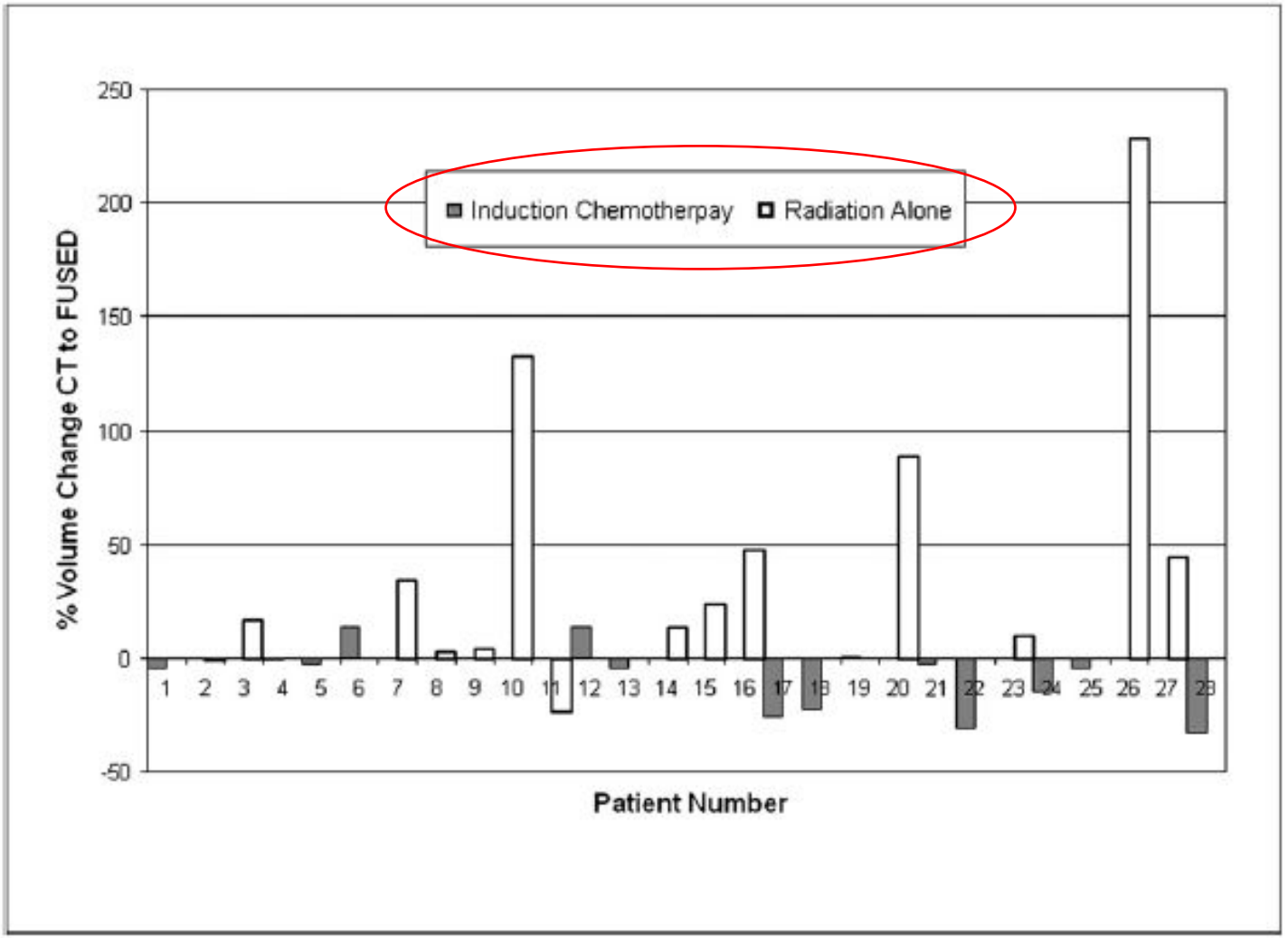

Fig 3. Quantitative relationship of volume change from gross tumor volume delineated on computed tomography (GTV_{CT}) to gross tumor volume delineated on fused (GTV_{FUSED}) outlining, expressed as percentage of ($GTV_{FUSED} - GTV_{CT}$)/ GTV_{CT}, to normalize GTV_{CT} volume. Positive values indicate larger GTV_{FUSED}; negative values indicate larger GTV_{CT}.

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Review

PET scans in radiotherapy planning of lung cancer

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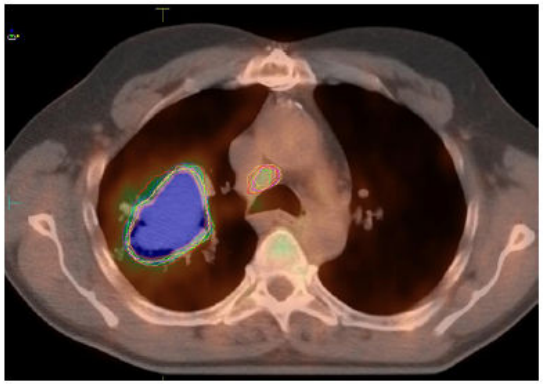

Fig. 1. Radiotherapy planning PET-CT image of a patient with NSCLC. Eight separate gross tumor volume (GTV) contours were drawn by blinded observers using a standardized visual contouring protocol. The image illustrates that standardization can produce a high level of reproducibility.

A B S T R A C T

Accurate delineation of the primary tumor and of involved lymph nodes is a key requisite for successful curative radiotherapy in non-small cell lung cancer (NSCLC). In recent years, it has become clear that the incorporation of FDG PET-CT scan information into the related processes of patient selection and radiotherapy planning has lead to significant improvements for patients with NSCLC. The use of FDG PET-CT information in radiotherapy planning allows better target volume definition, reduces inter-observer variability and encourages selective irradiation of involved mediastinal lymph nodes. PET-CT also opens the door for innovative radiotherapy delivery and the development of new concepts. However, care must be taken to avoid a variety of technical pitfalls and specific education is necessary, for clinicians and physicists alike.

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CLINICAL INVESTIGATION **Thoracic Cancer**

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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Background: Radiation Therapy Oncology Group (RTOG) 0515 is a Phase II prospective trial designed to quantify the impact of positron emission tomography (PET)/computed tomography (CT) compared with CT alone on radiation treatment plans (RTPs) and to determine the rate of elective nodal failure for PET/CT-derived volumes.

Methods: Each enrolled patient underwent definitive radiation therapy for non–small-cell lung cancer (≥60 Gy) and had two RTP datasets generated: gross tumor volume (GTV) derived with CT alone and with PET/CT. Patients received treatment using the PET/CT-derived plan. The primary end point, the impact of PET/CT fusion on treatment plans was measured by differences of the following variables for each patient: GTV, number of involved nodes, nodal station, mean lung dose (MLD), volume of lung exceeding 20 Gy (V20), and mean esophageal dose (MED). Regional failure rate was a secondary end point. The nonparametric Wilcoxon matched-pairs signed-ranks test was used with Bonferroni adjustment for an overall significance level of 0.05.

Results: RTOG 0515 accrued 52 patients, 47 of whom are evaluable. The follow-up time for all patients is 12.9 months (2.7–22.2). Tumor staging was as follows: II = 6%; IIIA = 40%; and IIIB = 54%. The GTV was statistically significantly smaller for PET/CT-derived volumes (98.7 vs. 86.2 mL; $p < 0.0001$). MLDs for PET/CT plans were slightly lower (19 vs. 17.8 Gy; $p = 0.06$). There was no significant difference in the number of involved nodes (2.1 vs. 2.4), V20 (32% vs. 30.8%), or MED (28.7 vs. 27.1 Gy). Nodal contours were altered by PET/CT for 51% of patients. One patient (2%) has developed an elective nodal failure.

Conclusions: PET/CT-derived tumor volumes were smaller than those derived by CT alone. PET/CT changed nodal GTV contours in 51% of patients. The elective nodal failure rate for GTVs derived by PET/CT is quite low, supporting the RTOG standard of limiting the target volume to the primary tumor and involved nodes.

Table 2. Differences between CT only and PET/CT

Variable	CT only	PET/CT	Difference (PET/CT – CT only)	*p* value*
GTV primary volume (cm^3)				
Mean (standard deviation)	98.7 (102.5)	86.2 (88.1)	−12.5 (61.5)	<0.0001
Median (range)	66.1 (2.3–441.7)	59.9 (0.7–471.2)	−4.4(−215.3 to 112.9)	
Number of included nodes				
Mean (standard deviation)	2.1 (2.1)	2.4 (2.3)	0.2 (2.0)	0.41
Median (range)	2 (0–10)	2 (0–12)	0 (–6 to 10)	
Mean lung dose				
Mean (standard deviation)	19.0 (8.0)	17.8 (7.2)	−1.2 (4.0)	0.06
Median (range)	19.0 (7.2–49.0)	16.3 (6.3–43.6)	−0.4(−13.1 to 6.4)	
V20				
Mean (standard deviation)	32.0 (13.8)	30.8 (14.4)	−1.1 (6.2)	0.21
Median (range)	31 (10–80)	27 (9–74)	−1(−13 to 13)	
Mean esophageal dose				
Mean (standard deviation)	28.7 (12.6)	27.1 (10.8)	−1.4 (9.4)	0.30
Median (range)	26.8 (0.9–57.5)	25.1 (8.9–57.1)	−1.8(−25.3 to 21.3)	

* Wilcoxon matched-pairs signed-rank test.

Table 6. Impact of FDG-PET on radiation planning in patients with NSCLC

Author	Number of patients	Fusion method	Impact on radiation planning
Nestle (1)	34	Visual	35%
Kiffer (2)	15	Visual	47%
Vanuystel (3)	73	Software	67%
Munley (4)	35	Visual	34%
Brianzoni (5)	24	Hardware	50%
Kalff (6)	105	Visual	50%
MacManus (7)	102	Visual	67%
Mah (8)	30	Software	40%
Giraud (9)	11	Software	45%
Erdi (10)	11	Software	100%
Bradley (11)	26	Software	58%
Deniaud-Alexandre (12)	92	Visual	49%
Faria (13)	32	Hardware	56%

Abbreviations: FDG-PET = 18F-deoxyglucose positron emission tomography; NSCLC = non–small-cell lung cancer.

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PHYSICS CONTRIBUTION

DEFINING RADIOTHERAPY TARGET VOLUMES USING ^{18}F-FLUORO-DEOXY-GLUCOSE POSITRON EMISSION TOMOGRAPHY/COMPUTE TOMOGRAPHY: STILL A PANDORA'S BOX?

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Purpose: We discuss the effect of ^{18}F-fluoro-deoxy-glucose (FDG) positron emission tomography (PET)/computed tomography (CT) data on target volume definition for radiotherapy planning. We compared the effect of various thresholding methods on the PET-based target volume vs. the standard CT-based tumor volume.

Methods and Materials: Different thresholding methods were reviewed and compared to our PET-based gross tumor volume data obtained from a cohort of 31 non–small-cell lung carcinoma patients who had undergone pre-operative PET/CT scans for staging. The feasibility and limitations of FDG-based PET/CT data on target volume delineation in radiotherapy planning have been demonstrated with frequently used approaches for target outlining such as the qualitative visual method and the fixed 15% or 40% of the maximal iso-uptake value threshold methods.

Results: The relationship between PET-based and CT-based volumes generally suffers from poor correlation between the two image data sets, expressed in terms of a large statistical variation in gross tumor volume ratios, irrespective of the threshold method used. However, we found that the maximal signal/background ratios in non–small-cell lung carcinoma patients correlated well with the pathologic results, with an average ratio for adenocarcinoma, large cell carcinoma, and squamous cell carcinoma of 10.5 ± 3.5, 12.6 ± 2.8, and 14.1 ± 5.9, respectively.

Conclusion: The fluctuations in tumor volume using different quantitative PET thresholding approaches did not depend on the thresholding method used. They originated from the nature of functional imaging in general and PET imaging in particular. Functional imaging will eventually be used for biologically tailored target radiotherapy volume definition not as a replacement of CT- or magnetic resonance imaging-based anatomic gross tumor volumes but with the methods complementing each other in a complex mosaic of distinct biologic target volumes.

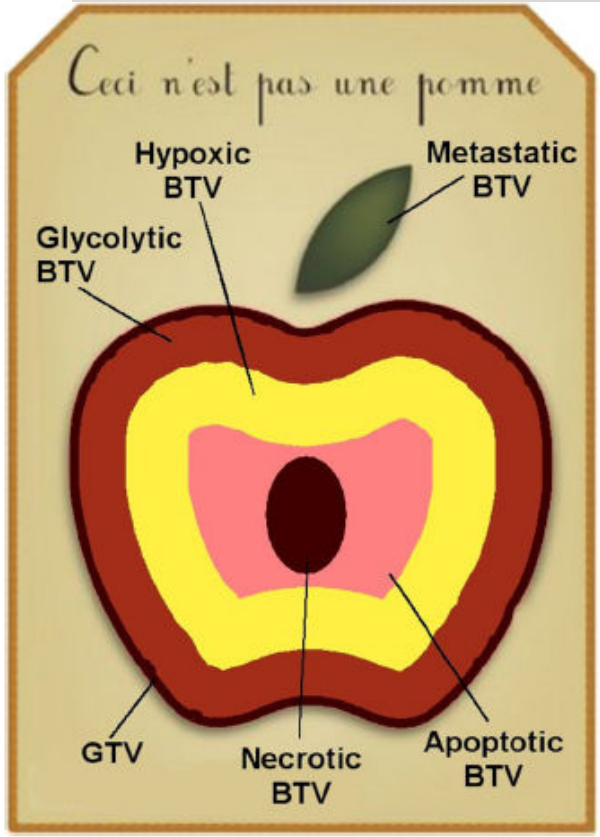

Fig. 4. Biologic planning target volume (BTV) mosaic, according to Rene Magritte (1898–1967). GTV = gross tumor volume. French text: "This picture is not an apple."

Conclusioni

- Integrazione con altri specialisti (medico nucleare, radiologo) per la contornazione dei TV
- Tecniche per il controllo della fisiologica motilità degli organi interni
- Orientamento verso una contornazione dei volumi bersaglio post-chemio *(RT post-CHEM)*
- Irradiazione dei potenziali siti di malattia microscopica endotoracici *(RT post-CHIR)*
- Introduzione di strategie adaptive per ridurre i volumi di trattamento
- Impiego della PET-TC nella definizione del GTV T e GTV N, per ridurre la variabilità inter-osservatore

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Personalizzazione del trattamento, riduzione dei volumi, possibilità di dose escalation