TOMOTERAPIA IN ITALIA: ESPERIENZE A CONFRONTO

L' Esperienza di Roma – San Camillo - Polmone

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Rome

Bard 19.XI.2010

DEPT. RADIOTHERAPY

SAN CAMILLO FORLANINI HOSPITAL

ROME, ITALY

FOUNDED IN 1938

- 3 LINAC (MLC, mMLC, Artiste*)
- 1 SIMUL CT (Toshiba)
- IGRT
- TOMOTHERAPY
- IORT (NOVAC)
- BRACHYTERAPY (HDR)
- HYPERTHERMIA*

S.Camillo/Forlanini Tomotherapy Unit

Helical Tomotherapy treatments started in our unit on January 2008

Our interests are assessed especially on treatment of tumors localized in critical areas (Brain, H-N, Lung) and is finalized to obtain an escalation dose with simultaneous boost tecnique ("moderate hypofractionation") according with biological equivalent dose (BED) criteria

S.Camillo/Forlanini Tomotherapy Unit

Our interest was focalized especially on multimodal treatments

- Lung Cancer (135 pts)
- Brain Malignancies- critical areas (40 pts)
- Head and Neck Cancer (75 pts)

S.Camillo/Forlanini Tomotherapy Unit

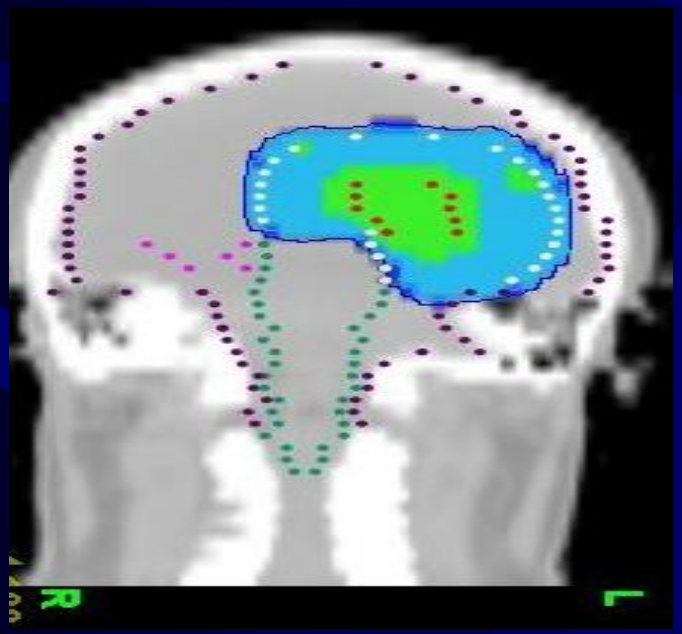
BRAIN MALIGNANCIES in critical area

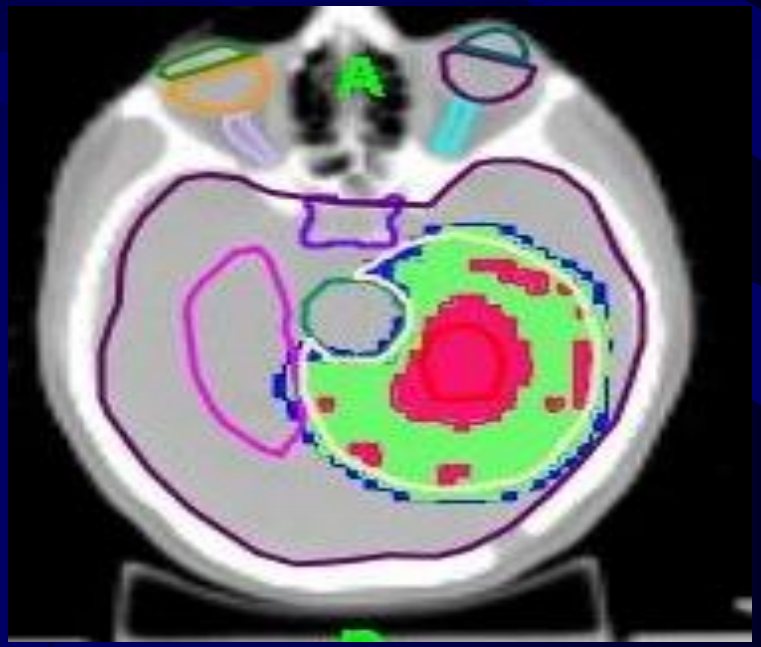
40 patients

Tomotherapy schedule

PTV1 (GTV) 2.2 Gy each day until 66 Gy total dose

PTV2 (CTV+2.5 cm) 2.0 Gy/day total dose 60 Gy

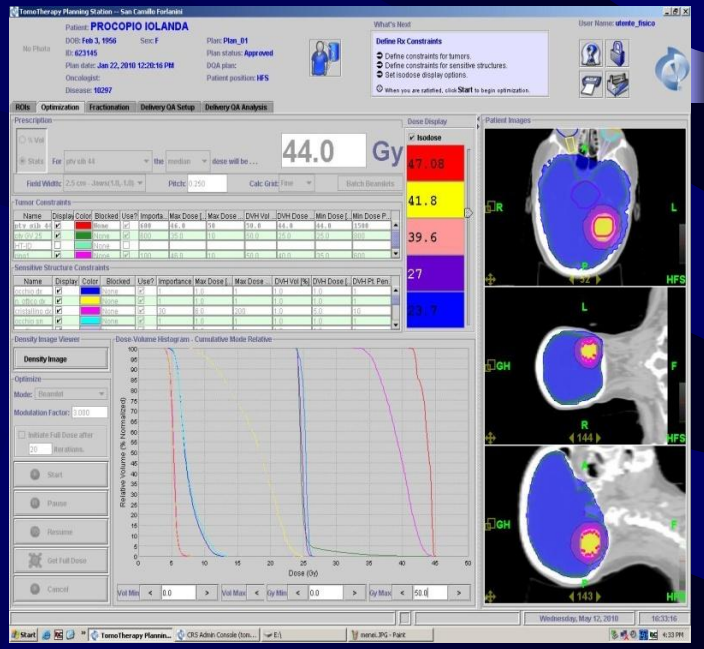




Nuove prospettive di studio con Tomoterapia Elicoidale

(Protocollo randomizzato: San Camillo Forlanini)

RADIOTERAPIA WHOLE BRAIN CON RISPARMIO DELL'IPPOCAMPO E SIMULTANEOUS INTEGRATED BOOST (SIB) SULLE METASTASI CEREBRALI CON TOMOTERAPIA ELICOIDALE



Head and Neck Cancer (75 pts)

Definitive Radiation Therapy a
concomitant chemotherapy

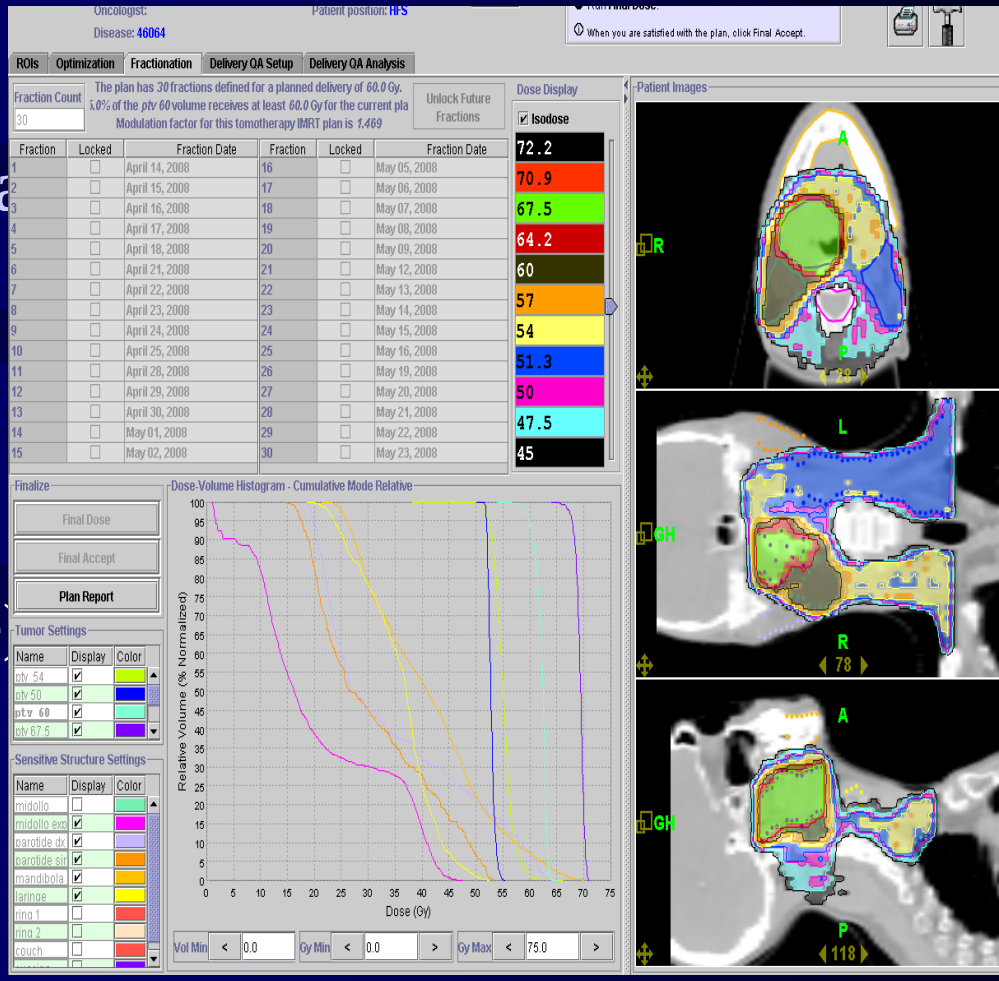
Simultaneous Boost TomoTherapy

PTV1 (GTV) 67.5 Gy (2.25 Gy/die
82.7 Gy

PTV2 (N+) 63.6 Gy (2.12 Gy/die)

PTV3 (N-) 54 Gy (1.8 Gy/die)

RP-RC 78% - 83%



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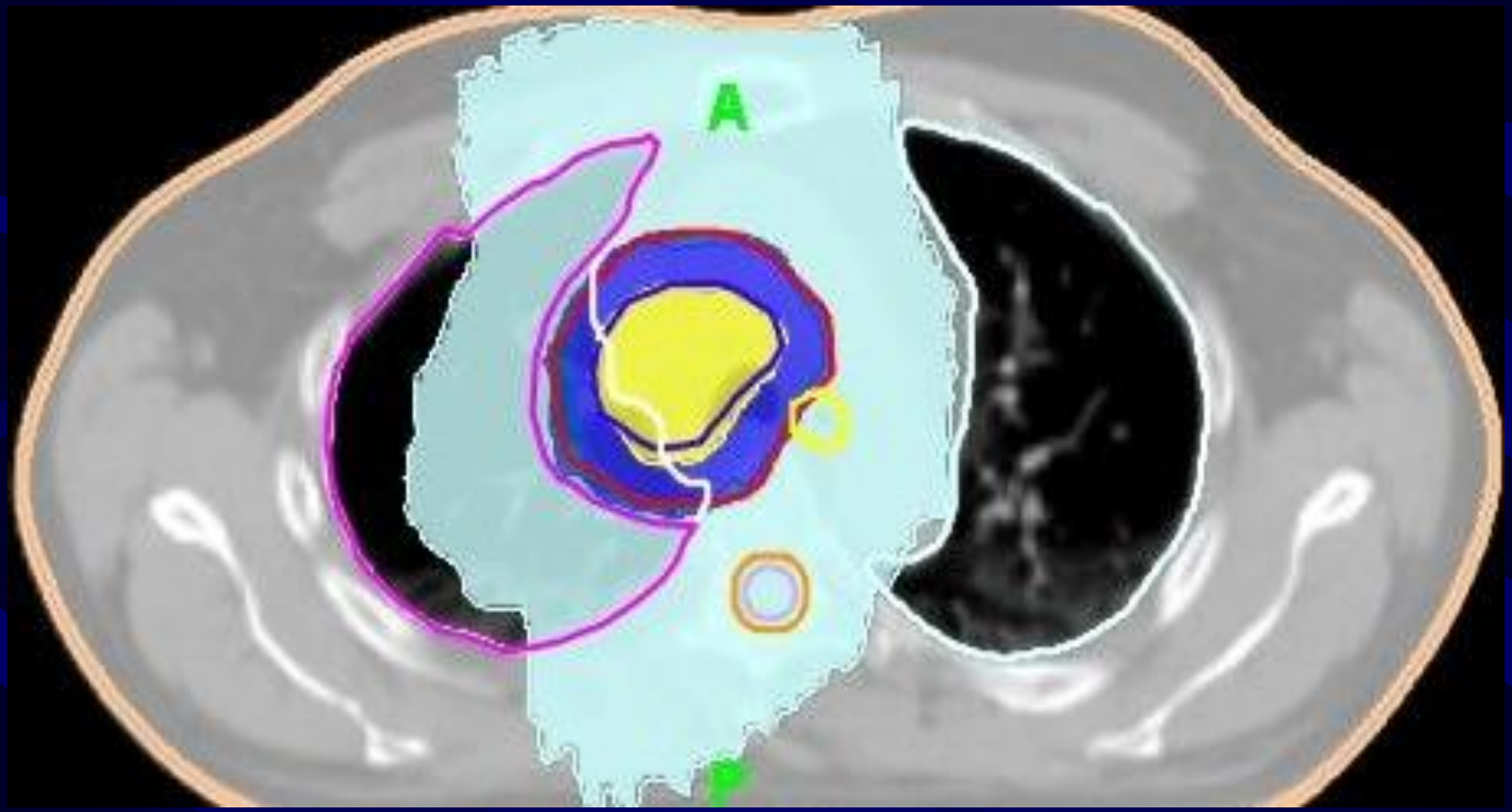
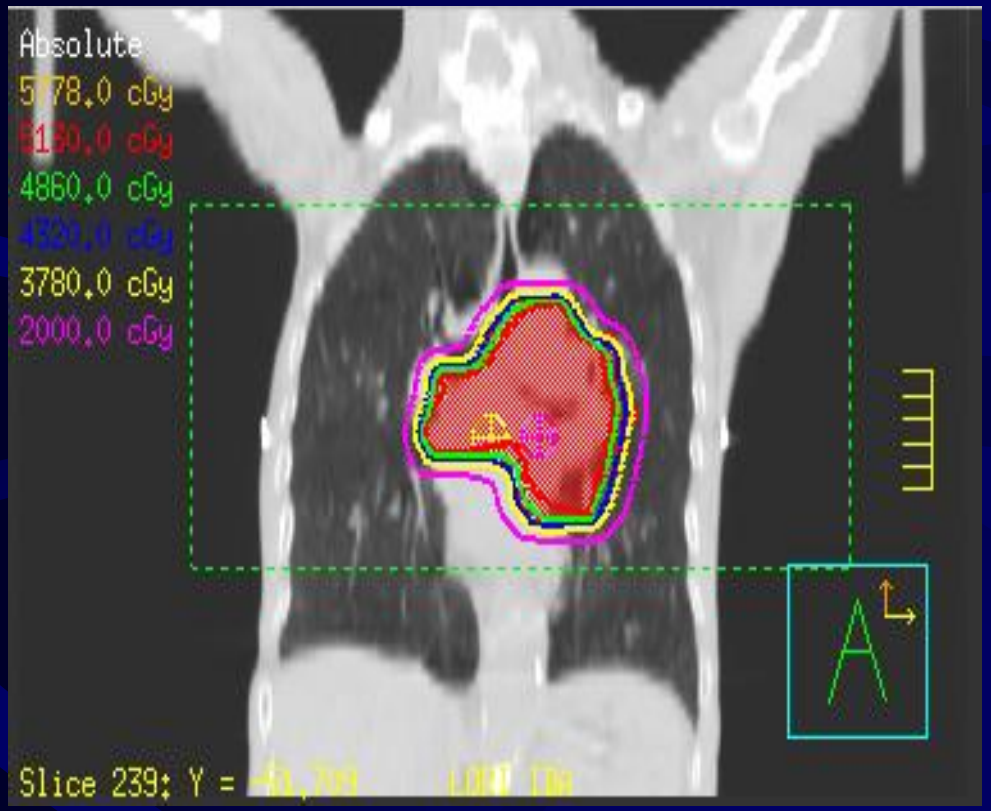
Lung Cancer Management “A new ART”



“New” volume



Involved Field Irradiation

Erik P Sulman Ritsuko Komaki et al.**Exclusion of elective nodal irradiation is associated with minimal elective nodal failure in non-small cell lung cancer** ***Radiation Oncology*** **2009**, **4**:5 doi:10.1186/1748-717X-4-5

Radiobiology

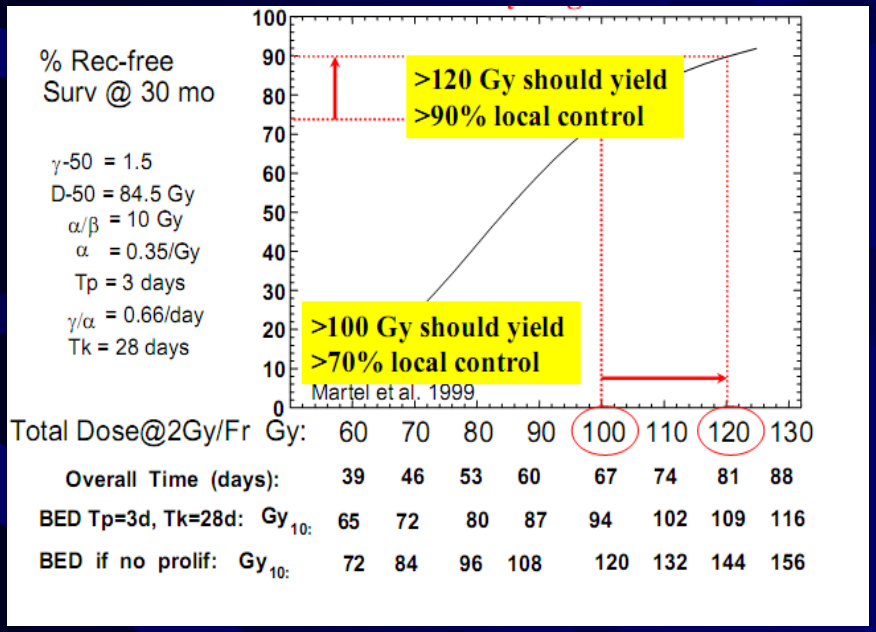
Clonogenic cells start reproducing themselves about 20-30 days after the start of radiation. A conventional treatmet of 70 Gy delivered in 35 fractions (2.0 Gy/fraction, 5 fractions a week) can result in a tumor control probability (TCP) of about 25%.

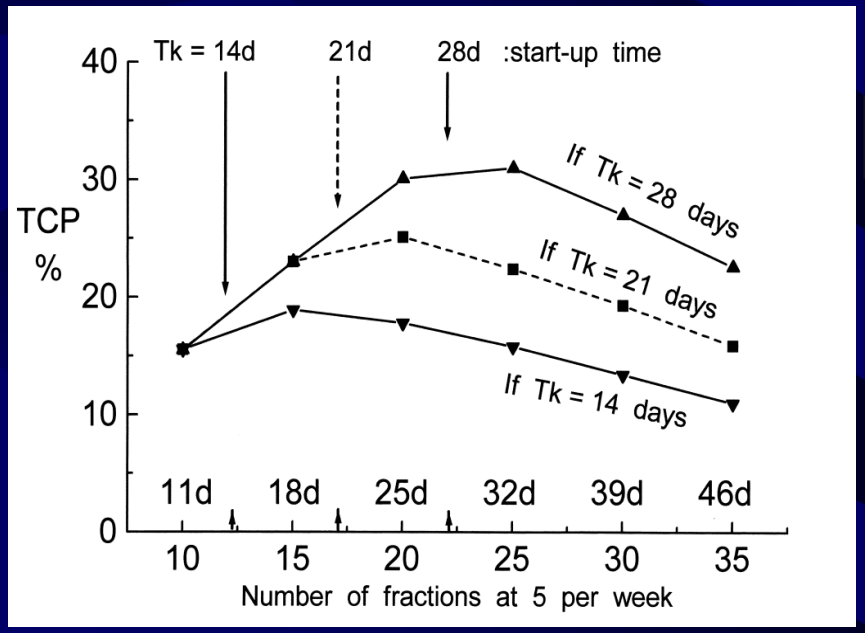
Calculated biological effective dose is BED 10= 84 Gy and BED 3= 116.6 Gy

"New" dose

- Decrease volume RT
- Increase dose RT

CONFORMAL DOSE-PER-FRACTION ESCALATION





Mehta et al 2001Int. J. Radiation Oncology Biol. Phys

Martel et al, 1999 3-D dose escalation Lung Ca

NSCLC Collaborative Group Meta-Analysis - Concomitant versus Sequential CT-RT.” New” CT/RT

- Overall survival favored concomitant CT-RT
  - Absolute benefit of 5.9% (18.1% sequential vs. 24% concomitant) at 3 years.
  - HR = 0.85, (95% CI = [0.75–0.95], p = 0.0066)
- Loco-regional progression favored concomitant CT-RT
  - HR = 0.76, (95% CI = [0.62–0.94], p = 0.011)
- No difference for distant progression
  - HR = 1.04, (95% CI = [0.86–1.25], p = 0.669)
- Concomitant CT-RT improved survival

Rolland E, et al. Concomitant Radio-chemotherapy (CT-RT) versus Sequential CT-RT In Locally Advanced Non-Small-Cell Lung Cancer (NSCLC): A Meta-Analysis. ASTRO 2007; #9.

conclusion and new perspectives

- 60-66 Gy yields poor local control (Dose)
- Few elective nodal failures occur with involved field irradiation (Volume)
- Concurrent chemotherapy improves local control and overall survival (Chemotherapy)

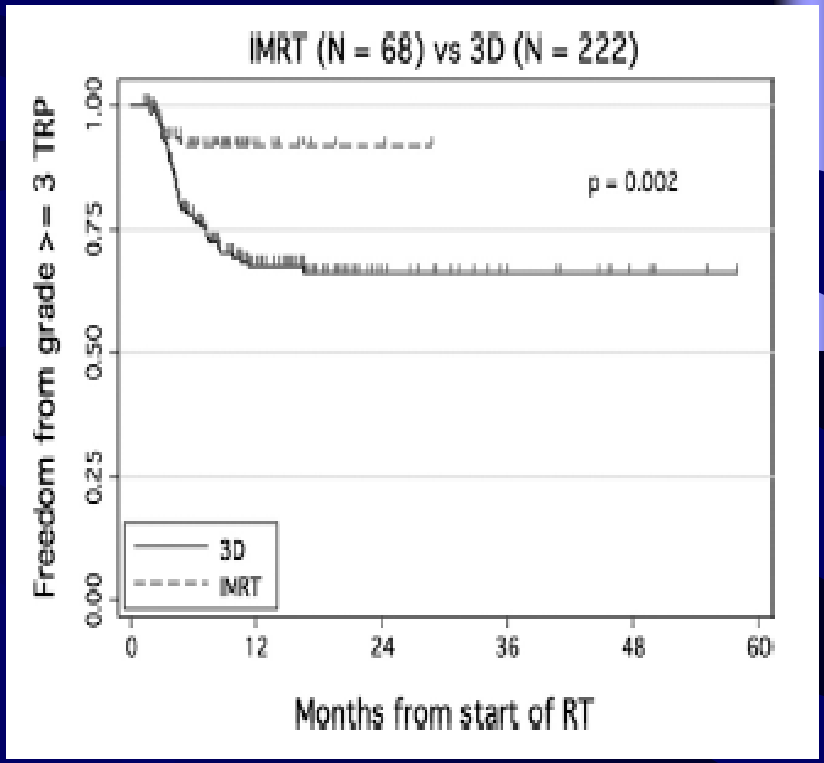
Technological advances (IMRT,…)

- Concurrent chemotherapy will likely be achievable in the context of dose-escalated radiation therapy
  - Toxicity profiles

Technological advances
IMRT vs. 3D-CRT

- Retrospective review of NSCLC patients receiving concurrent chemotherapy
- Median dose of 63 Gy
- Grade ≥ 3 treatment-related pneumonitis at 12 months:

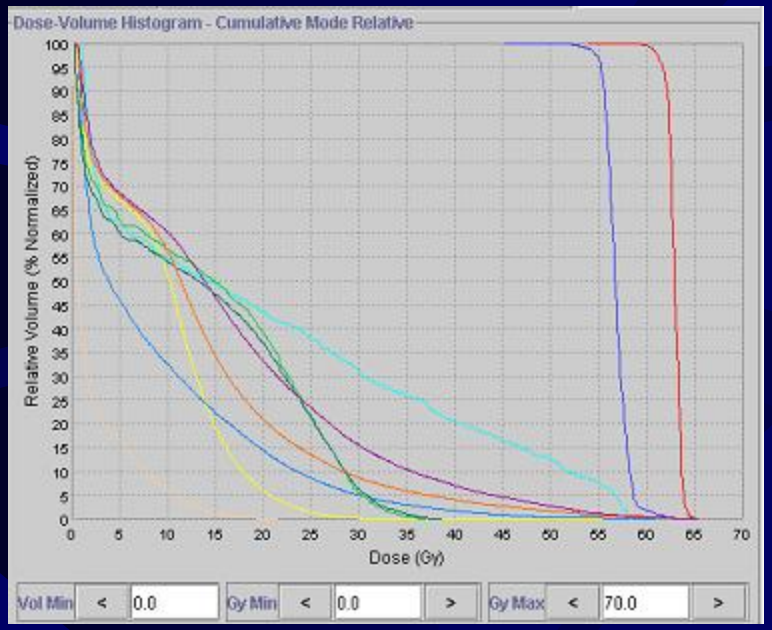
  8% IMRT vs. 32% 3D-CRT, p=0.002



Yom SS, et al. Initial evaluation of treatment-related pneumonitis in advanced NSCLC patients treated with concurrent chemotherapy and IMRT. *Int J Radiat Oncol Biol Phys* 2007;68(1): 94-102.

New treatment and toxicity

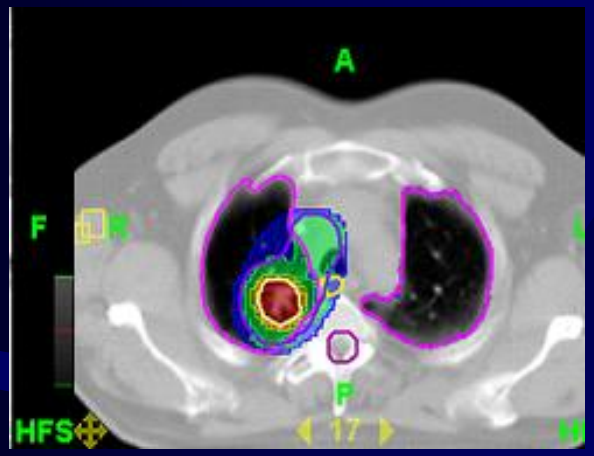
To maintain dose constraint OAR is mandatory …



Spine cord	Esophagus	Lung	Heart
Dose Max 45 Gy	Dose Media<34Gy	V5<42%	V50<20%
	V20<45 Gy	V20<25%	V30<50%
	V35<30Gy		
	V50<50Gy		

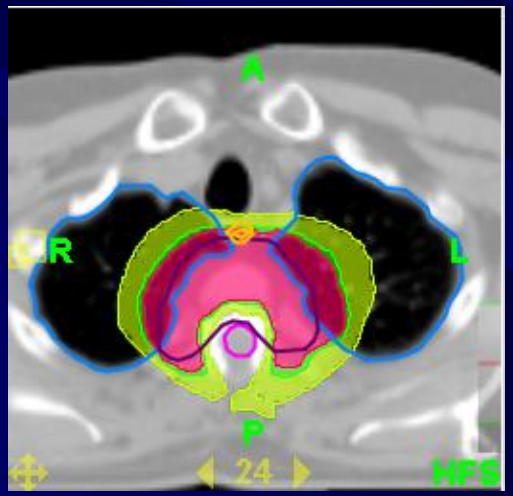
…a new technology

New technology : Elical Tomotherapy in lung cancer



Dose-Escalation

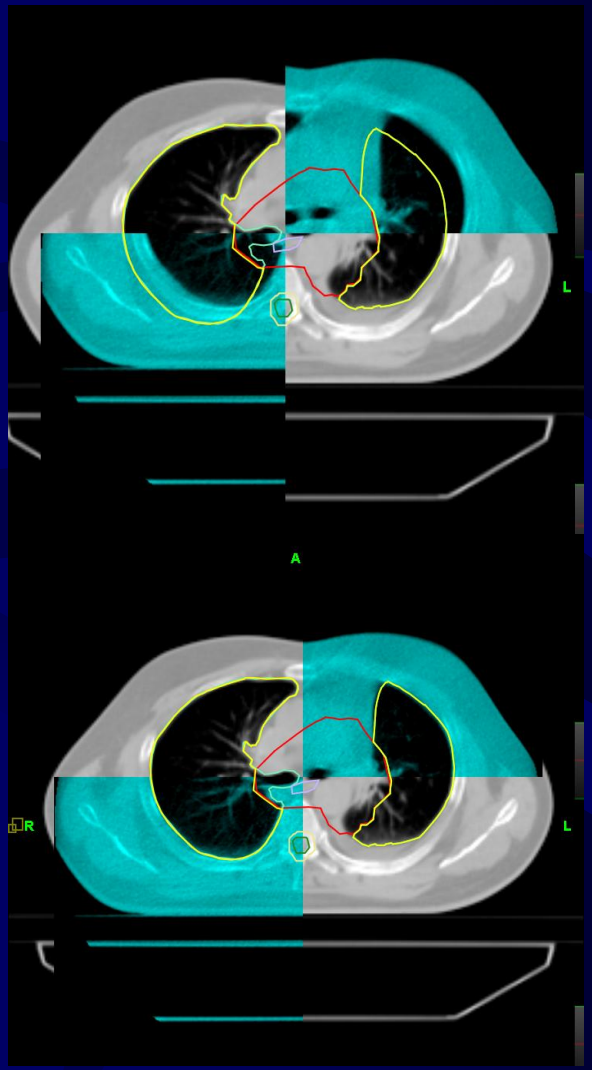
Conformal Avoidance



Elical Tomotherapy in lung cancer

MV CT- IGRT

The advantage of MV-CT lies in the possibility of obtaining more accurate anatomic details than those available in the conventional portal imaging and of verifying the correct positioning of the patient before treatment by comparing to CT images used in the treatment planning



Tomotherapy Unit
San Camillo Forlanini Hospital
Lung Cancer (135 pts)

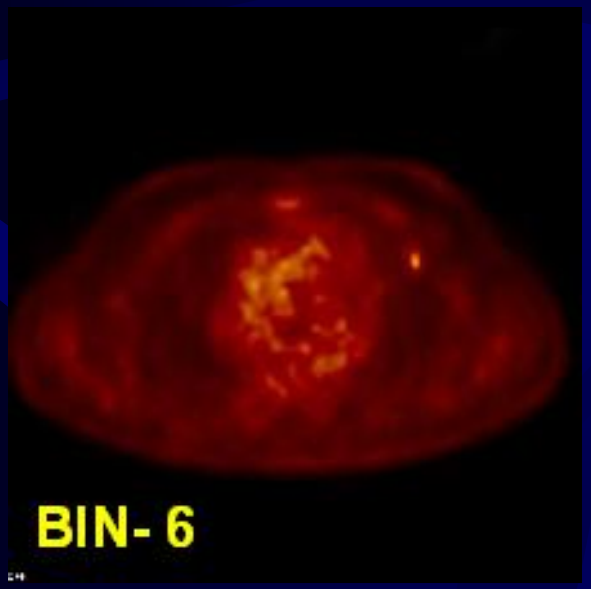
- Stereotactic RT (32 pts)
- Stage IIIA (Bulky) and IIIB

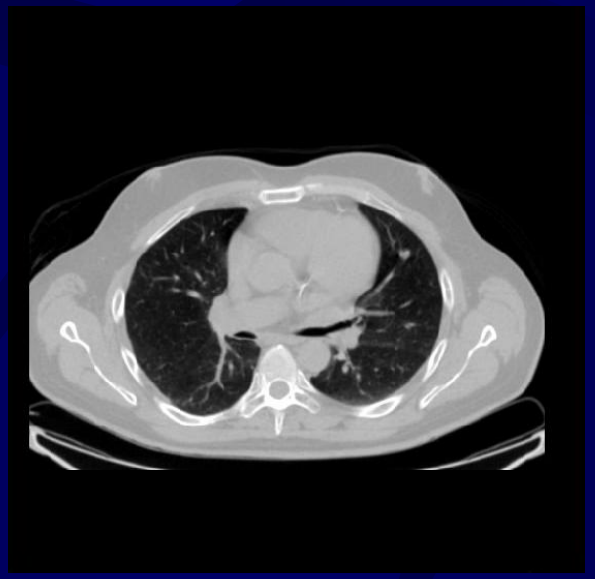
CT → sequential RT and/or alone RT (68 pts)

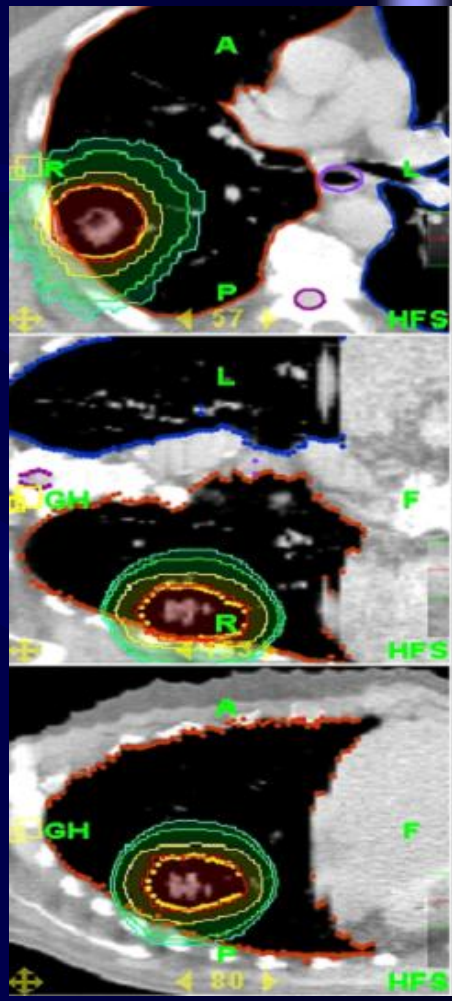
CT → RT and concomitant CT (35 pts)

Stereotactic RT (32 pts)

- lung lesions (primary tumors)
- 9/10 Gy x 5 fr ,5w>>>







Stereotactic RT (32 pts) –

Toxicity

	oesophageal	pulmonary
G1	0	15
G2	0	7

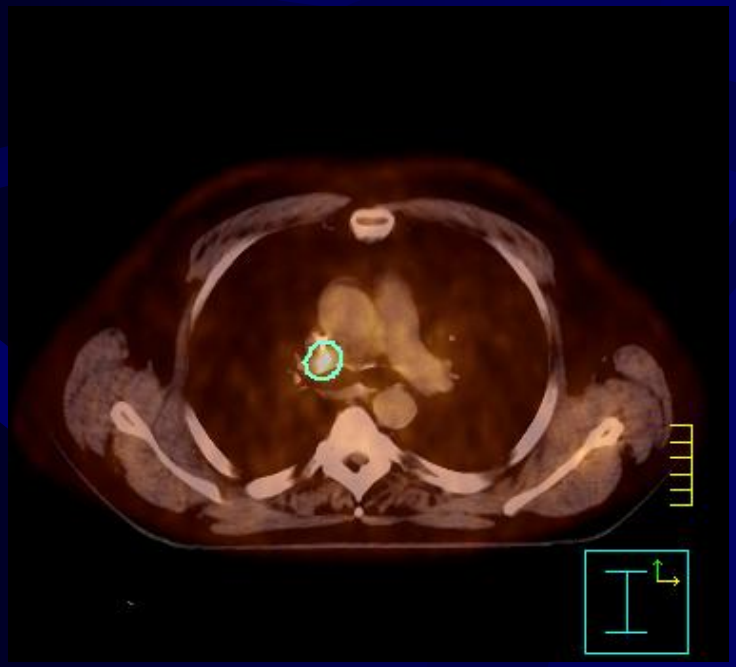
Response

PD	SD	PR / CR
0	9	23

Radiotherapy in advanced stage lung cancer IIIA (bulky)- IIIB lung cancer

The main intent was to realize a moderate hypofractionation and SIB

- ✓Sequential or alone treatment o
- ✓Concomitant chemo/radiation



PET/CT can be used in connection with RT for treatment planning and for evaluating response to treatment.

Hypofractionated radiation and dose escalation: references

Blackstocck et al. observed the tolerance of a radiochemotherapy treatment combined with an escalated dose of 60-74 Gy.

Belderbos et al. Following a phase I/II study demonstrated the possibility of applying a daily fractioning of 2.25 in 30 fractions up tp total dose of 67.5 Gy (IJROBP 2006), presented a randomized phase III study (EORTC 08972-22973) with combined a chemotherapy to a sequential radiochemotherapy treatment

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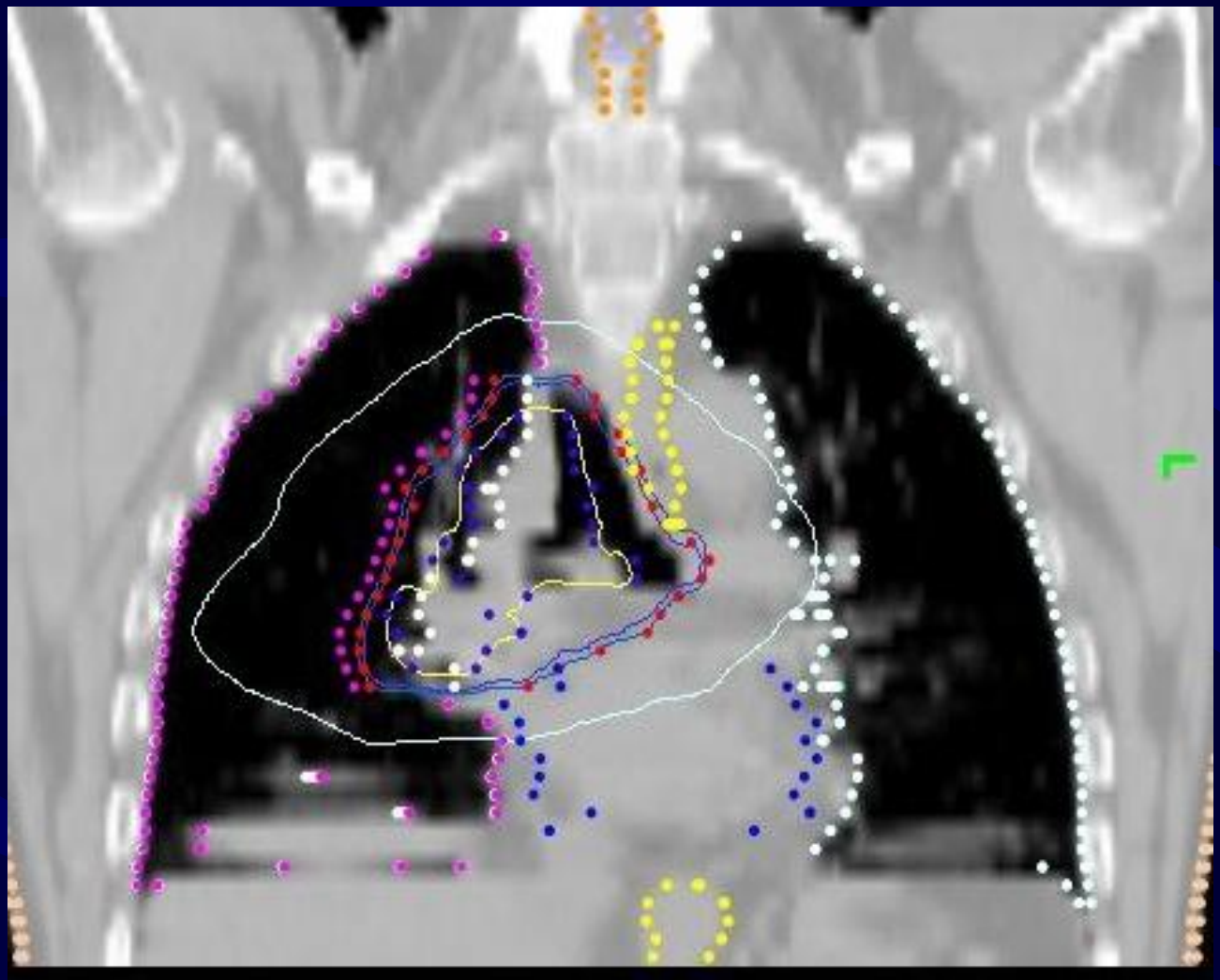
Volume treatment



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Lung Cancer Management

Sequential Treatment (68 pts)
in IIIA(bulky) IIIB NSCLC

DDP based induction chemo 4/6 cycles

PTV 1(GTV+ N+) 2.25 Gy each day until 67.5 Gy
BED $_{10}$ 83 Gy* BED $_{3}$ 118 Gy*

- BED10 for conventional dosage 2 Gy x35 fract. 84
- BED 3 for conventional dosage 2 Gy x35 fract. 117

S.Camillo/Forlanini Tomotherapy Unit

Lung Cancer Management

TIME TO RESPONSE

AFTER 40-60 DAY BY THE ENDING OF TREATMENT

FIRST FOLLOW UP EVALUATION WITH A CT SCAN

And

THE SECONDARY EVALUATION AFTER 6 MONTHS MORE WITH CT/PET

And

AT 12 MONTHS WITH CT SCAN

Esclusive / sequential RT (68 pts) – Toxicity

	oesophageal	pulmonary
G1	38	15
G2	16	4

- Response

PD	SD	PR / CR
3	37	28

Esophageal toxicity

Radiotherapy and Oncology , 2005 75(2), 157-164 J

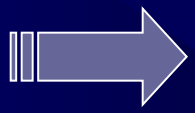
Acute esophageal toxicity in non-small cell lung cancer patients after high dose conformal radiotherapy

Belderbos , W . Heemsbergen , M . Hoogeman , K . Pengel , M . Rossi , J . Lebesque

Tohoku J. Exp. Med. 2006, 208, 299-306

Predictive Factors for Acute Esophageal Toxicity in Thoracic Radiotherapy

Ken Takeda, Kenji Nemoto, Haru Saito, Yoshihiro Ogawa, Yoshihiro Takai and Shogo Yamada.



V35

Radiother Oncol. 2005 Nov;77(2):176-81. Epub 2005 Oct 26. Links

Normal tissue complication probability modeling for acute esophagitis in patients treated with conformal radiation therapy for non-small cell lung cancer.

Chapet O, Kong FM, Lee JS, Hayman JA, Ten Haken RK.

Acute esophageal toxicity in patients with non-small cell lung cancer treated with helical tomotherapy

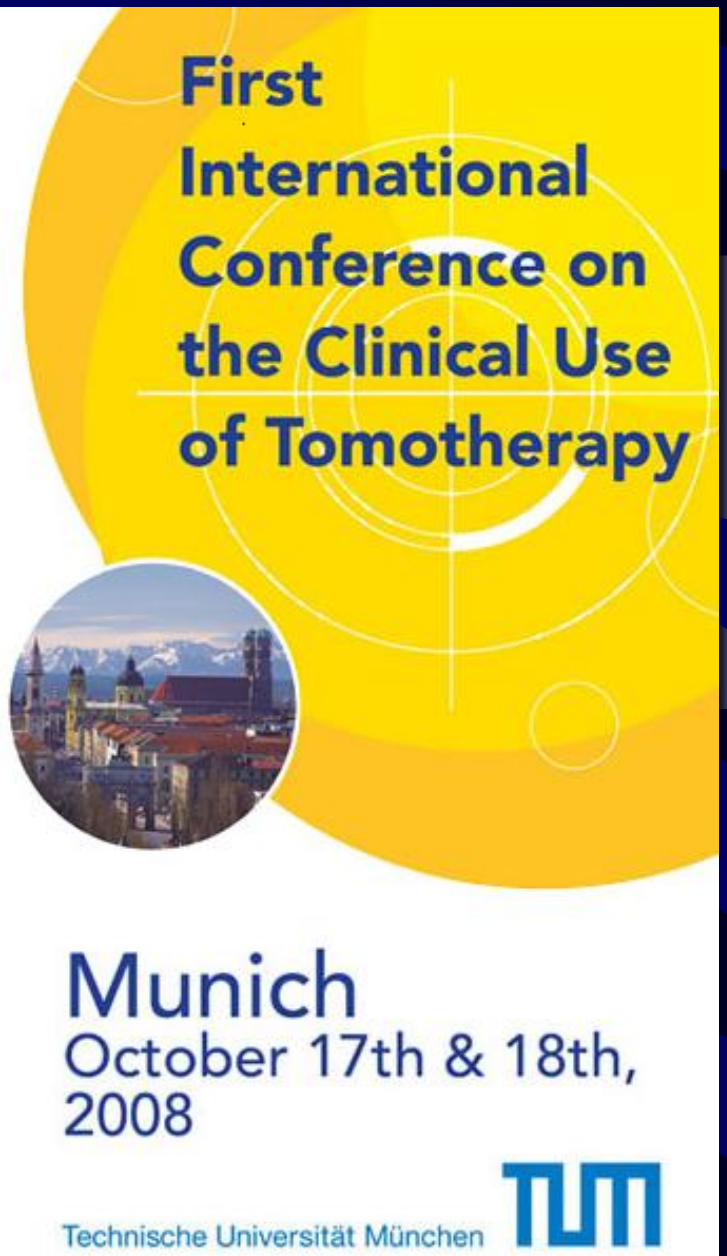
Monaco A. , Caruso C. , Giammarino D. , Cianciulli M. , Pressello M.C. , Pacilio M.* , Donato V.*

*Unità Operativa Complessa Radioterapia, Azienda Ospedaliera San Camillo – Forlanini, Roma; *Unità Operativa Complessa Fisica Sanitaria, Azienda Ospedaliera San Camillo – Forlanini, Roma*

Radiobiological modelling of Helical Tomotherapy lung treatments: preliminary results on oesophageal toxicities

M.C. Presselloa, M. Pacilioa, R.Raucoa, M. Bettia, A. Monacob , D. Aragnoa, V. Donatob and E. Santinia

a Medical Physics Department, Az. Osp. San Camillo Forlanini, Rome Italy
b Radiotherapy Department, Az. Osp. San Camillo Forlanini, Rome Italy



S.Camillo/Forlanini Tomotherapy Unit

Lung Cancer Management

NSCLC

Concomitant Treatment (35 pts)

DDP based concomitant chemo as sensitizer adminstred the first day of every treatment week

PTV1 (GTV plus path. nodes):2.15 Gy/day 64.5 Gy
(BED $_{10}$ 78 BED $_{3}$ 111)
PTV2 (N-) 2.0 Gy/day 60 Gy

CT → concomitant RT-CT (35 pts)

Toxicity

	oesophageal	pulmonary
G1	16	7
G2	6	1

Response

PD	SD	PR / CR
0	16	19

TRIMODALITY TREATMENT IN pN2 NSCLC

A San Camillo-Forlanini Institutional Phase II Trial Design

Induzione con Gemcitabina, docetaxel e cisplatino più chemioterapia concomitante a radioterapia toracica in pazienti con NSCLC in stadio III

S. De Santis, V. Donato, C. Caruso, MR. Migliorino, B. Tedesco, R. Belli, S. Valentino, F. De Marinis.

ASCO 2008

- **Cisplatin 35 mg/m2**
- **Gemcitabine 1000 mg/m2**
- **Docetaxel 30 mg/m2**
  day 1&8 every 21 days

↓ **Responder/Stable**

TRT 45 Gy over 4 wks + **Cisplatin 50 mg/m2 d 1&8**
Docetaxel 20 mg/m2 wkly x 4

↓ **Responder**

SURGERY

Outline to new trial

- Role of chemotherapy in conjunction with RT: induction and concomitant (1)

- Establishment of standard of care dose RT (2)
- New technology: Tomotherapy dose-per-fraction escalation trial

Induction chemotherapy followed by concomitant ChT/RT (1)

CALGB 9431: randomized phase II trial designed to examine the effectiveness and toxicity of 3 different ChT regimes followed by RT and concomitant administration of the same ChT in reduced doses.

Response rates of 67%-74% Esophageal toxicity 3-4 25%-52% Median survival 14.8- 18.3 ms and 12%-28% 3 ys

This method is not easily applicable although it is more convenient from an organizational point of view than the immediately concomitant treatment

Hypofractionation to new schedule (2) (Mehta M. 2001)

- Fewer and larger fractions are delivered within 5 weeks
- The starting fractionation scheme of 2.28 Gy x 25 = 57 Gy has the same biologic effective dose (BED) for late effects equal to that of 60 Gy in 2 Gy fractions ($\alpha/\beta = 3$, BED=100)
- An optimum fractionation resolves conflicting interests
  - Tumor cell kill increases since rapid repopulation is avoided with shorter overall treatment times
  - Tumor cell kill decreases since total dose is reduced with larger fractions to avoid late effects

LUNG Trial San Camillo Hospital radiobiology

2.28 Gy/fraction in 30 fractions up to a total dose of 68.4 Gy in order to achieve a BED_3= 120.38 Gy with a value approaching the one achieved in conventional treatment with a total dose 74 Gy in 37 fractions of 2 Gy, but delivering 7 fractions less while increasing TCP by about 6% (TCP=31%)

TRIAL DESIGN : NSCLC IIIA(bulky) or inoperable IIIB

CDDP (75 mg/mq on day 2) + GEM (1250 mg/mq on days 1 and 8 every 21 days)

2 cycles

ARM A:

RT total dose 68.4 Gy in 30 fr

ARM B:

RT 68.4 Gy + CDDP (50mg/mq on day 1)

+ VP 16 (50 mg/mq on days 1-2-3- every 21 days)

TRIAL (planning treatment) : NSCLC IIIA(bulky) or inoperable IIIB

GTV1: lesion (T+N) present at the onset of disease, prior to induction of chemotherapy

GTV2: residual lesion after chemotherapy induction shown by post-chemotherapy CT

When no evident reduction (>30%) after chemotherapy GTV1=GTV2

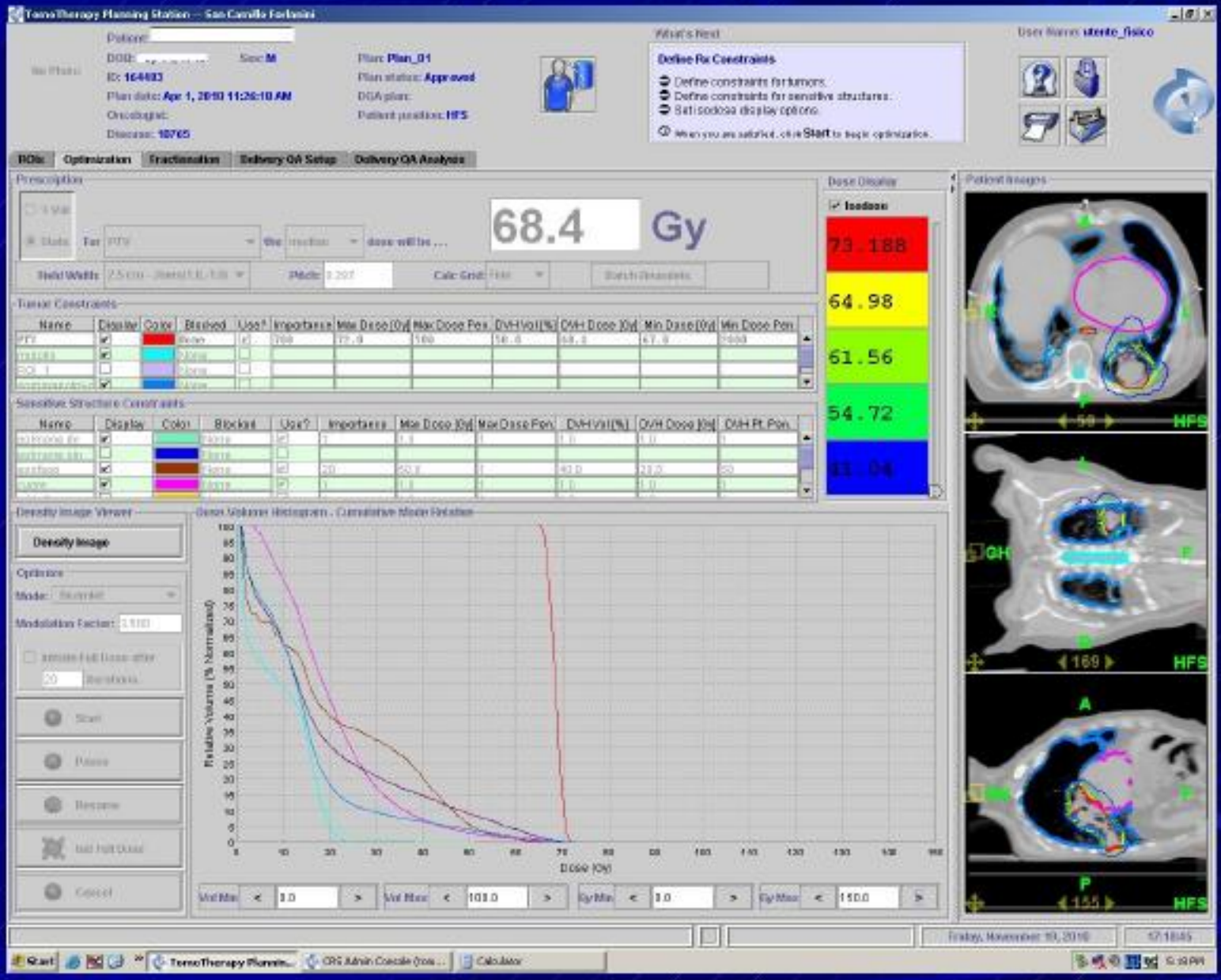
Total margin between GTV and PTV up to 6-8 mm

Doses:

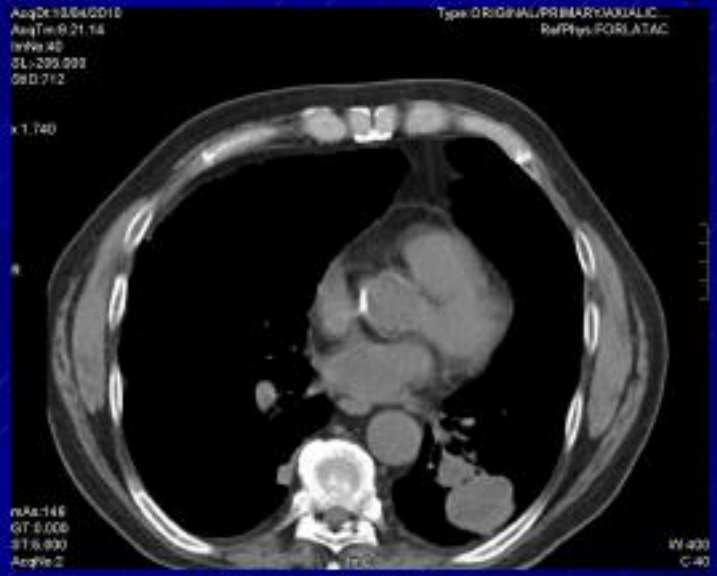
PTV2= 2.28 Gy x 30 fr dose 68.4 Gy (BED10:83.99 BED3:120.38)

PTV1= 1.80 Gy x 30 fr total dose 54.0 Gy (BED10:63.72 BED3:86.4)

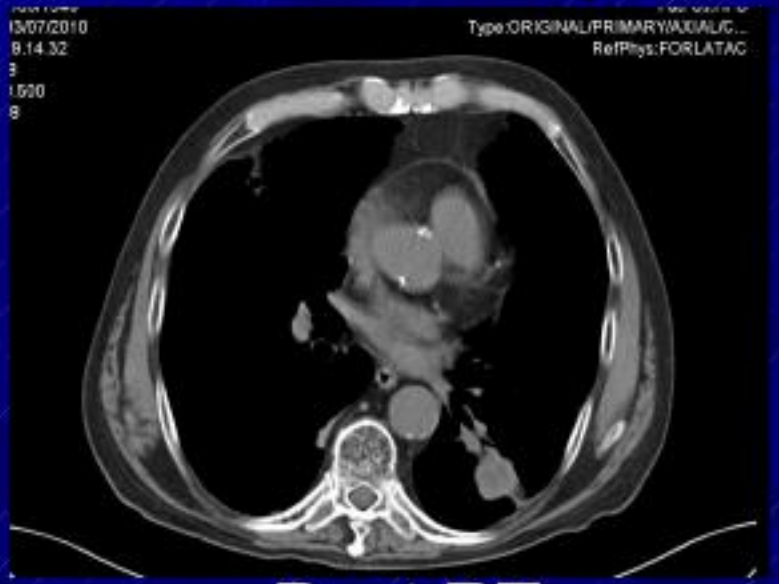
If PTV1=PTV2 a total dose delivered includes 30 fractions of 68.4 Gy


TomoTherapy Planning Station -- San Camillo Forlanini
Define Rx Constraints
Define constraints for tumors.
Define constraints for sensitive structures.
Set isodose display options.
When you are satisfied, click Start to begin optimization.
ROIs
Optimization
Fractionation
Delivery QA Setup
Delivery QA Analysis
Prescription
68.4
Gy
Tumor Constraints
Sensitive Structure Constraints
Dose Display
Isodose
73.188
64.98
61.56
54.72
Patient Images
Density Image Viewer
Density Image
Optimize
Start
Pause
Resume
Cancel
Dose Volume Histogram - Cumulative Mode Relative
Relative Volume (% Normalized)
Dose (Gy)
HFS

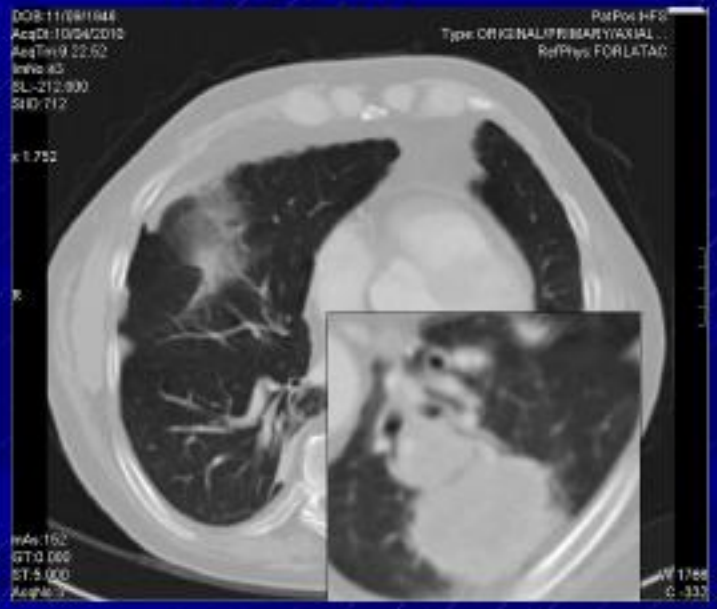
Risultati al primo follow-up

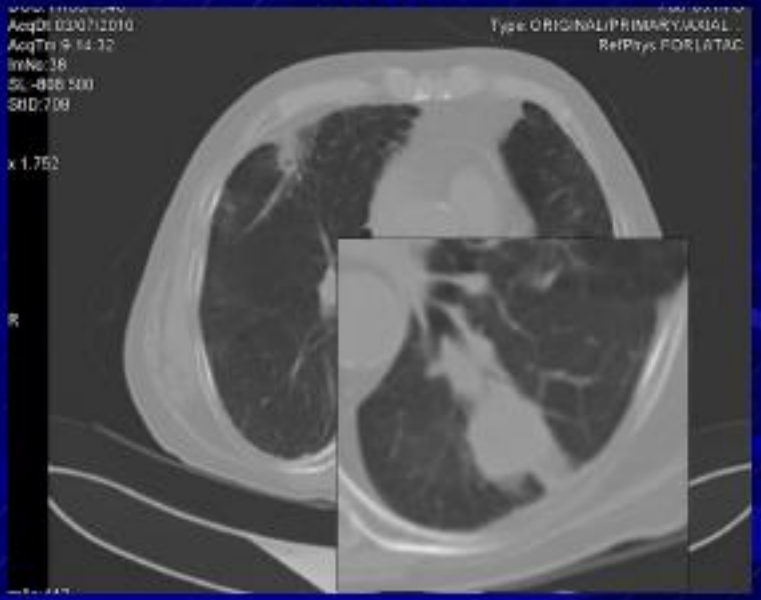


Pre RT

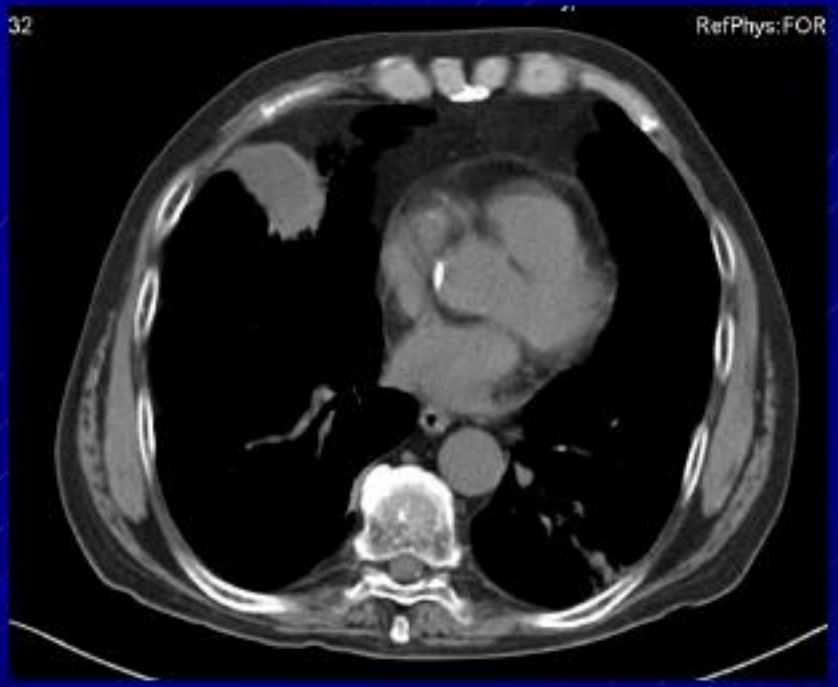


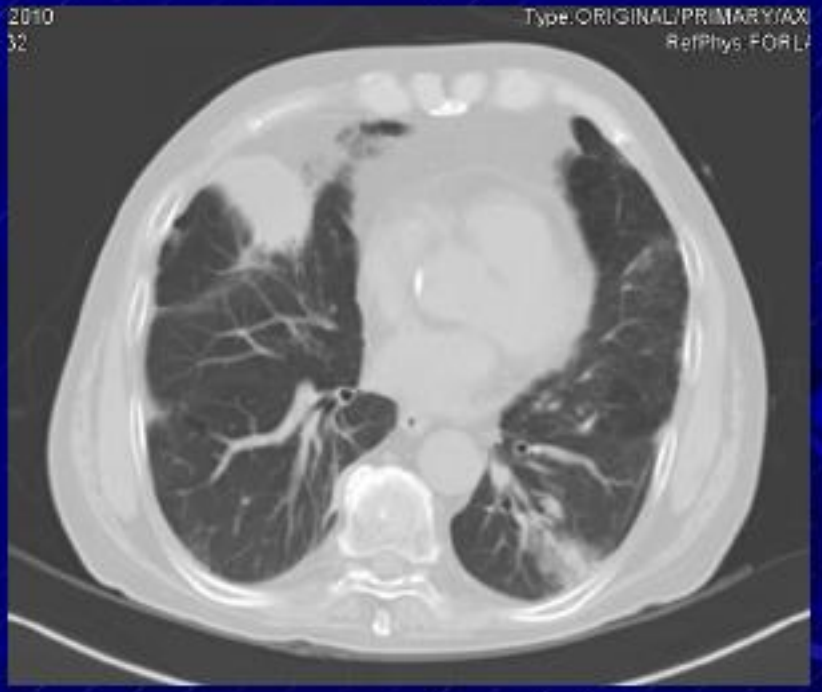
Post RT





Secondo Follow-up

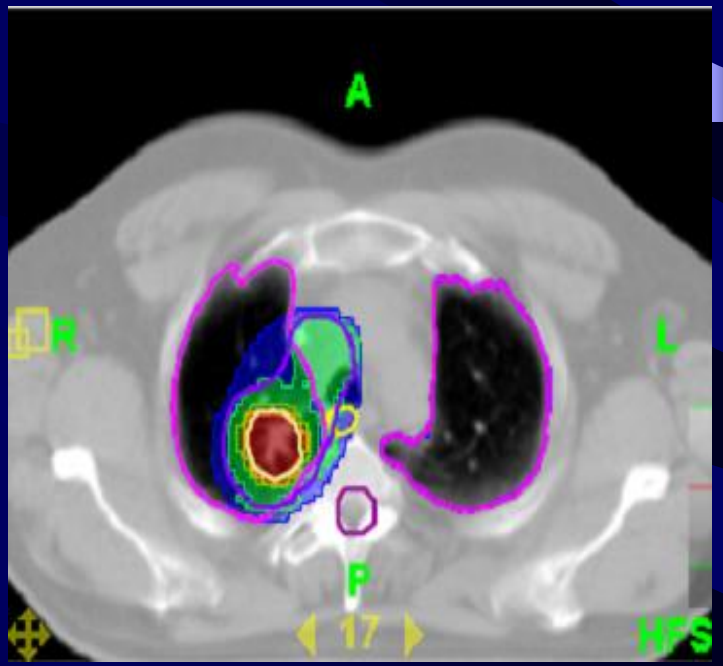




Nuove prospettive di studio con Tomoterapia Elicoidale

(Protocollo randomizzato San Camillo Forlanini)

Trattamento radiochemioterapico concomitante dopo chemioterapia di induzione dei pazienti affetti da carcinoma polmonare non a piccole cellule in stadio localmente avanzato



vdonato@scamilloforlanini.rm.it

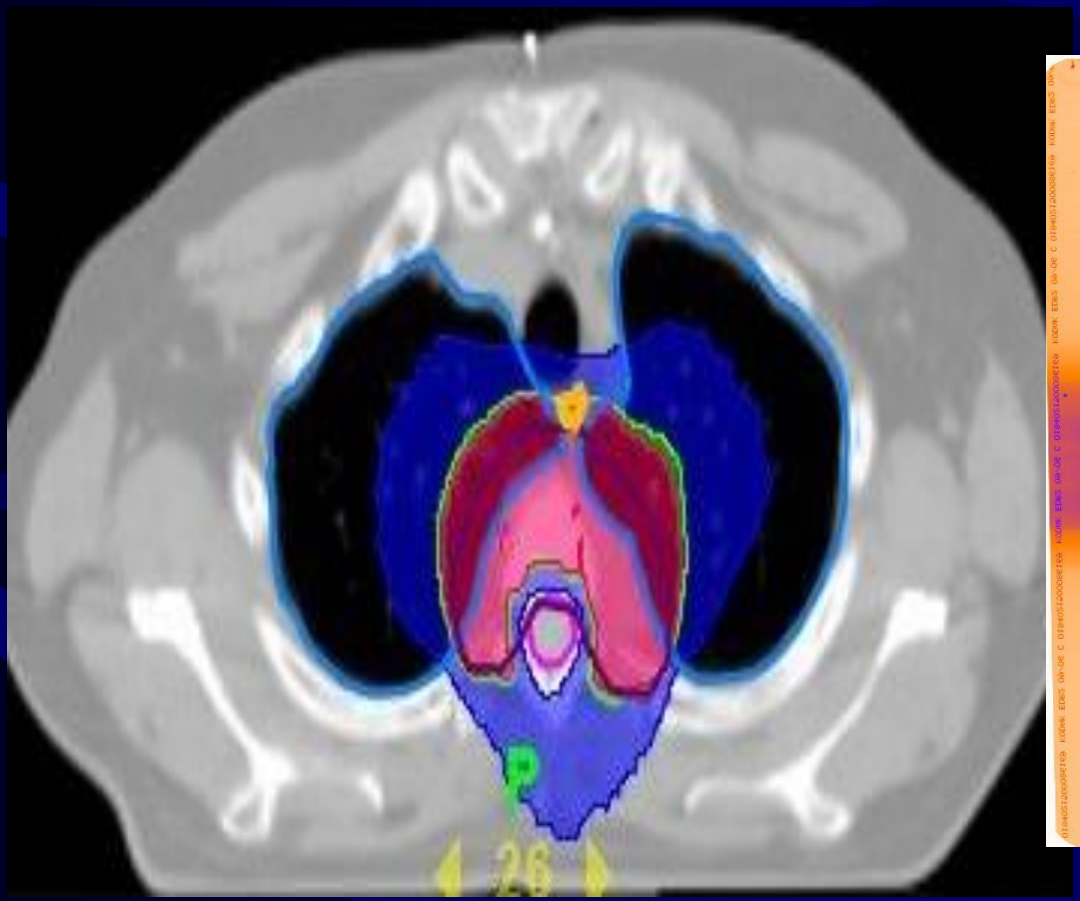
Ackerman, Lauren and Juan A. Del Regato., Cancer, Diagnosis, Treatment and Prognosis. St. Louis, Mo.,The C. V. Mosby Co. **1947.**

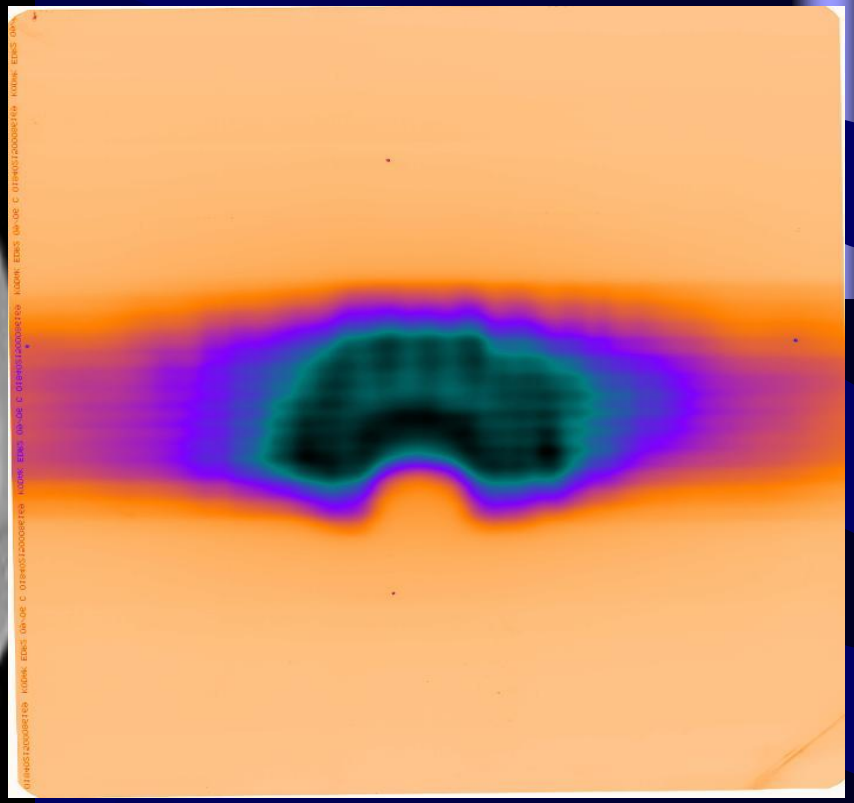
A high percentage of lung cancer, when discovered, is inoperable, thus irradiation therapy in the amelioration of symptoms in these inoperable patients should be utilized.

... the administration of roentgen therapy often results in a diminution in size of the tumor, re-establishment of bronchial permeability, disappearance of atelectasis, pleural fluid, and pain. Although life may not be pro-longed following x-ray therapy, it is made more endurable. It results in a survival period of a comparatively high degree of comfort...

S.Camillo/Forlanini Tomotherapy Unit

miscellaneous (retreatment)





ELICAL TOMOTHERAPY

Intensity Modulated Radiotherapy (IMRT)

CONFORMAL DOSE-PER-FRACTION ESCALATION

CONFORMAL AVOIDANCE

Image Guide Radiotherapy (IGRT)

Set-up Margin< PET-CT biological target

S.Camillo/Forlanini Tomotherapy Unit

Concomitant Chemoradiation: CBDCA infusion 100mg/mq week

During the tomo treatment

Every day a MVCT CT images registration is performed for each patient

Simultaneous Boost TomoTherapy

PTV1 (GTV) 66 Gy (2.2 Gy/die) (BED 10 80.5 Gy)

PTV2 (N+) 61.5 Gy (2.05 Gy/die)

PTV3 (N-) 54 Gy (1.8 Gy/die)

Adaptive Radiotherapy

RP-RC 83%

PRINCIPLES OF RADIATION THERAPY (3 of 5)

Recommended Radiation Doses:

Treatment type	Total dose	Fraction size
Preoperative*[1]	45-50 Gy	1.8-2 Gy
Postoperative[2,3]		
• Negative margins	50 Gy	1.8-2 Gy
• Extracapsular nodal extension or microscopic positive margins	54-60 Gy	1.8-2 Gy
• Gross residual tumor	up to 70 Gy	1.8-2 Gy
Definitive		
• Without concurrent chemotherapy[4]	up to 77.4 Gy (keep V20 ≤ 35%)	2-2.15 Gy
• With concurrent chemotherapy[5] (mainly carboplatin + paclitaxel)[5]	up to 74 Gy	2 Gy

*Doses greater than 50 Gy in the preoperative setting have been reported to be safe at selective institutions (Cerfolio et al, Ann Thorac Surgery 2005;80(4):1224; Kwong et al, J Thorac Cardiovasc Surg 2005;129(6):1250; Sonnett et al, Ann Thorac Surg 2004;78(4):1200). However, this is still considered experimental.

For Dose Volume Constraints for the Thorax see NSCL-C 4 of 5

For Dose Volume Data for Radiation Pneumonitis see NSCL-C 5 of 5

[1] Rusch VW, Giroux DJ, Kraut MJ, et al. Induction chemoradiation and surgical resection for superior sulcus non-small cell lung carcinomas: long-term results of Southwest Oncology Group Trial 9416 (Intergroup Trial 0160). J Clin Oncol 2007;25(3):313-8.

[2] Bradley JD, Paulus R, Graham MV, et al. Phase II trial of postoperative adjuvant paclitaxel/carboplatin and thoracic radiotherapy in resected stage II amd IIIA non-small cell lung cancer: promising long-term results of the Radiation Therapy Oncology Group--RTOG 9705. J Clin Oncol 2005;23(15):3480-7.

[3] Keller SM, Adak S, Wagner H, et al. A randomized trial of postoperative adjuvant therapy in patients with completely resected stage II or IIIA non-small cell lung cancer. Eastern Cooperative Oncology Group. N Engl J Med 2000;343(17):1217-22.

[4] Bradley J, Graham MV, Winter K, et al. Toxicity and outcome results of RTOG 9311: a phase I-II dose-escalation study using three-dimensional conformal radiotherapy in patients with inoperable non-small cell lung cancer. Int J Radiat Oncol Biol Phys 2005;61(2):318-28.

[5] Socinski MA, Rosenman JG, Halle J, et al. Dose-escalating conformal thoracic radiation therapy with induction and concurrent carboplatin/paclitaxel in unresectable stage IIIA/B non-small cell lung carcinoma: a modified phase I/II trial. Cancer 2001;92(5):1213-23.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

Results

Patient	PTV 1		PTV 2			ESOPHAGUS		
	$V_{95\%}$	$V_{105\%}$	$V_{90\%}$	$V_{95\%}$	Vol. (cc)	V35	Vol.(cc)	Toxicity RTOG
1	98.8 %	0.0 %	88.5 %	74.0%	331.8	30.1%	34.2	G1
2	100.0 %	0.0 %	100.0 %	99.0%	175.4	29.6%	28.5	G0
3	99.7 %	0.0 %	100.0 %	99.5%	50.4	38.5%	18.4	G0
4	98.6 %	0.1 %	99.9 %	99.4%	219.5	25.7%	35.5	G1
5	98.0 %	0.0 %	99.2 %	96.4%	237.0	38.6%	21.8	G0