La Radioterapia nel trattamento integrato del carcinoma polmonare non microcitoma

Irradiazione profilattica dei linfonodi e volumi post-chemioterapia

Umberto Ricardi
Università di Torino

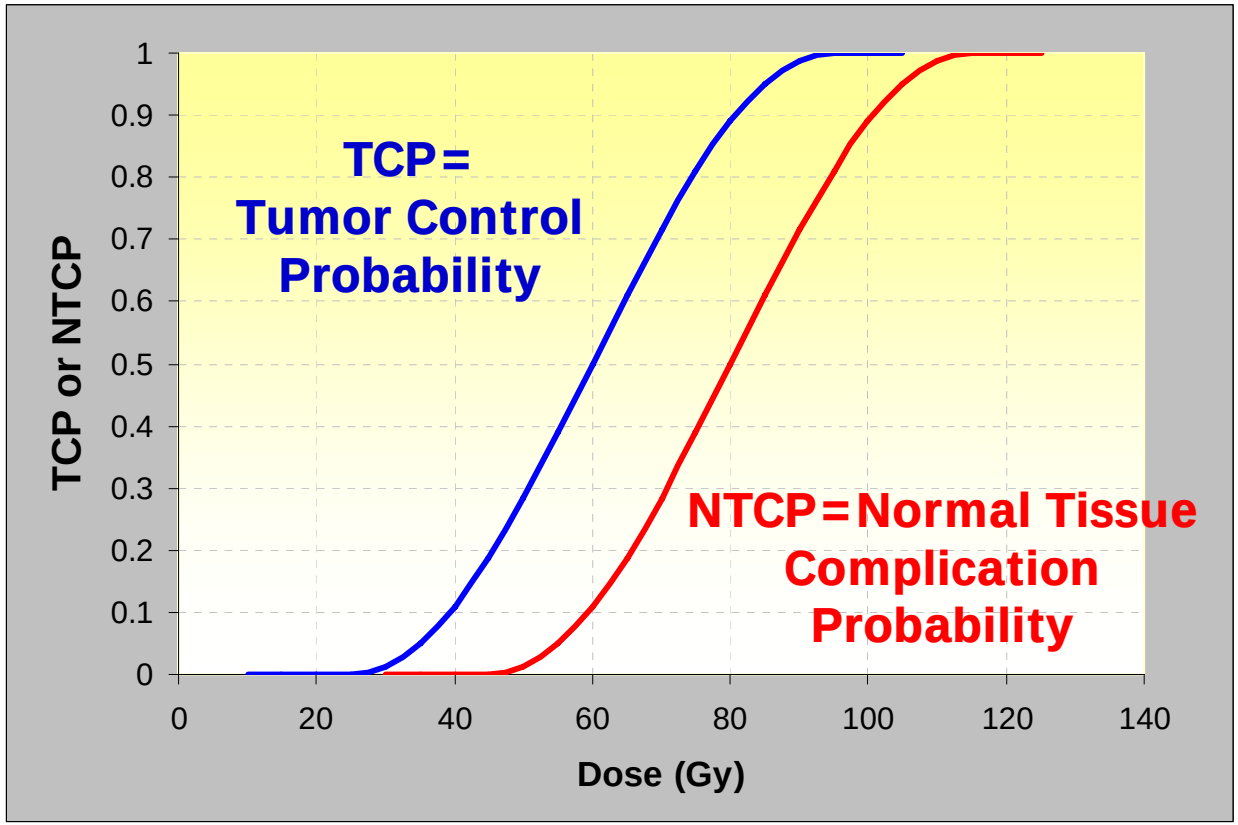
Unsuccessful outcome after Radiation Therapy in locally advanced NSCLC is caused by

- **Inadequate dose to tumor**
  (TCP very low with standard doses)

- **Excessive dose to normal tissues**

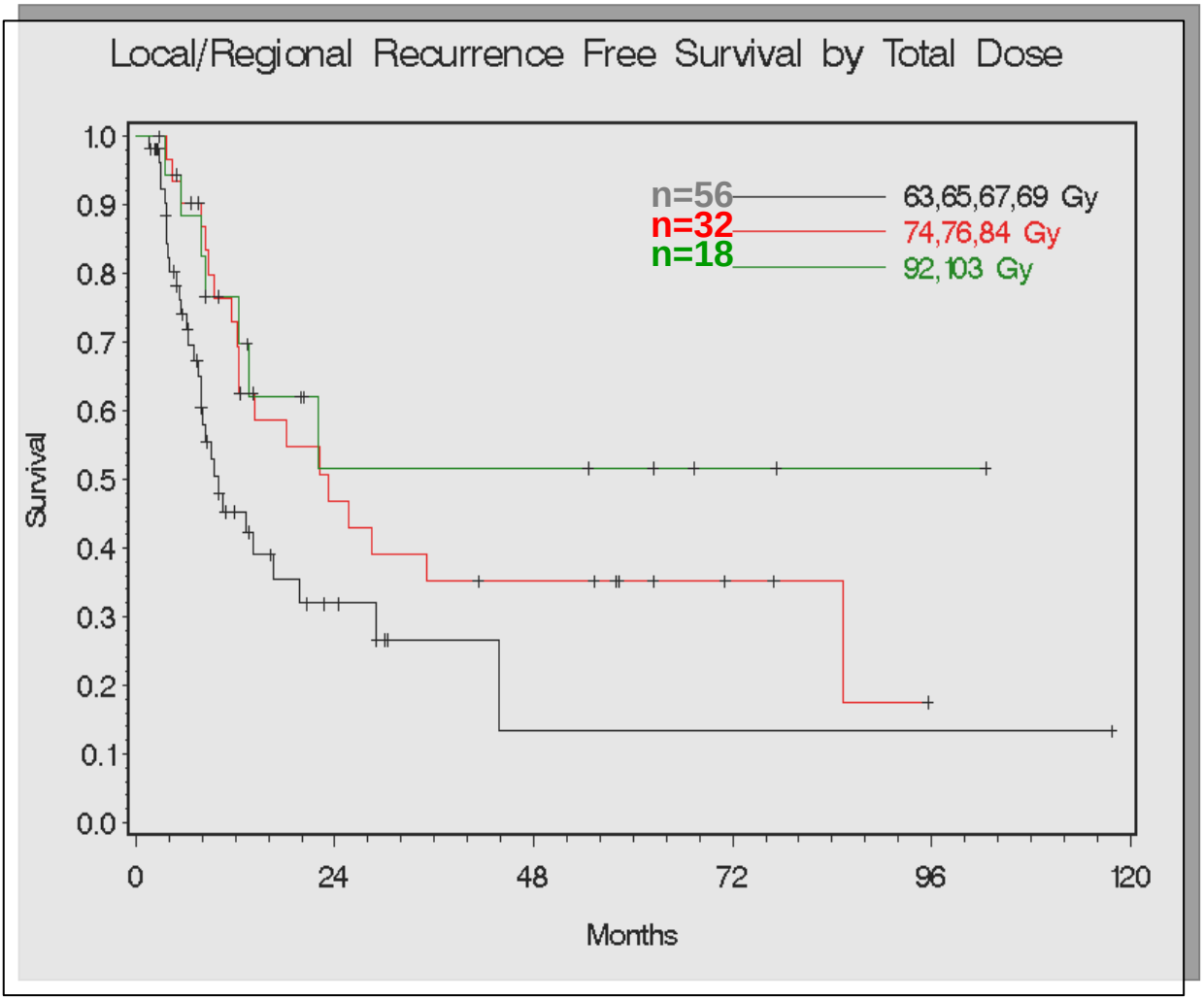
Need for dose intensification able to achieve a better “uncomplicated tumor control”

Challenges In Radiation Therapy



Dose of radiation is limited by normal tissue tolerance

Dose Matters to Tumor Control



Total RT Dose is the only significant independent predictor for local control (p=0.015)

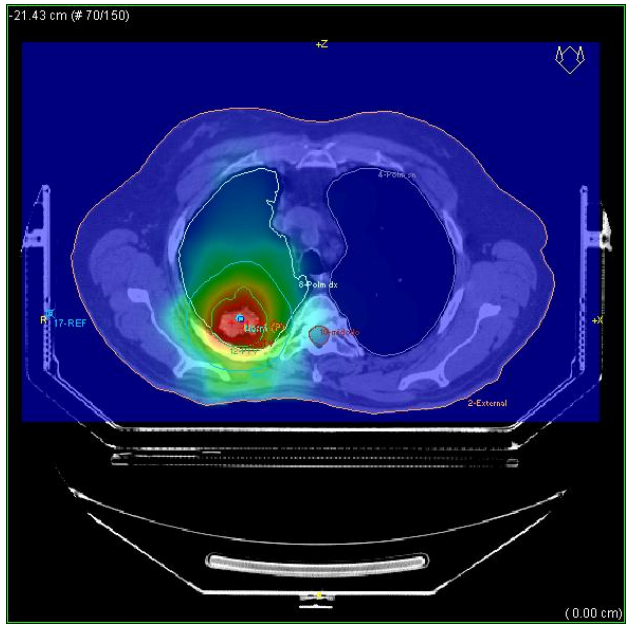
Above 63-69 Gy, every Gy+ ~ 1+% improvement

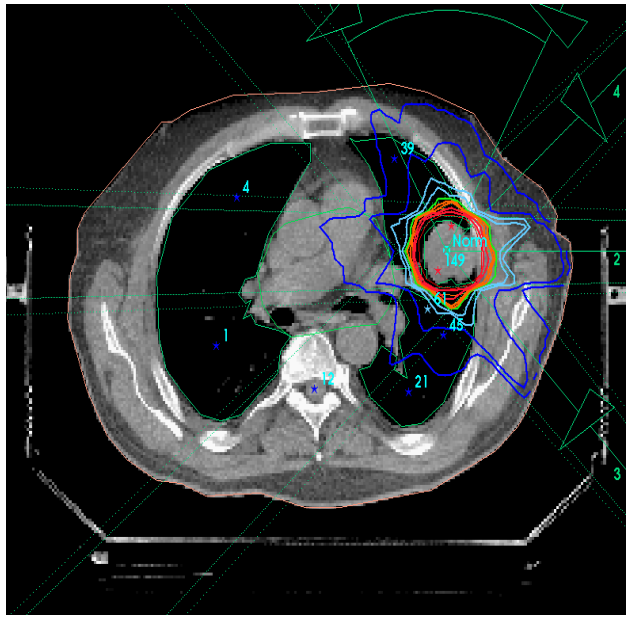
Michigan University

Optimized radiotherapy techniques to improve results

Stage I NSCLC

Local control rates >85% for small peripheral tumors treated with stereotactic radiotherapy (Onishi ’04)



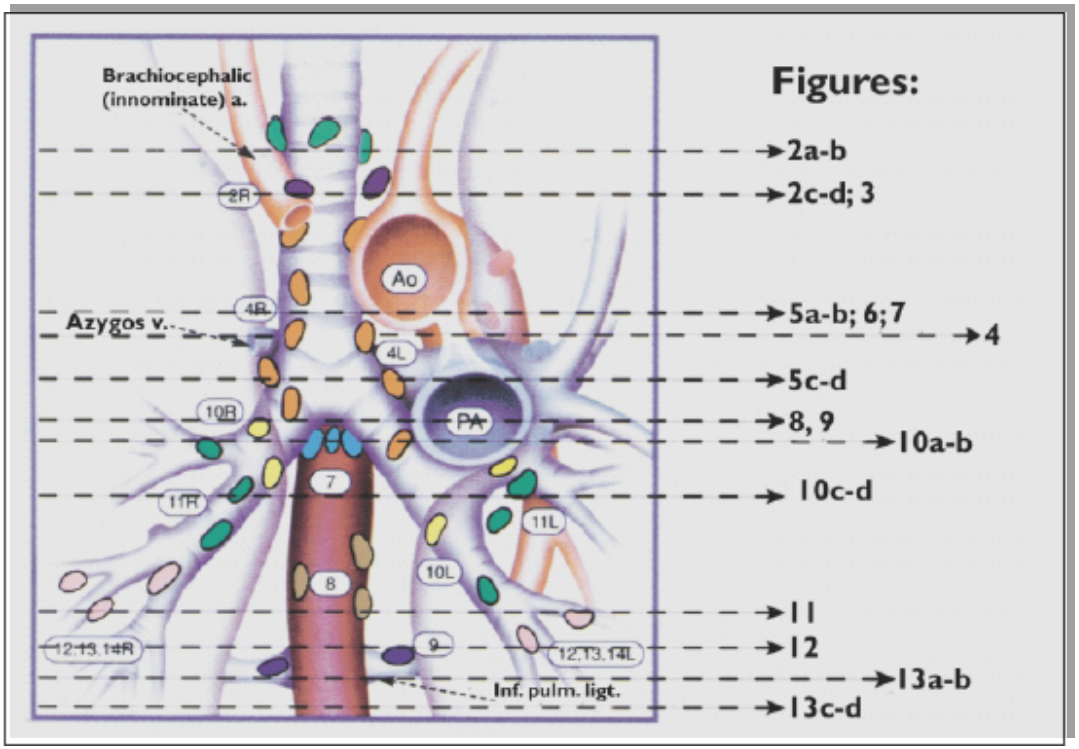


Radiotherapy: new developments

- Involved-field conformal radiotherapy
- Integration of PET into radiotherapy planning
- Image-guided 4D radiotherapy
- Concurrent chemo-radiotherapy

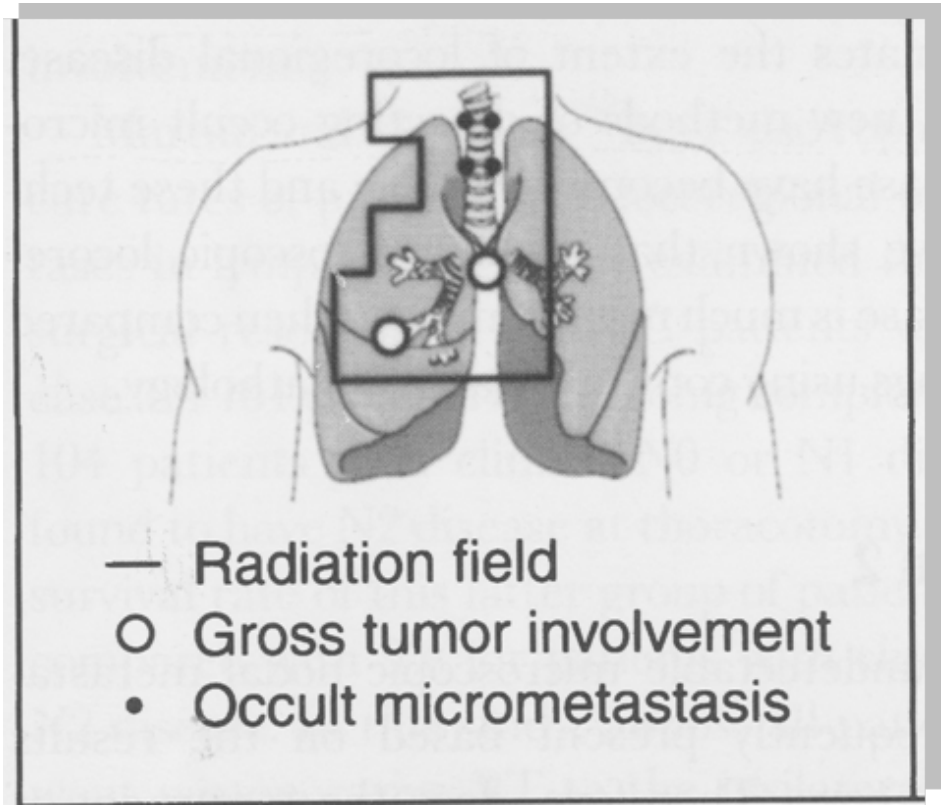
The Elective Nodal Irradiation (ENI) Paradigm

Background



In surgical series systematic nodal dissection in stage I and II detected 10-20% of microscopic mediastinal metastases

The Elective Nodal Irradiation (ENI) Paradigm



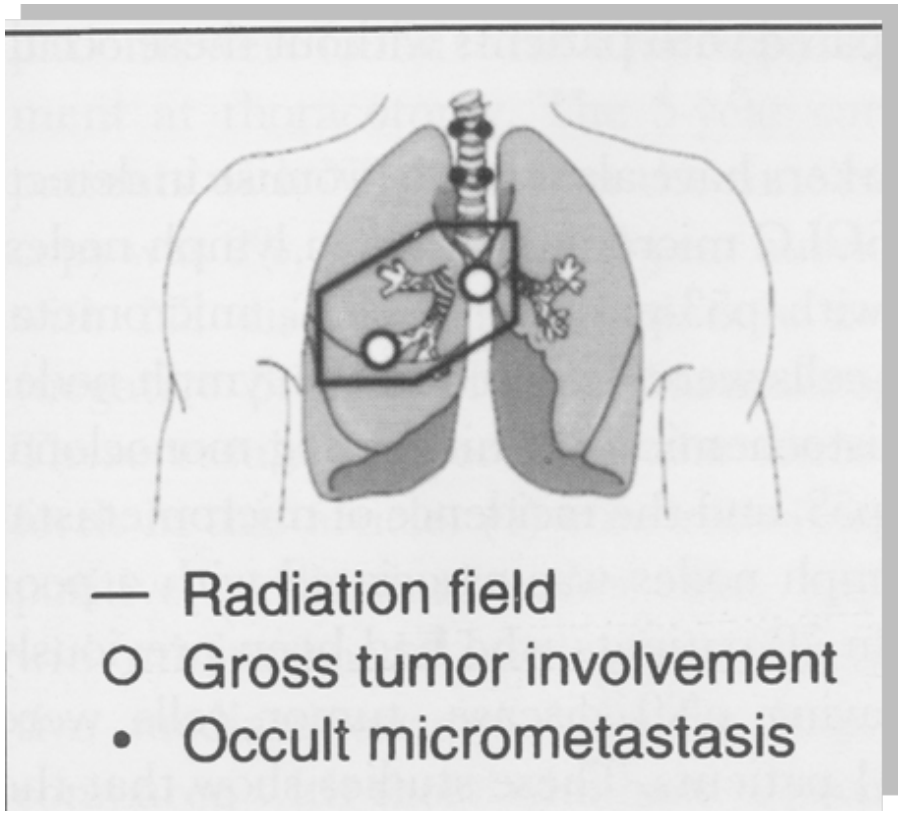
PROS

-Some dose escalation for gross disease is still possible with ENI

-Very high doses for gross disease are unlikely to result in a benefit that offsets the potential benefits of treating occult micrometastases

-Occult micrometastases in regional lymphnodes are present in 20-60% of cases. Some of these patients can be cured

High dose for Gross disease Paradigm



CON

-High doses for gross disease will increase local control. Potential survival benefit

-High doses cannot be safely delivered and still give ENI

-ENI of occult micrometastases is of marginal or no benefit as these patients will also have distant metastases

Int. J. Radiation Oncology Biol. Phys., Vol. 50, No. 3, pp. 681–685, 2001

0360-3016/01/$–see front matter

PII S0360-3016(01)01482-1

CLINICAL INVESTIGATION **Lung**

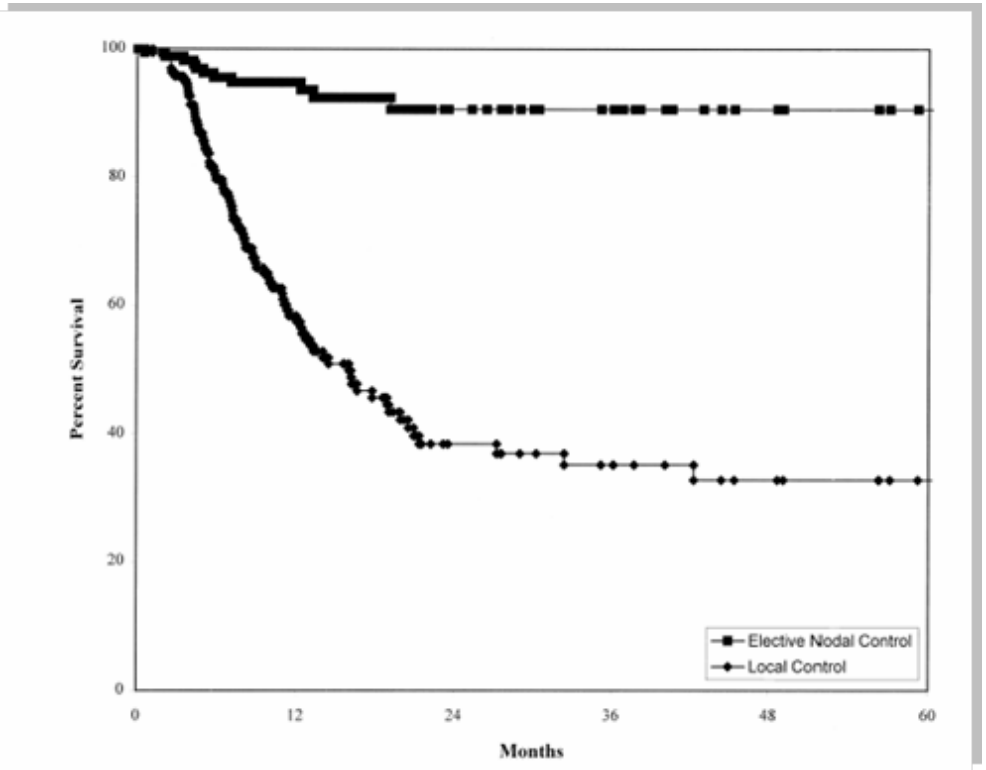
ELECTIVE NODAL IRRADIATION IN THE TREATMENT OF NON–SMALL-CELL LUNG CANCER WITH THREE-DIMENSIONAL CONFORMAL RADIATION THERAPY

KENNETH E. ROSENZWEIG, M.D.,* SANG E. SIM, M.D.,* BORYS MYCHALCZAK, M.D.,* LOUISE E. BRABAN, B.S.,† RACHEL SCHINDELHEIM, M.S.,* AND STEVEN A. LEIBEL, M.D.*

Departments of *Radiation Oncology and †Medical Physics, Memorial Sloan-Kettering Cancer Center, New York, NY

- **171 pts with NSCLC treated with 3D-CRT at MSKCC**
- **Only lymph node regions involved with tumor were included in GTV**
- **Median dose 68.4 Gy (50.40-81 Gy)**
- **Elective nodal failure was defined as a recurrence in an initially uninvolved lymph node in the absence of local failure**
- **The mediastinum was divided into 7 anatomic regions and the dose to these regions was determined**

Rosenzweig, IJROBP, 2001



Local control and elective nodal failure

- 6.4% elective nodal failure
- 2ys EN control 91%
- 2ys primary tumor control 38%
- Median time to ENF 4 months
- Multiple lymph node failures

The main cause of failure is local progression of the disease (62% at 2 ys)

Only 6% of pts developed a failure in uninvolved nodes

Rosenzweig, IJROBP, 2001

ELSEVIER

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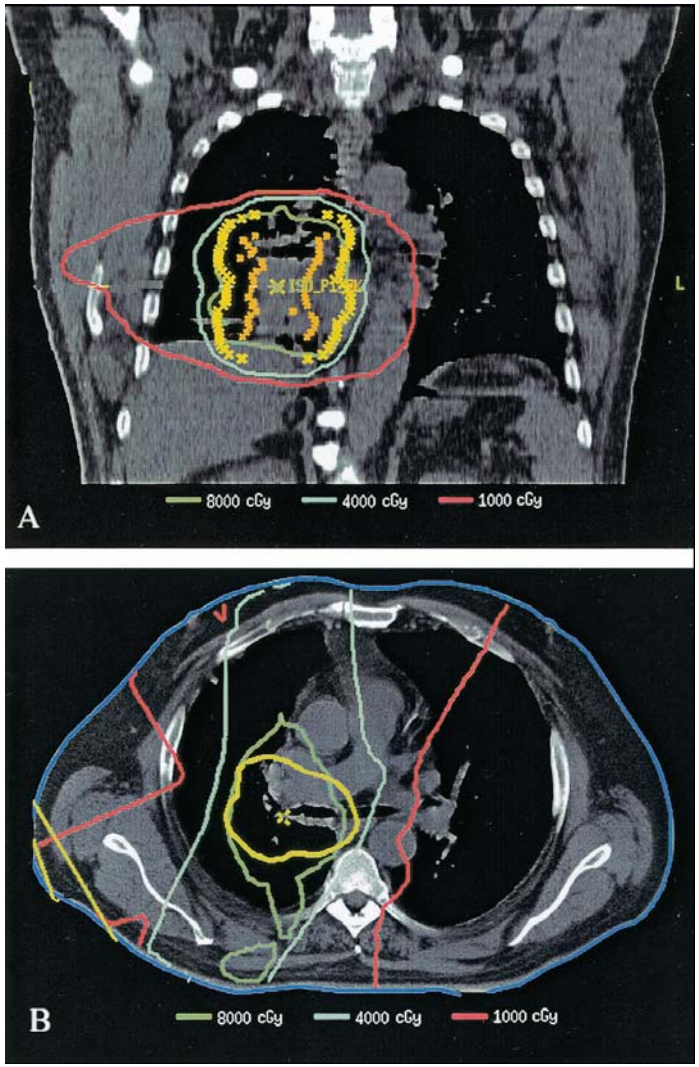
Conclusions

Since the inclusion of ENI leads to higher rates of predicted pulmonary toxicity, we are wasting radiation on sites that have no evidence of disease rather than focusing the high dose levels of radiation on regions with known tumor

Rosenzweig, IJROBP, 2001

Involved-field Radiotherapy

ENF by mediastinal lymphnode region



Region	No	Median Dose	Dose>40Gy	Failure Rate
Ipsil supraclav.	151	0	9%	1%
Contr supraclav.	160	0	0%	3%
Ipsil superior mediastinum	134	1800	34%	0%
Contr superior mediastinum	156	510	7%	1%
Ipsil inferior mediastinum	75	5940	64%	4%
Contr inferior mediastinum	141	1800	20%	1%
Subcarinal	107	3193	41%	2%

Rosenzweig, IJROBP, 2001

Involved-field Radiotherapy

ENF by mediastinal lymphnode region

Patient	Tumor stage	Primary disease location	Site of elective nodal failure	Dose to site of failure (cGy)
1	IIB	Left upper lobe, hilum	Contralateral inferior mediastinum	1400
2	IIIB	Right upper lobe, hilum	Contralateral supraclavicular	0
3	I	Left lower lobe	Bilateral inferior mediastinum	0, 0
4	IIIA	Left upper lobe, superior mediastinum	Contralateral inferior mediatinum	1000
5	IIIB	Bilateral paratracheal	Contralateral supraclavicular	3900
6	IIIB	Right upper lobe, inferior mediastinum	Subcarinal	5700
7	IIIB	Left upper lobe, inferior mediastinum	Contralateral superior mediastinum	750
8	IIIB	Right upper lobe, inferior mediastinum, superior mediastinum, supraclavicular	Subcarinal, contralateral mediastinum	6000, 3650
9	IIIB	Left upper lobe, contralateral inferior mediastinum, subcarinal	Contralateral superior mediastinum, ipsilateral inferior mediastinum	0, 2000
10	IIIB	Right upper lobe, bilateral inferior mediastinum	Ipsilateral supraclavicular, Contralateral supraclavicular	1800, 0
11	IIIB	Left upper lobe, bilateral inferior mediastinum	Ipsilateral supraclavicular, Contralateral supraclavicular	0, 0

Rosenzweig, IJROBP, 2001

Changes in radiotherapy fields

Involved-field Radiotherapy

3D-CRT doses of 69.3-84 Gy to Gross Tumor Volume resulted in:

- **100 % of the ipsilateral hilum**
- **59 % of the 4 station**
- **57 % of the 5 station**
- **97 % of the 7 station**
- **57 % of the controlateral hilum**

...receiving >50Gy

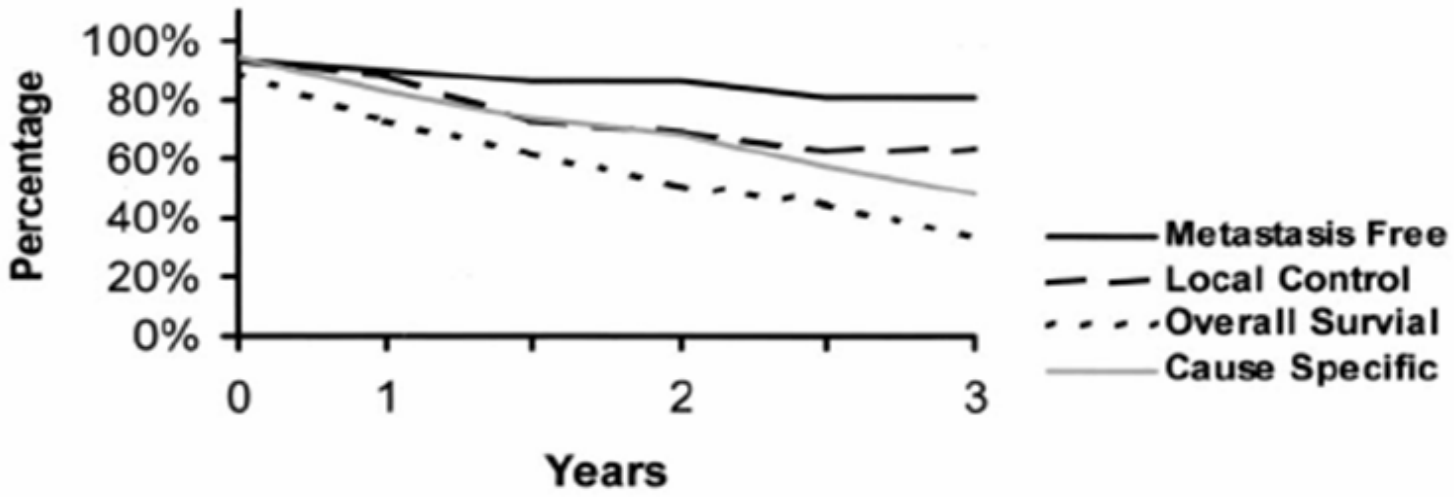
Martel, IJROBP, 1999

ENF in medically inoperable patients with Stage I NSCLC treated with limited Radiotherapy fields

- 56 pts with Stage I inoperable NSCLC (31 pts T1N0; 25 pts T2N0)
- Median dose 70 Gy (Range 60-84 Gy)
- ENI in 22 pts (39%)

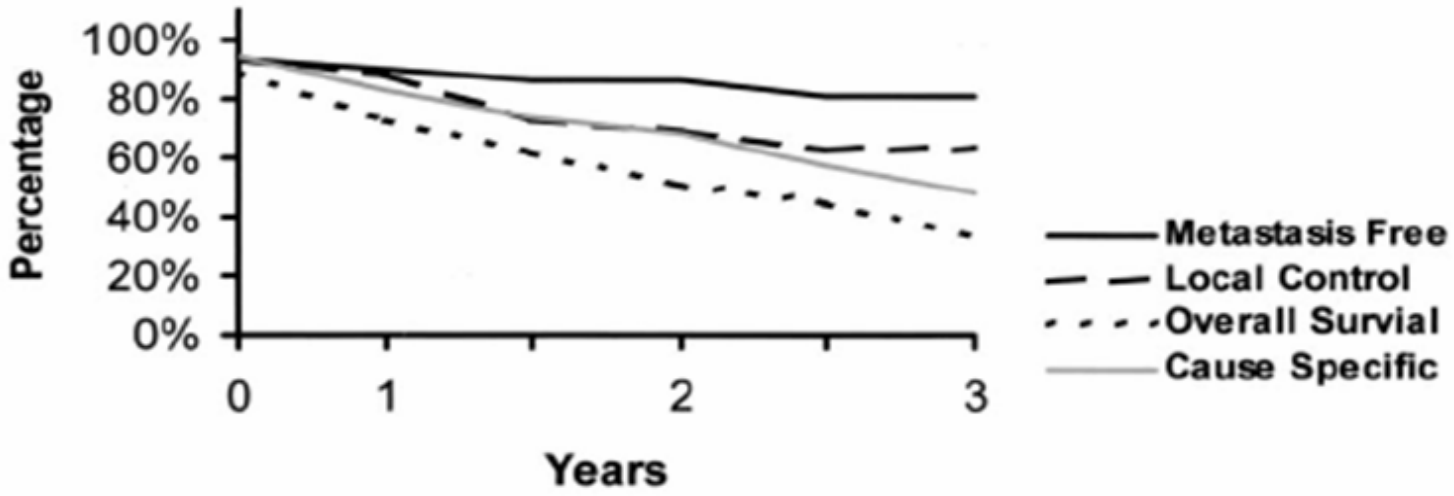
Bradley, 2003

ENF in medically inoperable patients with Stage I NSCLC treated with limited Radiotherapy fields



- Median follow-up 20 months
- Local control rate 88%, 69%, 63% at 1,2 and 3 years respectively
- Cause-specific survival rate 82%, 67%, 51% at 1,2 and 3 years respectively
- Overall survival rate 73%, 51%, 34% at 1,2 and 3 years respectively
- Metastasis free survival rate 90%, 85%, 81% at 1,2 and 3 years respectively

ENF in medically inoperable patients with Stage I NSCLC treated with limited Radiotherapy fields



No statistically significant difference in cause-specific or overall survival according to whether pts received ENI

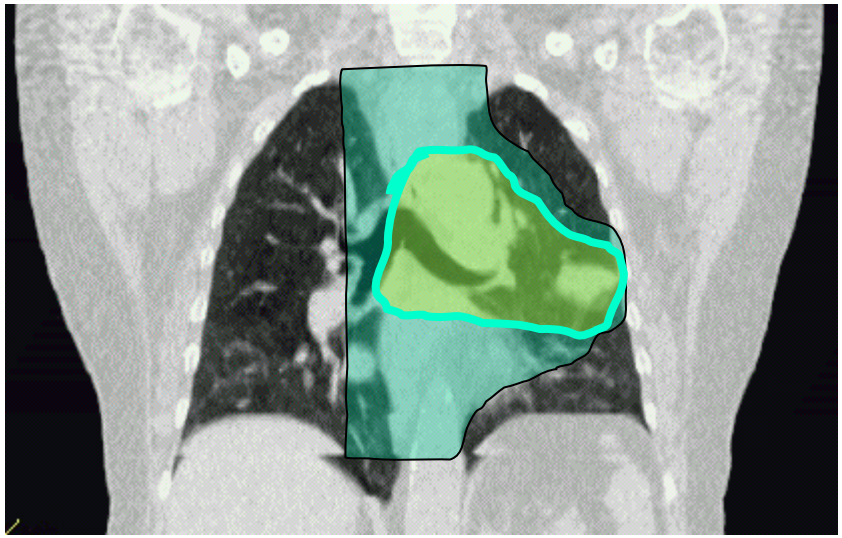
ENI or not ENI?

- There are no data to suggest that omitting ENI compromises either locoregional control or survival
- Eliminating ENI may allow tolerable dose escalation while maintaining the benefits of concurrent therapy
- Why worry about disease you cannot see, when you cannot control the disease that you can see….

General trend to limit radiation volumes

Changes in radiotherapy fields

Elective nodal radiotherapy



Involved-field radiotherapy

CTV = GTV

In specifying the CTV....

- ...the physician must **not only** consider microextensions of the disease near the GTV,..
- ....but also the natural avenues of spread for the particular disease and site including lymph node, perivascular, and perineural extensions. These may be designated CTV-N (and if necessary CTV-N1, CTV-N2, and so on)

Purdy JA, Seminars Radiation Oncology 2004

In specifying the CTV....

- Evaluation of microscopic tumor extension in NSCLC for 3D-CRT...

  ..The microscopic extension was different between ADC and SCC...

  ..The mean value of microscopic extension was 2.69 mm for ADC and 1.48 mm for SCC (p=0.01)

  ..A margin of 8 mm and 6 mm must be chosen for ADC and SCC respectively....

Giraud, 2000

Current Chemo-Radiotherapy protocols in locally advanced NSCLC

- **Pre-chemo or post-chemo volumes**
- **GTV-N Criteria**
- **Automatic tool in 3D software planning for PTV encountering CTV-T and CTV-N**

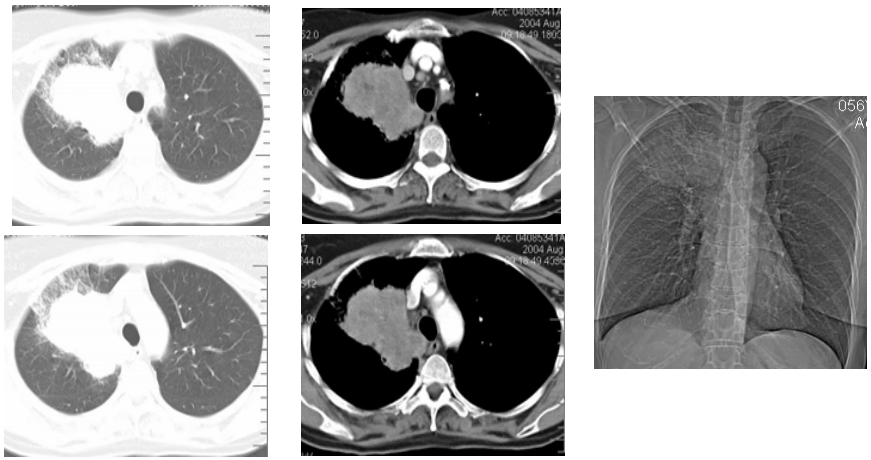
Current Chemo-Radiotherapy protocols in locally advanced NSCLC

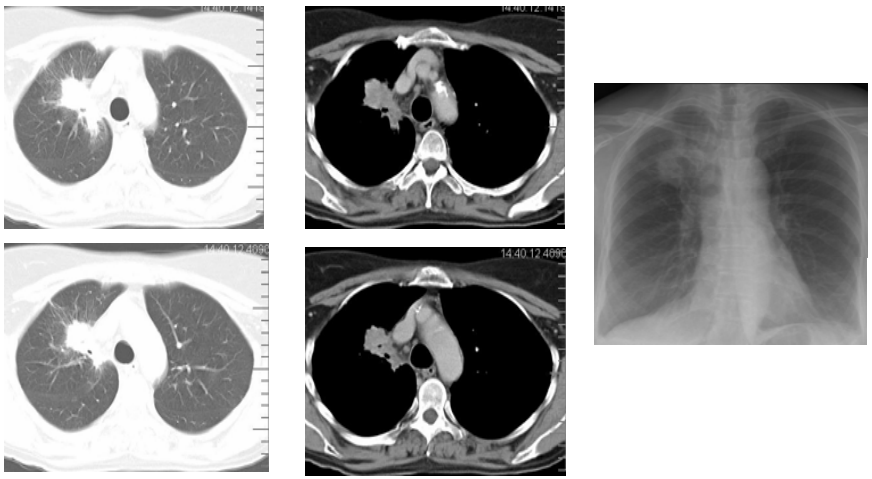
- Pre-chemo or post-chemo volumes

The Gross Tumor Volume (GTV) is the gross palpable,visible or clinically demonstrable location and extent of the malignant growth"

The GTV consists of primary tumor (GTV-T) and if present metastatic lymphadenopathy (GTV-N) or other metastases (GTV-M) ICRU 71

Current Chemo-Radiotherapy protocols in locally advanced NSCLC





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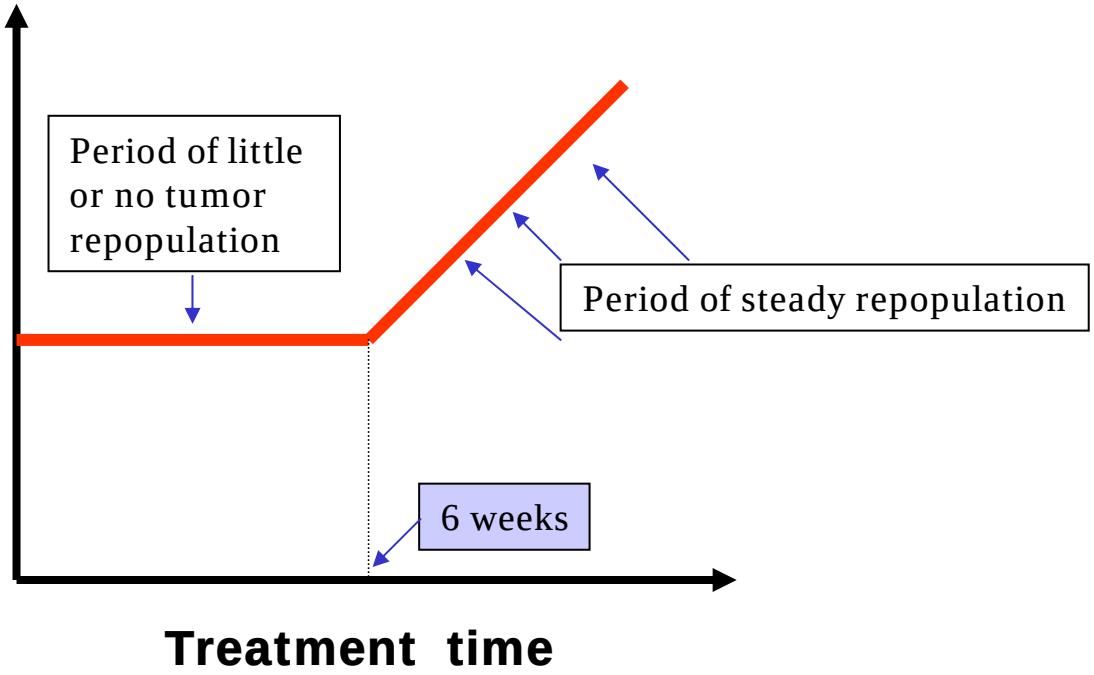
Post-chemo GTV

NSCLC: impact of tumor repopulation

Total dose required for given tumor control probability



Tumour repopulation results in a **1.6 % daily loss in survival** when overall treatment time is prolonged **beyond 6 weeks** [Fowler '00].

Chemoradiotherapy

What kind of combination?

Sequential Chemotherapy → Radiotherapy

Induction Chemotherapy X X

RT 

Concurrent Chemoradiotherapy

Chemotherapy (x) (x) (x)

RT 

Induction Chemotherapy → Concurrent Chemoradiotherapy

Induction Chemotherapy X X

Concurrent Chemotherapy (x) (x) (x)

RT 

Concurrent Chemoradiotherapy → Consolidation Chemotherapy

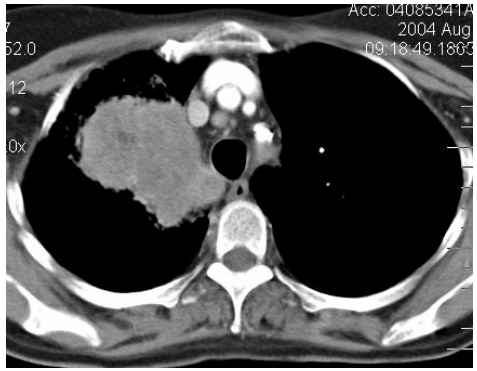
Concurrent Chemotherapy (x) (x) (x)

RT 

Consolidation Chemotherapy X X

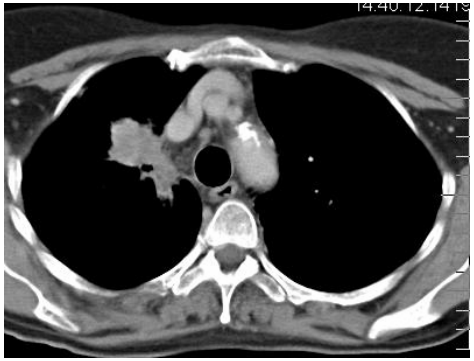
X: full dose (x): reduced dose ?

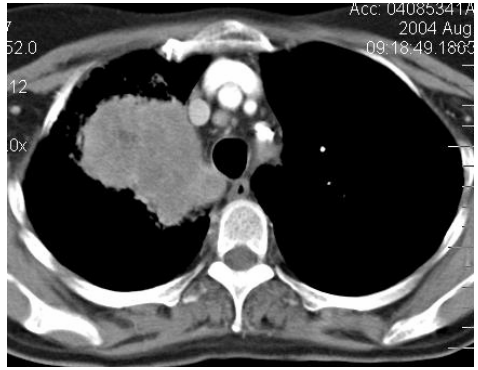
Which CT scan excites you??



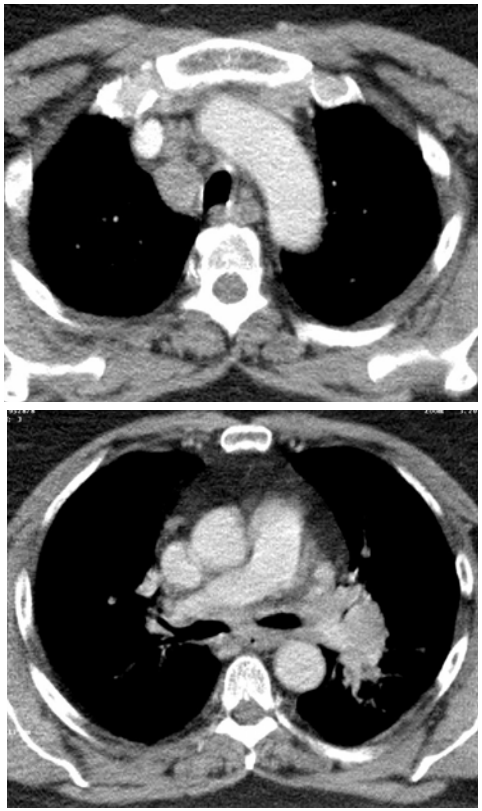
Induction chemotherapy

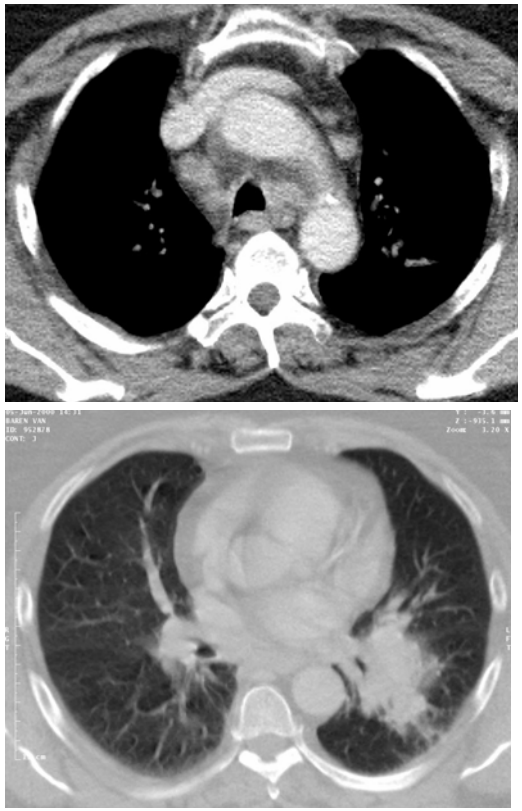
Concurrent chemo-RT

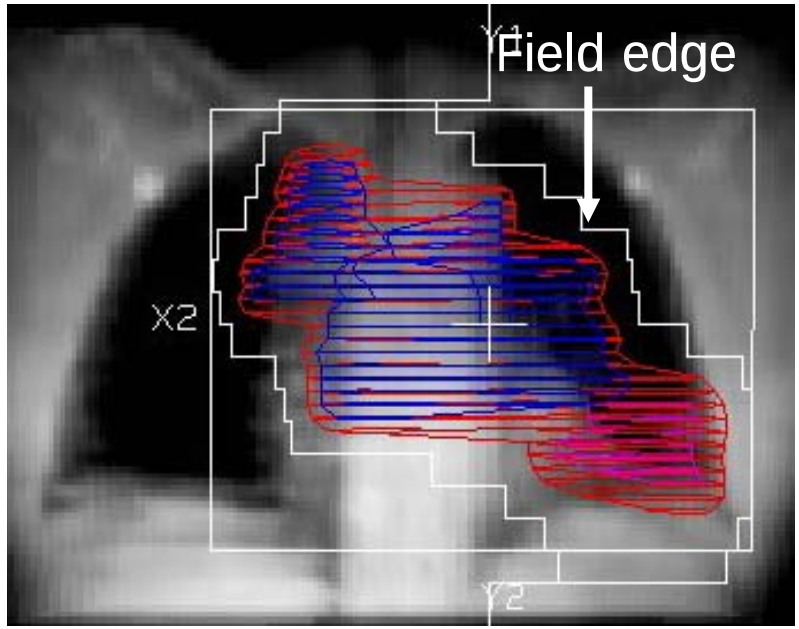




High-risk case: Lower lobe tumor + contralateral upper mediast. nodes





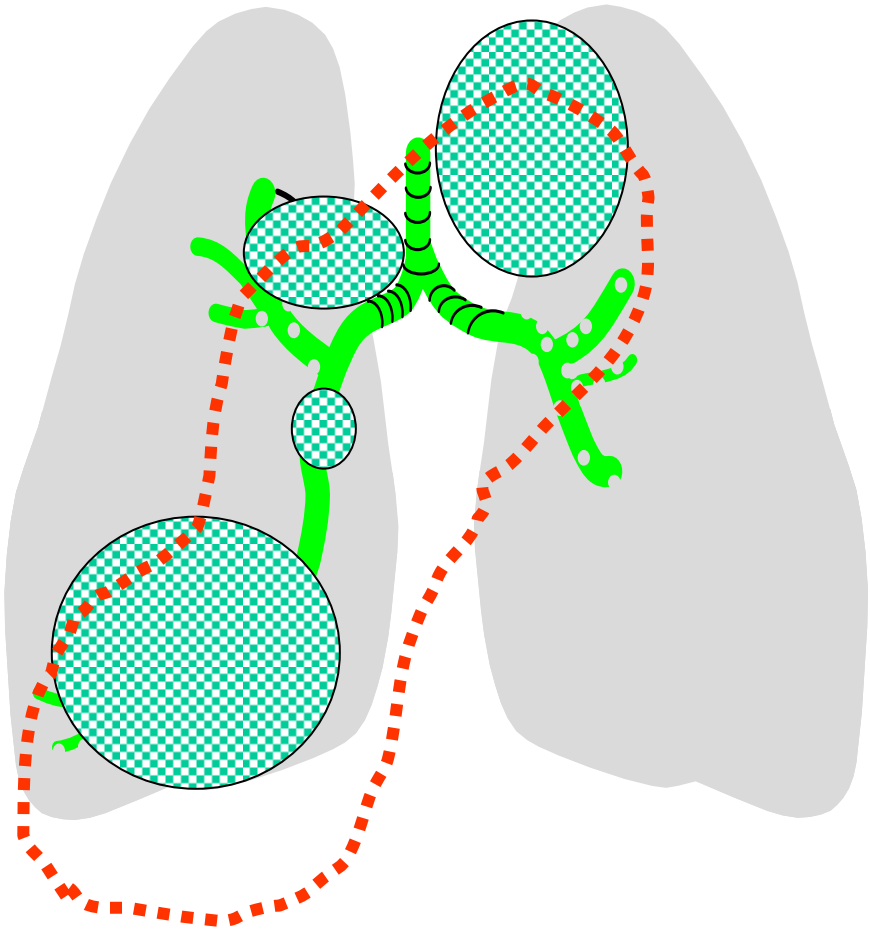


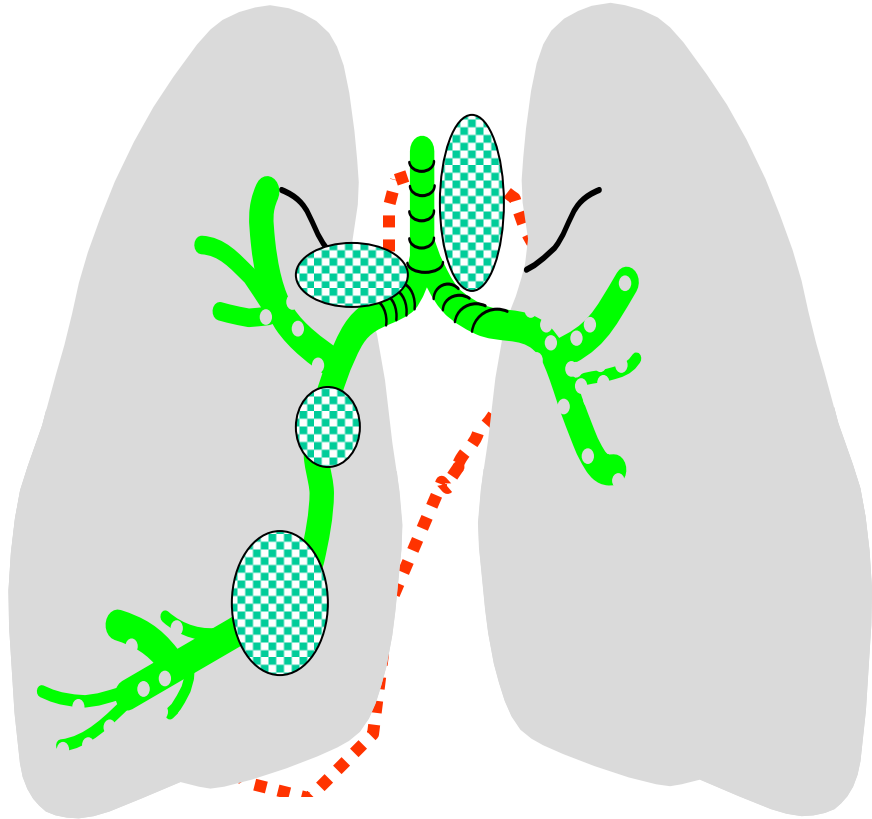
V_{20} = 47 %

High-risk patients: Sequential RT to post-chemo tumour volume

Pre-chemo, V_{20} = 47%

Post-chemo V_{20} = 28%





Current Chemo-Radiotherapy protocols in locally advanced NSCLC

- Pre-chemo or post-chemo GTV
- GTV-N Criteria
- Automatic tool in 3D software planning for PTV encountering CTV T and CTV N

Current Chemo-Radiotherapy protocols in locally advanced NSCLC

- Specify nodal stations using the Mountain/Dresler modifications from Naruke/ATS-LCSG map (1997).
- Include nodes with a short-axis diameter of ≥1cm in the GTV.
- FDG-PET scans superior to CT for mediastinal nodal metastases.

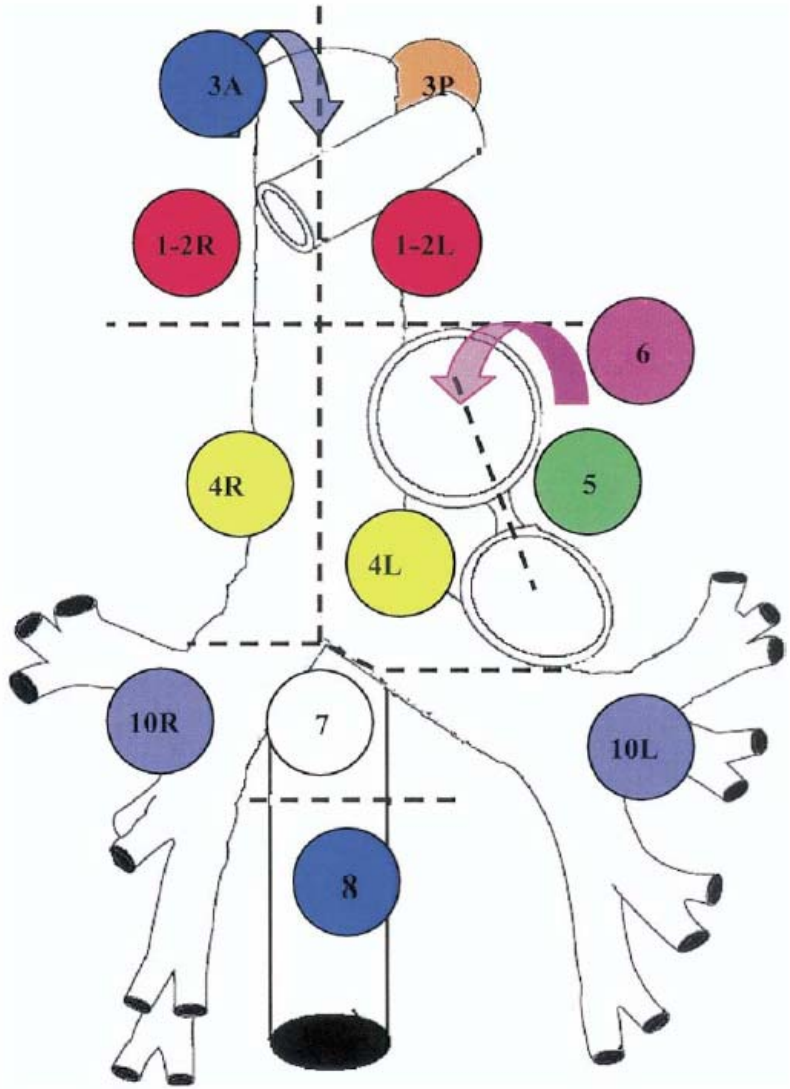


Fig. 1. Schema of Mountain and Dresler classification system, after Mountain and Dresler (1). Station 3A is anterior to Stations 1–2R and L and Stations 4R and L (blue arrow). Station 3P is posterior to trachea. Station 6 is anterior and lateral to aortic arch and ascending aorta (purple arrow).

Current Chemo-Radiotherapy protocols in locally advanced NSCLC

GTV-N

-The choice of the upper limit for normal nodal size is a complex issue, and may vary with nodal position: from 11 mm in the paratracheal to 3mm in the hilar regions

- CT specificity according to mediastinal node site varied from 72% for station 10R (right ilar) to 94% for station 10L (left hilar) when the criteria for positivity were 10 mm or over

- In the presence of obstructive pneumonitis the rate of false positive lymph node involvement increased to 45%

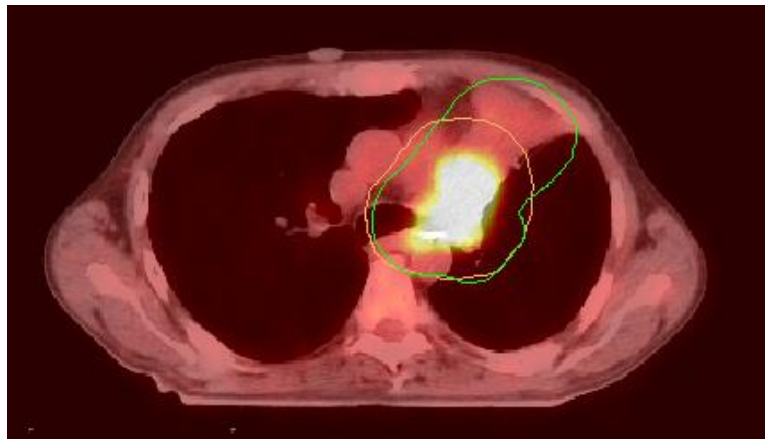
MacLoud,1992

CT

•The sensitivity of CT imaging is low for determining the extent of the nodal disease. Sensitivity and specificity for mediastinal staging is 57% and 84% respectively (Toloza et al.)

• CT assisted volume definition remains the gold standard for XRT

PET



• The sensitivity of PET imaging is high for determining the extent of the nodal disease. Sensitivity and specificity for mediastinal staging is 84% and 89% respectively (Toloza et al.)

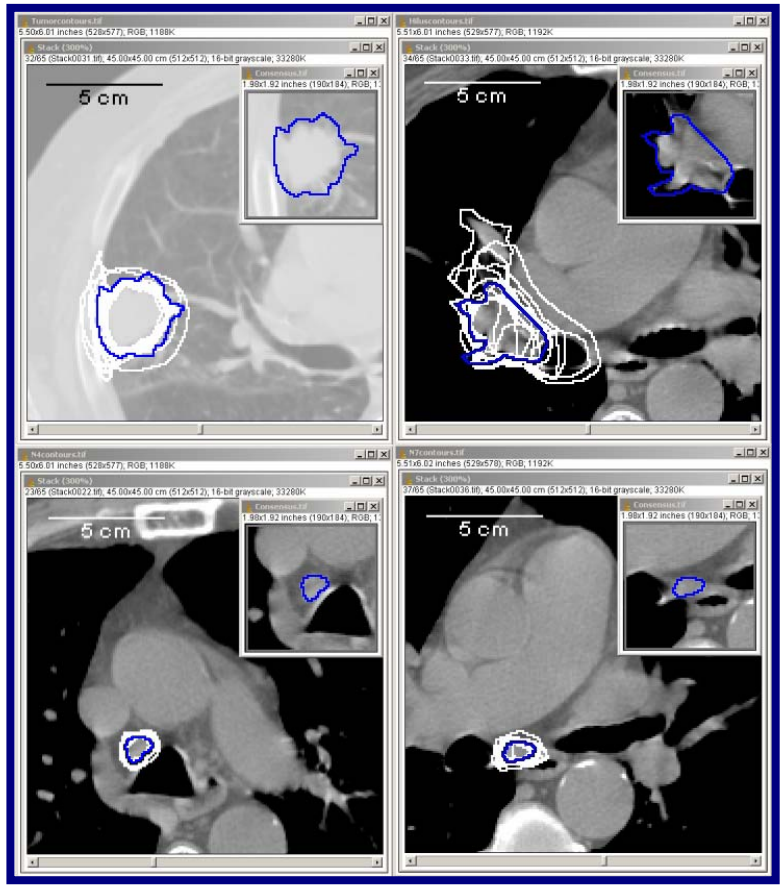
• PET provides information on biologically active tumor tissue

Multidimensional conformal Radiation Therapy (BTV)

Current Chemo-Radiotherapy protocols in locally advanced NSCLC

- **Pre-chemo or post-chemo GTV**
- **GTV N Criteria: size, biopsy, PET**
- **Automatic tool in 3D software planning for PTV encountering CTV T and CTV N**

Current Chemo-Radiotherapy protocols in locally advanced NSCLC



Current Chemo-Radiotherapy protocols in locally advanced NSCLC

- Fluoroscopy is not a reliable for 3D treatment planning.
- Adding ‘standard’ margins to CTV derived from a single rapid CT scan leads to inappropriately large PTV’s (or inadequate coverage)
- ‘Slow’ CT scans which capture reproducible target volumes for peripheral lung cancers.
- A 5 mm margin added to mediastinal nodes for mobility.

EORTC recommendations for treatment planning and execution in lung cancer

Generating Target Volumes

- Specify nodal stations using the Mountain/Dresler modifications from Naruke/ATS-LCSG map (1997).
- Include nodes with a short-axis diameter of ≥1cm in the GTV.
- FDG-PET scans superior to CT for mediastinal nodal metastases.
- ENI not shown to confer a survival benefit in curative RT of NSCLC
- **3D margins added to CTV to achieve specified tumor coverage probability (using known random and systematic set-up errors)**

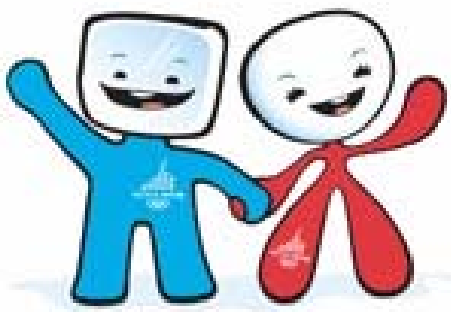
Literature based recommendations for treatment planning and execution for high precision radiotherapy in lung cancer.
Senan, 2004

EORTC recommendations for treatment planning and execution in lung cancer

High precision radiotherapy is a multi-step process, which is only as good as the weakest component

Literature based recommendations for treatment planning and execution for high precision radiotherapy in lung cancer.

Senan, 2004



torino 2006

Index

Decrease in therapeutic nihilism about stage III NSCLC

Co-op Group Trial	MST (months)	3-yr SV
CALGB 8433 (RT)	9.6	10%
CALGB 8433 seq C-RT	13.7	24%
RTOG 9104 conc C-RT	19.6	40%
RTOG 9410 seq C-RT	14.6	31%
RTOG 9410 conc C-RT	17.1	37%
SWOG 9504	27.0	40%

We have made some progress!