Radiation therapy in patients with lung cancer

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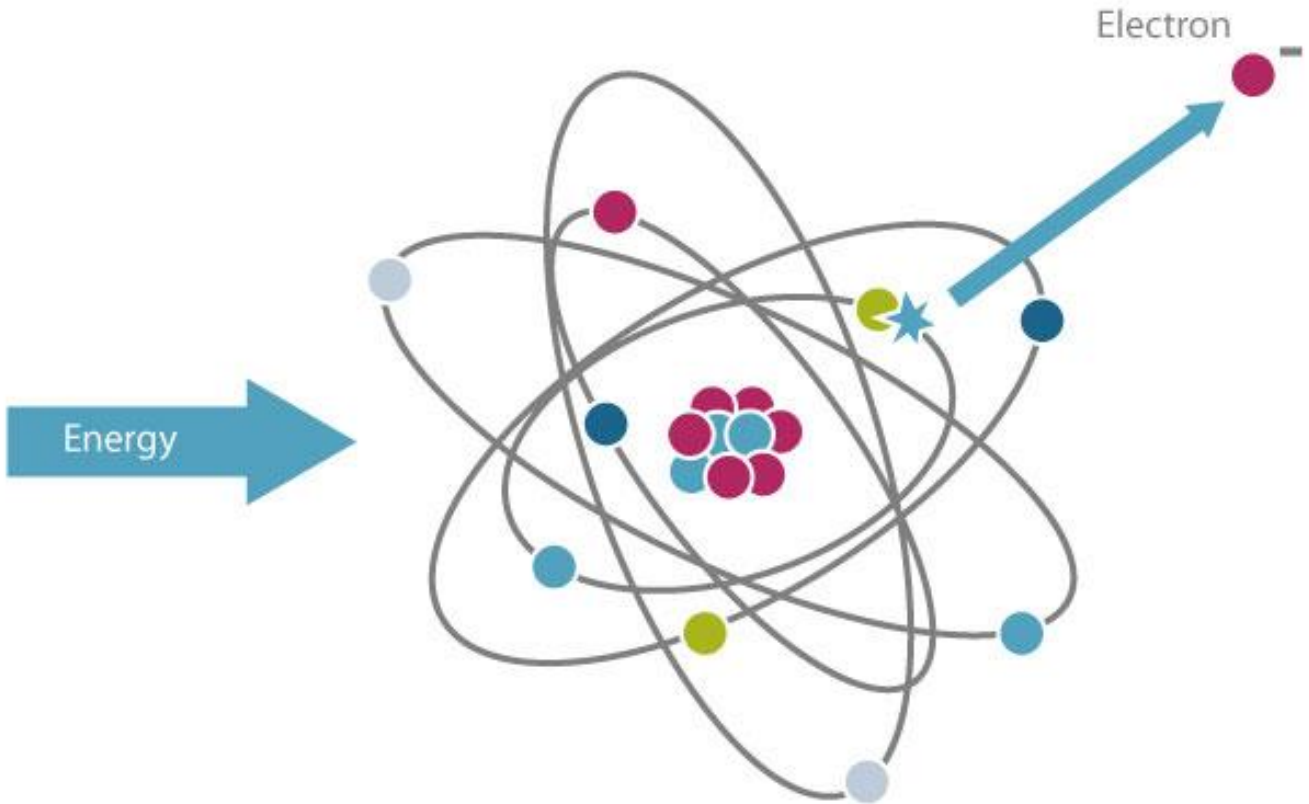
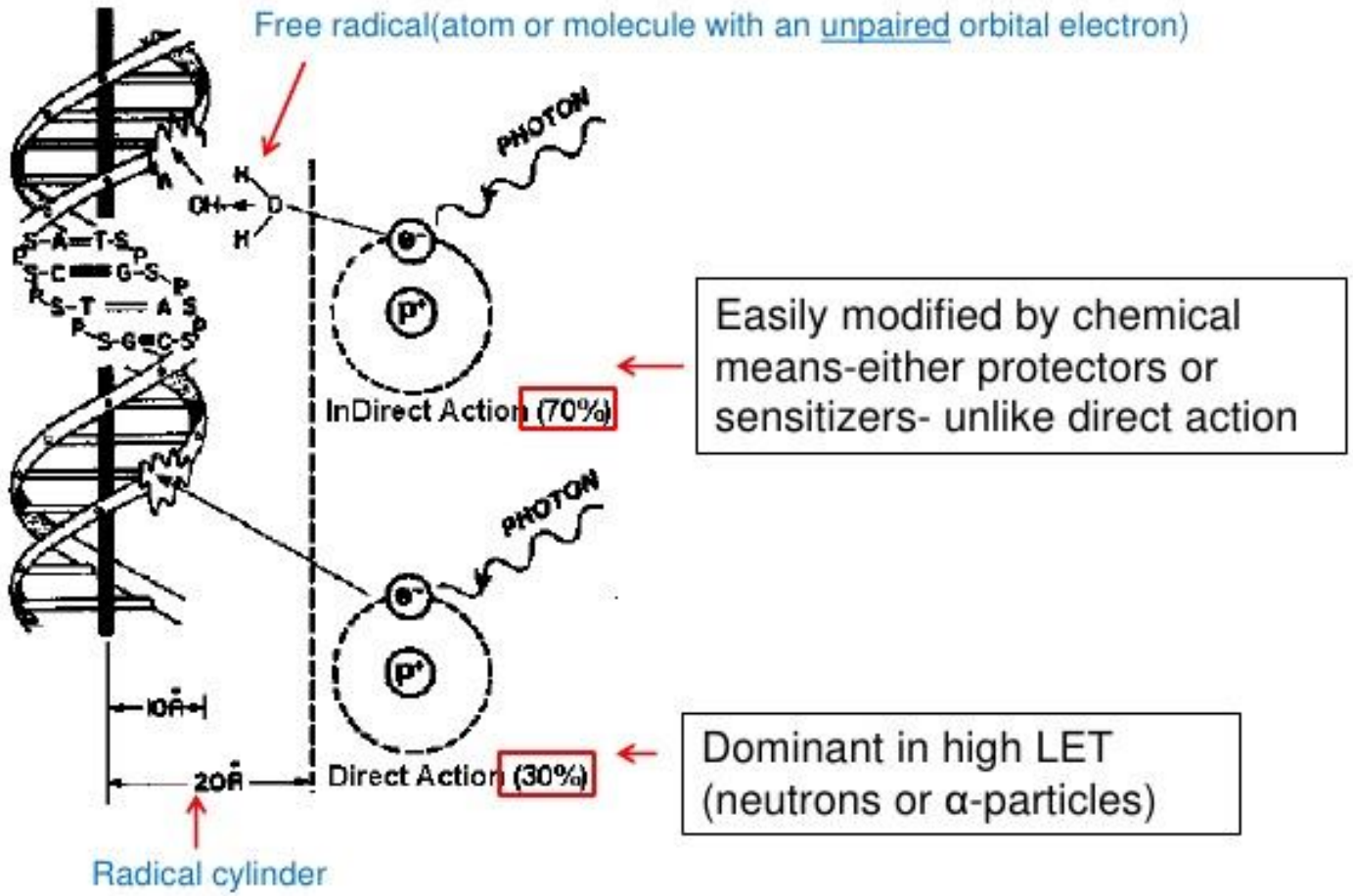
Radiation oncology department
Kim Young Il

Radiation is ENERGY.

Radiation definition

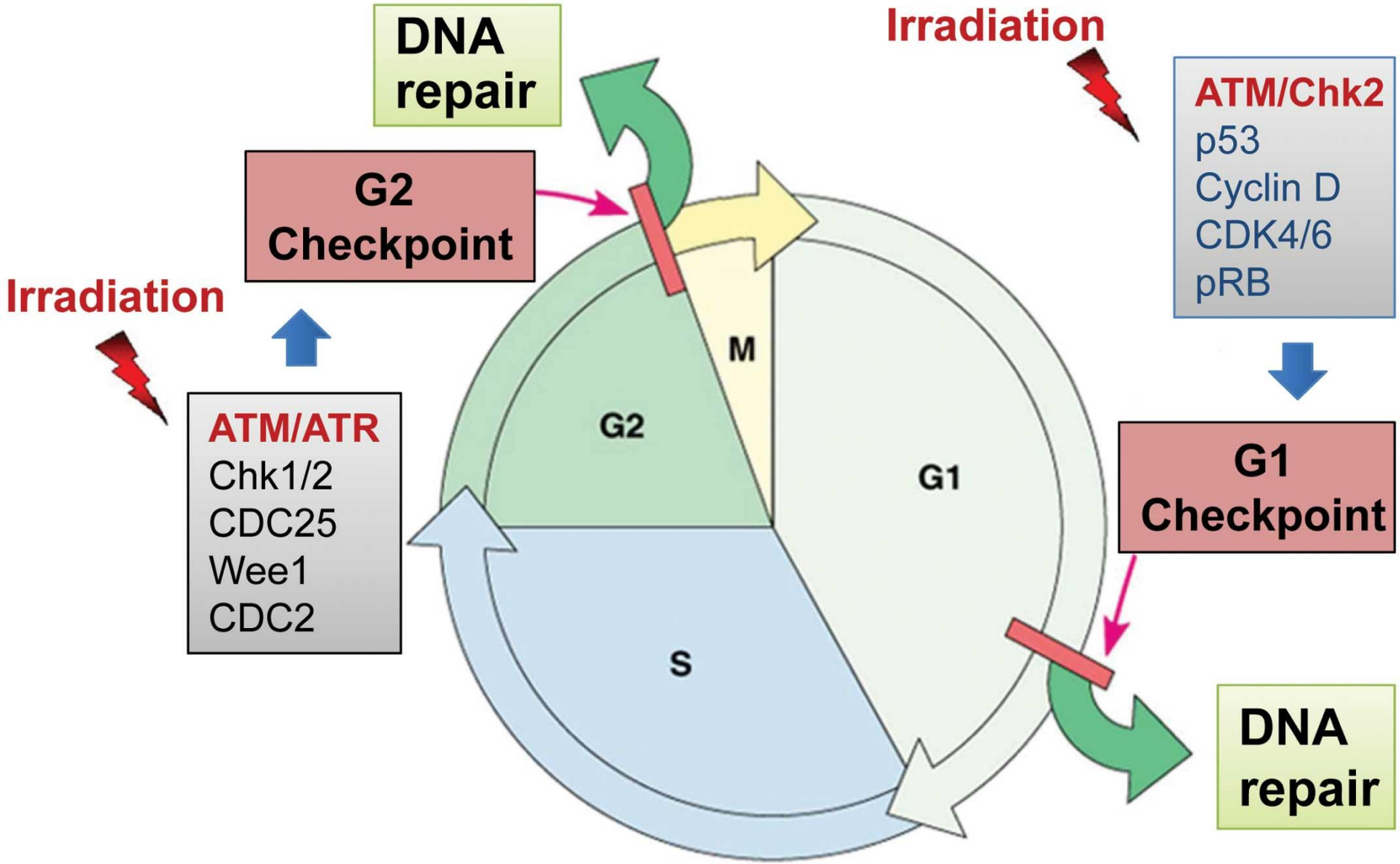


Direct and Indirect action of radiation



Easily modified by chemical means-either protectors or sensitizers- unlike direct action

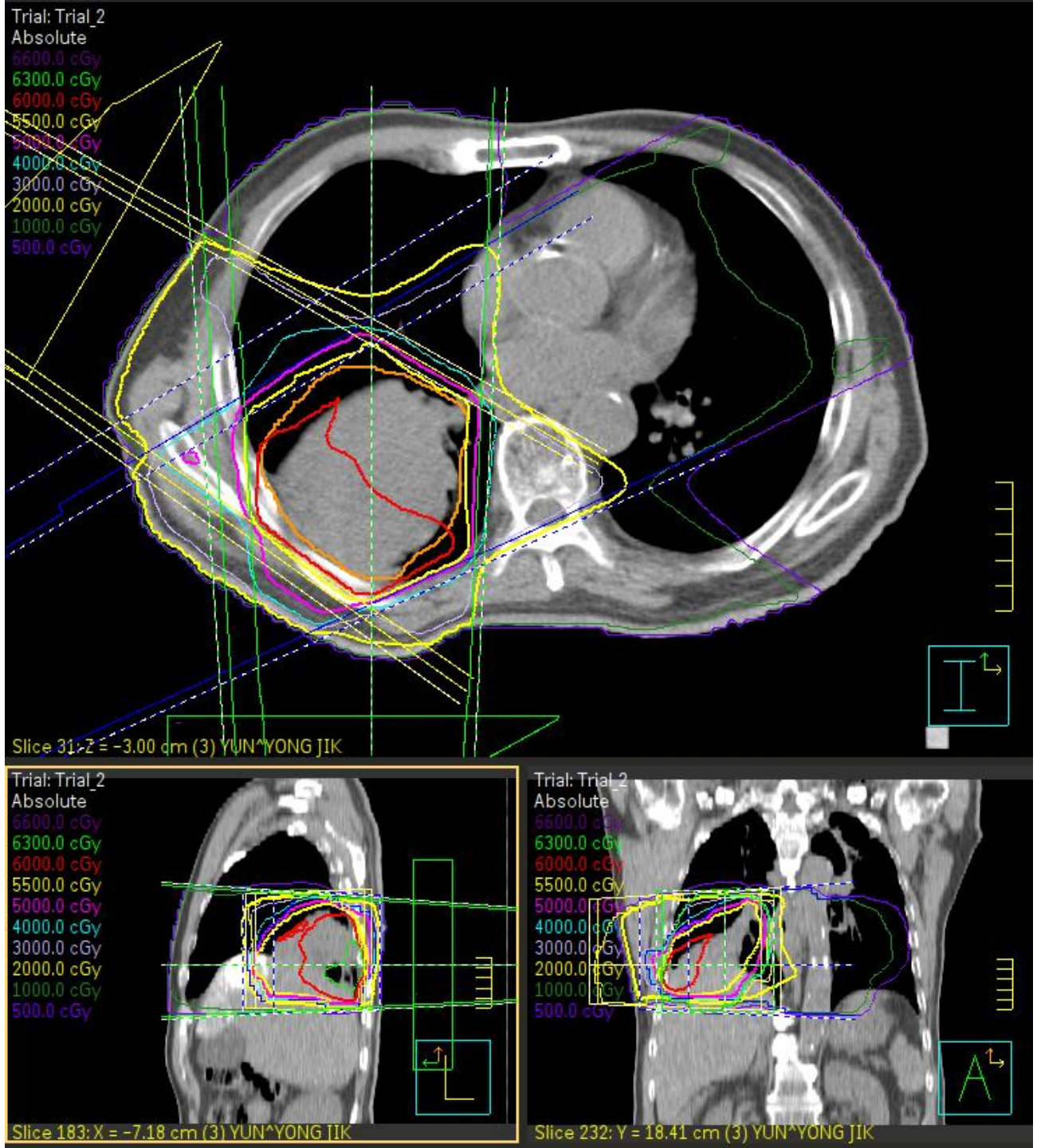
Dominant in high LET (neutrons or α-particles)

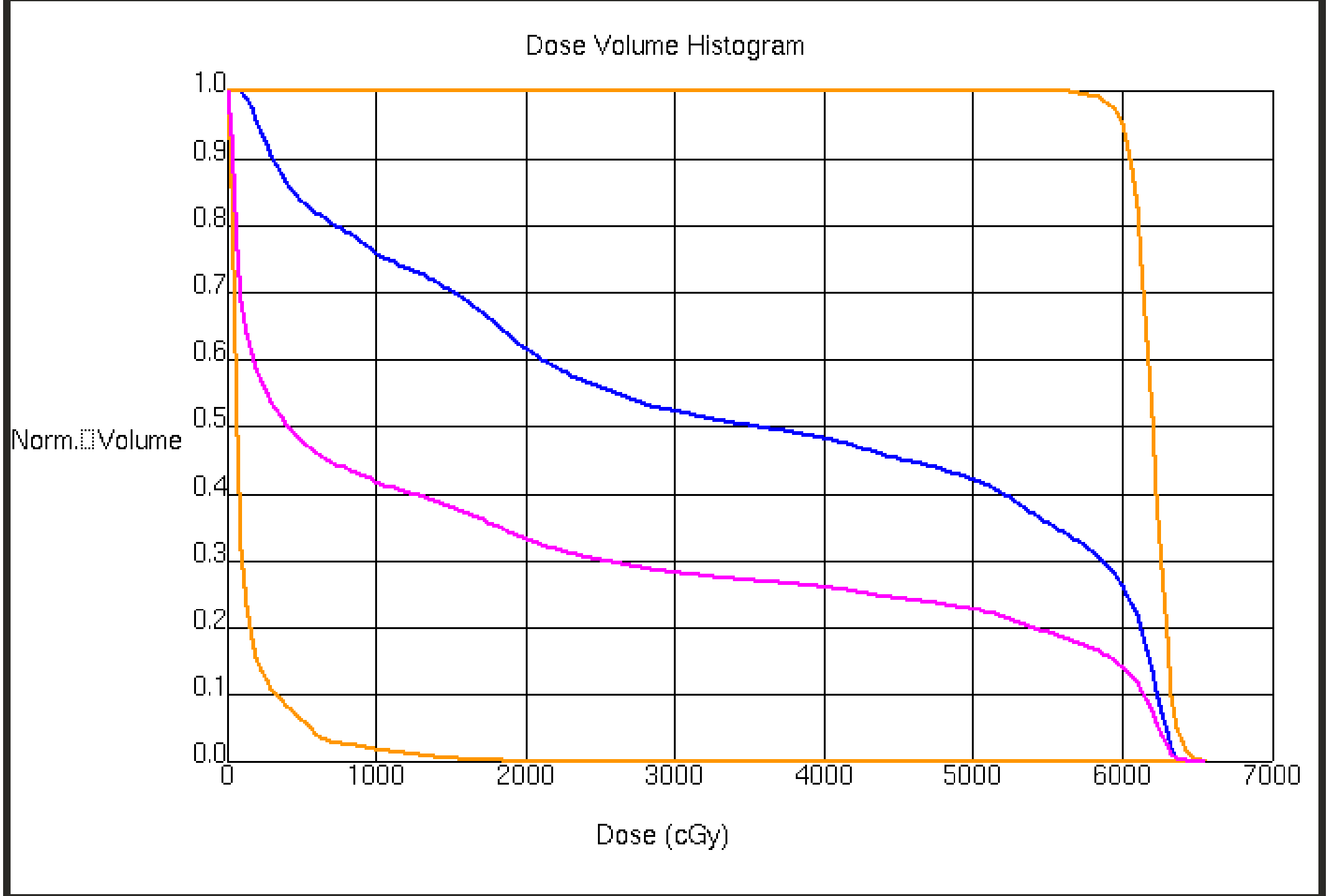

DNA repair
Irradiation
ATM/Chk2
p53
Cyclin D
CDK4/6
pRB
G2 Checkpoint
Irradiation
ATM/ATR
Chk1/2
CDC25
Wee1
CDC2
M
G2
G1
S
G1 Checkpoint
DNA repair

Radiation

- Energy : physics
- DNA damage : cell cycle
- OH- : Oxygen


Trial: Trial_2
Absolute
6600.0 cGy
6300.0 cGy
6000.0 cGy
5500.0 cGy
5000.0 cGy
4000.0 cGy
3000.0 cGy
2000.0 cGy
1000.0 cGy
500.0 cGy
Slice 31: Z = -3.00 cm (3) YUN^YONG JIK


Trial: Trial_2
Absolute
6600.0 cGy
6300.0 cGy
6000.0 cGy
5500.0 cGy
5000.0 cGy
4000.0 cGy
3000.0 cGy
2000.0 cGy
1000.0 cGy
500.0 cGy
Slice 31: Z = -3.00 cm (3) YUN^YONG JIK
Trial: Trial_2
Absolute
6600.0 cGy
6300.0 cGy
6000.0 cGy
5500.0 cGy
5000.0 cGy
4000.0 cGy
3000.0 cGy
2000.0 cGy
1000.0 cGy
500.0 cGy
Slice 183: X = -7.18 cm (3) YUN^YONG JIK
Trial: Trial_2
Absolute
6600.0 cGy
6300.0 cGy
6000.0 cGy
5500.0 cGy
5000.0 cGy
4000.0 cGy
3000.0 cGy
2000.0 cGy
1000.0 cGy
500.0 cGy
Slice 232: Y = 18.41 cm (3) YUN^YONG JIK

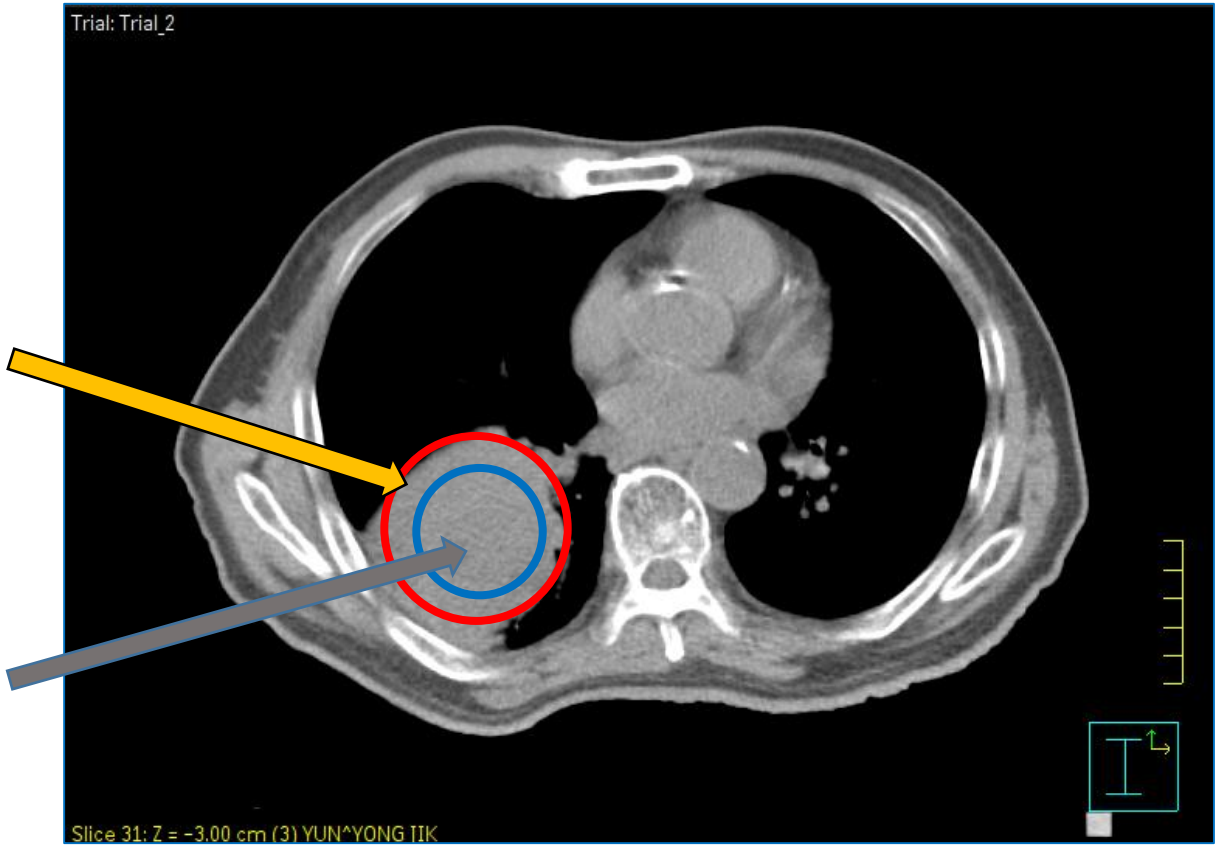

Dose Volume Histogram
Norm. Volume
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
0
1000
2000
3000
4000
5000
6000
7000
Dose (cGy)

Tumor control (Local control)

- Large tumor or small tumor

Tumor surface : oxic area

Tumor inner area : hypoxic area

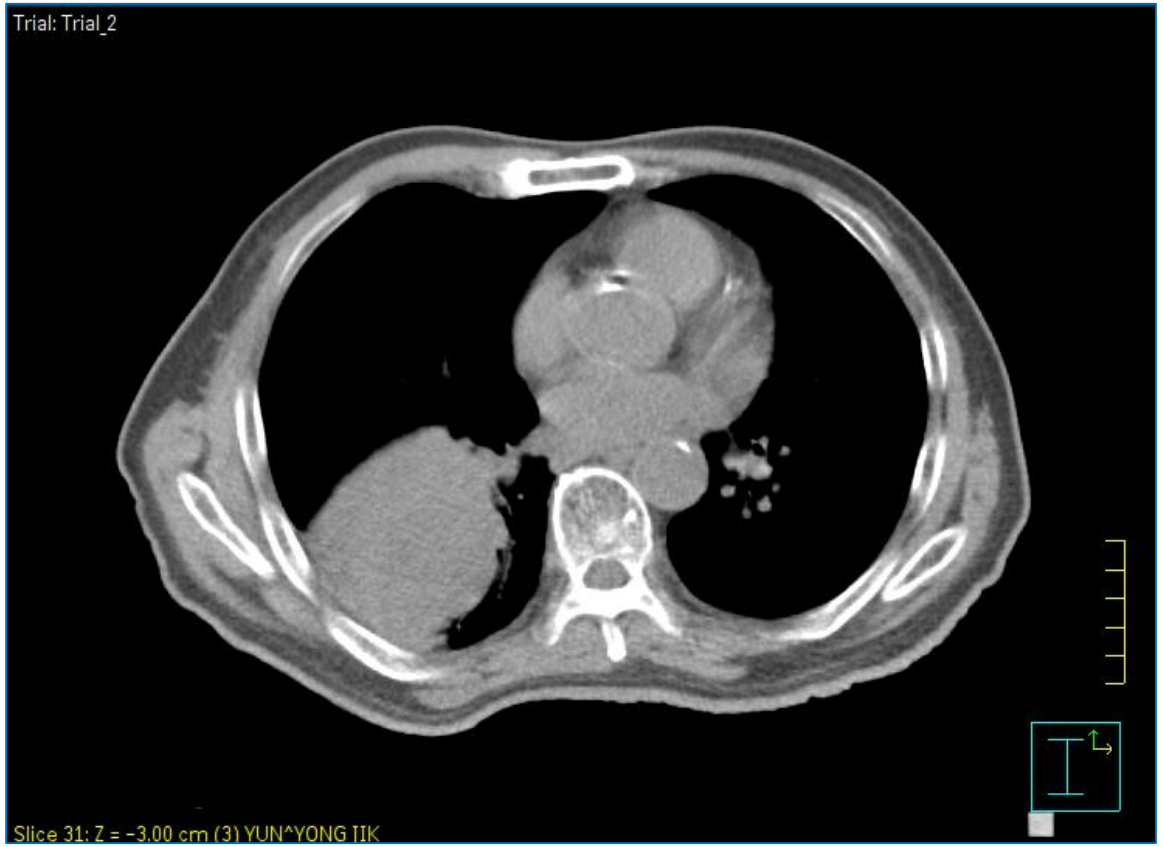


Tumor control (Local control)

- NSCLC (ex. Adenocarcinoma) vs SCLC

- Low Mitosis

  vs High Mitosis



Radiation complication

- Radiation pneumonitis
  -> Rt side (upper? lower?) Lt side (upper? lower?)

- Radiation esophagitis : probability?

- Spinal cord myelopathy?

- Tissue radiation sensitivity : mitosis

Case 1

- 69/M

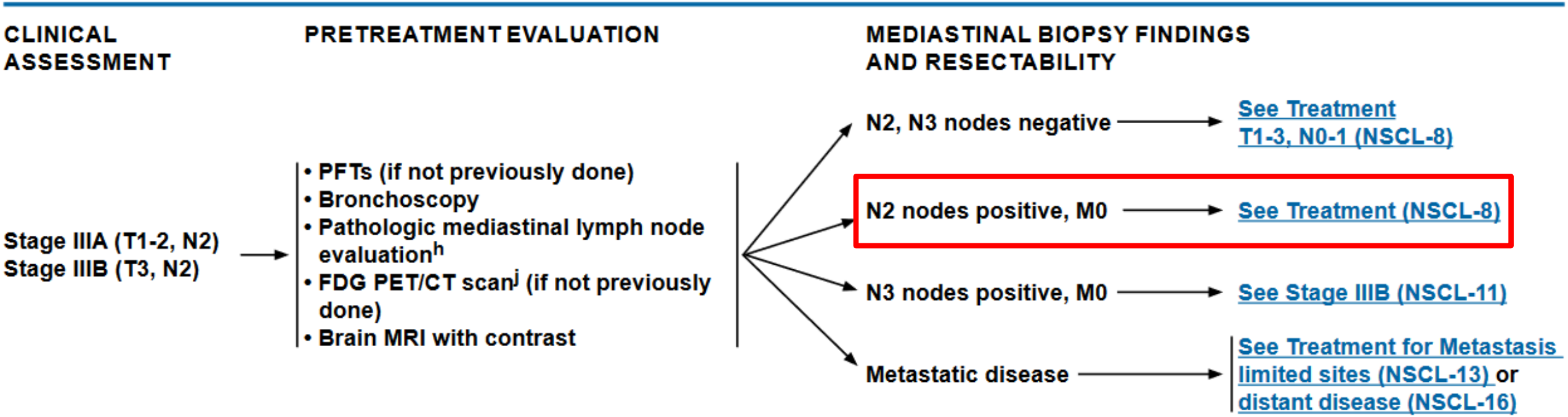
- X-ray abnormal finding
- FVC 2.52 63%, FEV1 2.14 78%, FEV1/FVC 85%
- 30 pack yrs smoking Hx.
- ECOG 0

Image study

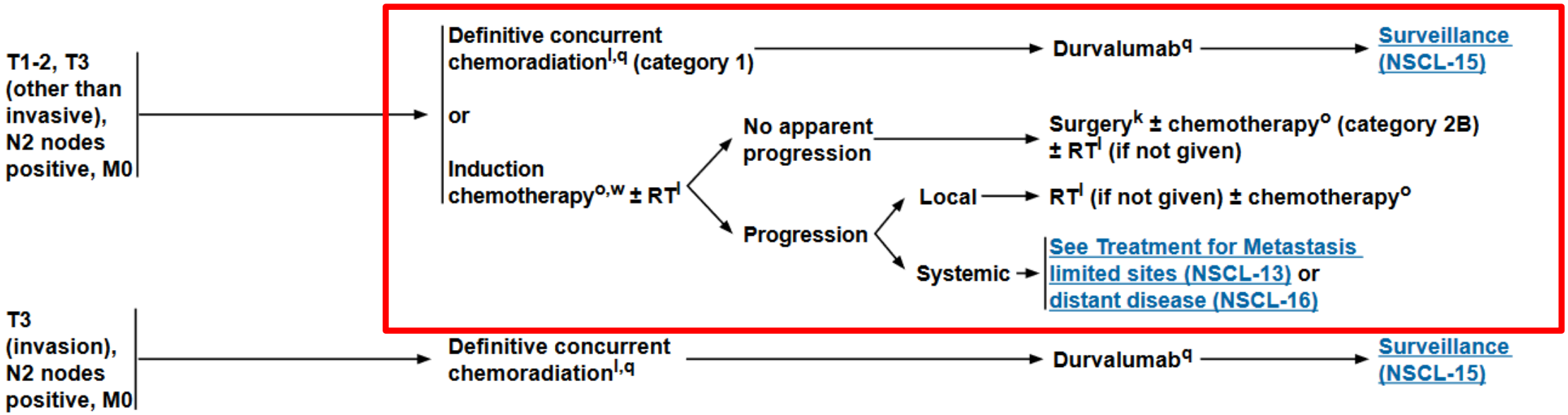
Treatment

1. Surgery
2. Radiation only
3. Chemo-radiation therapy
4. Observation

NCCN Guidelines



NCCN Guidelines



Case 2

- 71/M

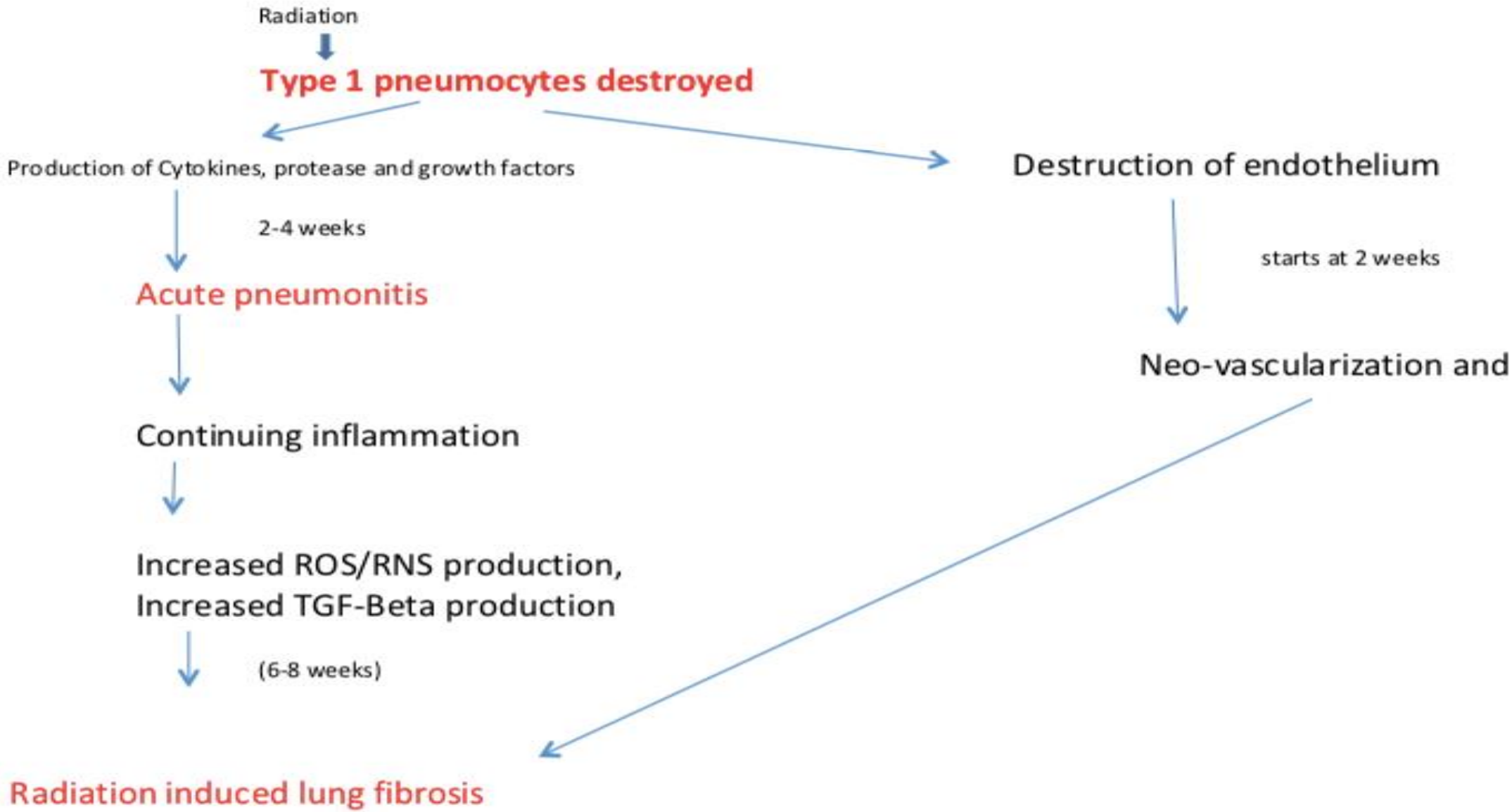
- Dyspnea, cough
- FVC 1.82 48%, FEV1 1.58 61%, FEV1/FVC 86%
- 40 pack yrs smoking Hx.
- ECOG 1

Image study

Treatment

1. Surgery
2. Radiation only
3. Chemo-radiation therapy
4. Observation

Radiation pneumonitis


Radiation
Type 1 pneumocytes destroyed
Production of Cytokines, protease and growth factors
2-4 weeks
Acute pneumonitis
Continuing inflammation
Increased ROS/RNS production,
Increased TGF-Beta production
(6-8 weeks)
Destruction of endothelium
starts at 2 weeks
Neo-vascularization and
Radiation induced lung fibrosis

Predictive Markers in Radiation Pneumonitis – patient related

- Old age > 65 years
- Poor performance status
- Presence of co-morbidities
- Smoking
- Poor PFT (decreased FEV1 and DLCO)

Ivan et al., 2012

- But poor PFT at baseline didn’t correlate with increased risk of pneumonitis

Wang et al., 2013

Predictive Markers in Radiation Pneumonitis – disease related

- Mid and lower lobe tumors of lung
  - ✓Move more with respiration
  - ✓May lead to more normal tissues getting irradiated
  - ✓Ventilation and perfusion increases from apex to base
  - ✓Increased oxygen free radical production
  - ✓Thus more damage

Predictive Markers in Radiation Pneumonitis – treatment related

- A lung-PTV V20>30% and lung-GTV V20>33% is predictive of symptomatic pneumonitis

  Palma et al., 2013

- A higher mean lung dose (>20Gy)

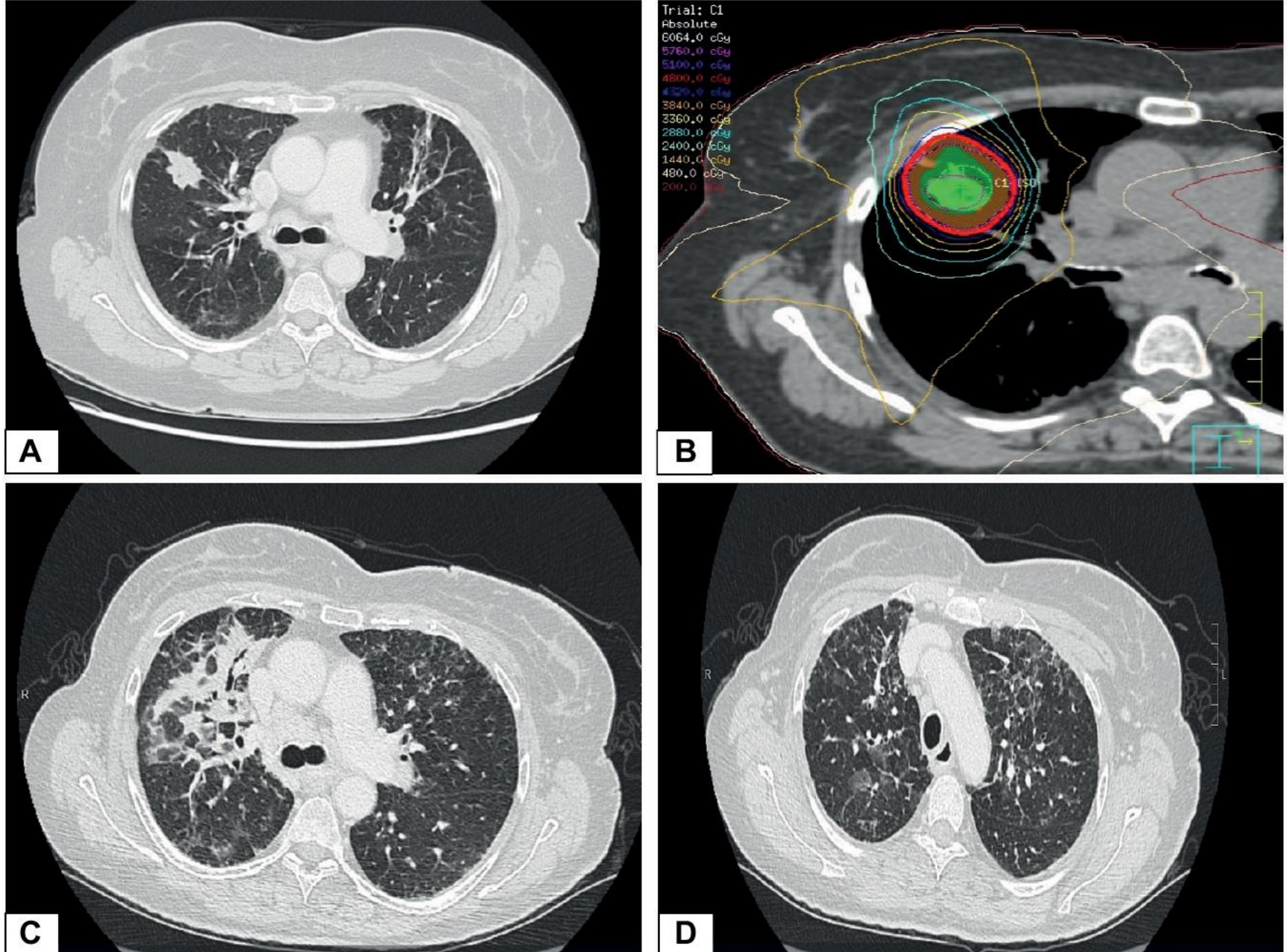
  Tsujino et al, 2003

- Large daily fraction (ex. SBRT)

  Palma et al., 2013

- V20>10% and mean lung dose>6Gy in SBRT

  Hideomi Yamashita et al., 2013


A
Trial: C1
Absolute
6064.0 cGy
5760.0 cGy
5100.0 cGy
4800.0 cGy
4320.0 cGy
3840.0 cGy
3360.0 cGy
2880.0 cGy
2400.0 cGy
1440.0 cGy
480.0 cGy
200.0 cGy
C1 ISO
B
C
R
D
R

Predictive Markers in Radiation Pneumonitis – treatment related

- A number of drugs
- Bleomycin, cyclophosphamide, vincristine, taxanes, doxorubicin, dactinomycin, mitomycin, gemcitabine and targeted agents like erlotinib and bevacizumab

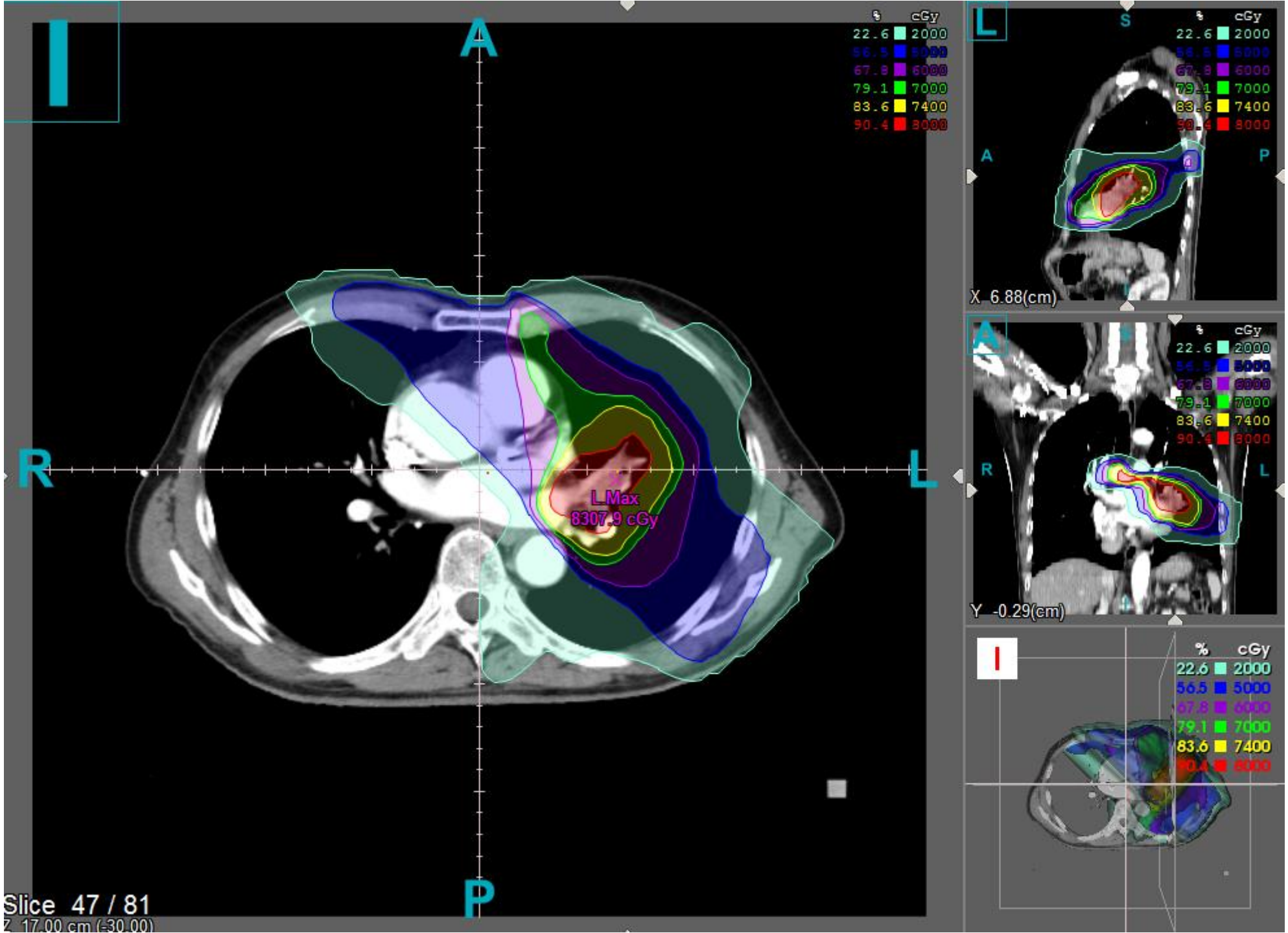
- Concurrent >> sequential

Taghian et al., 2001

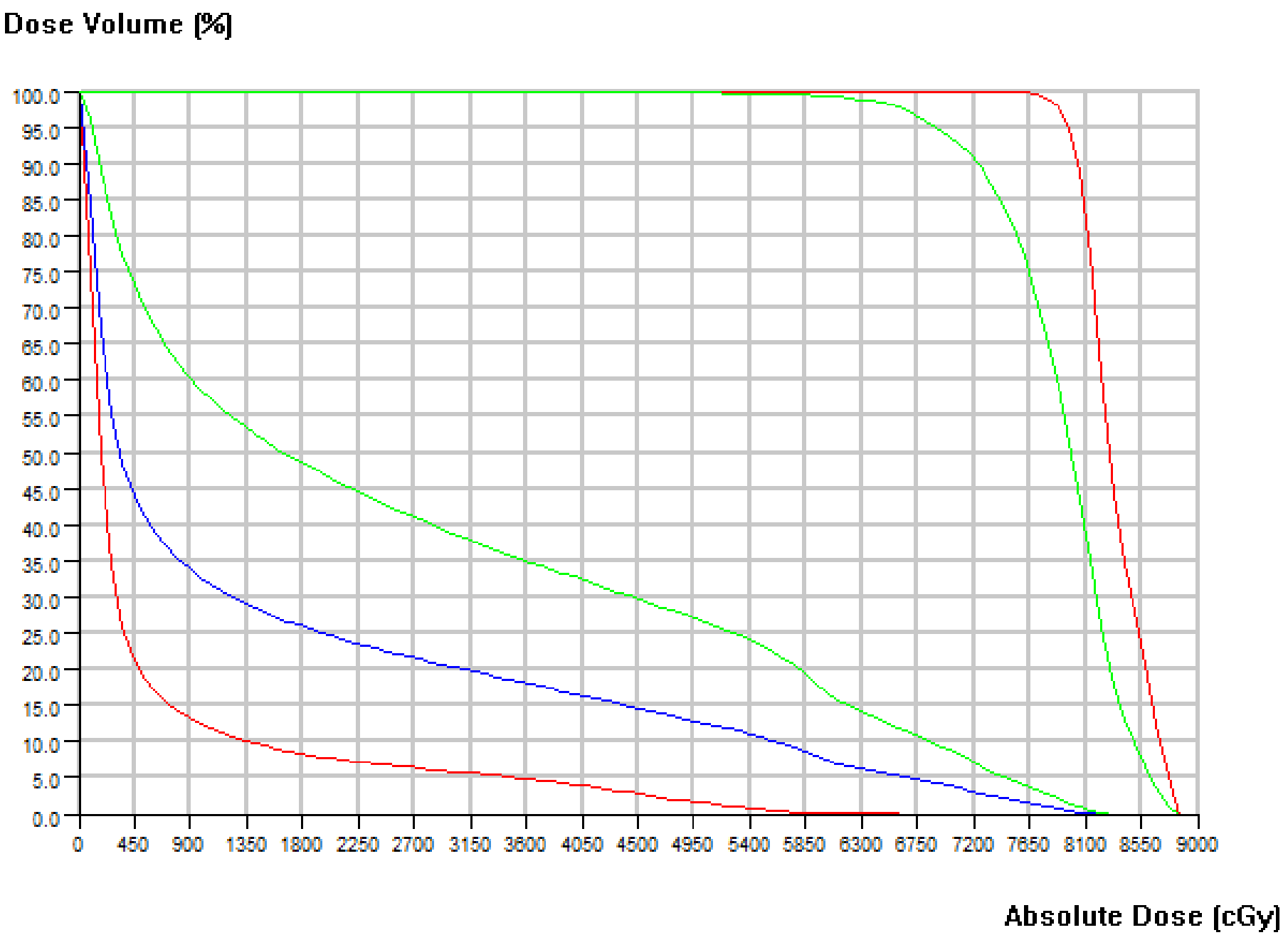
- Sequential >> concurrent

Ivan et al., 2012

Radiation pneumonitis treatment


I
A
P
R
L
% cGy
22.6 2000
56.5 5000
67.8 6000
79.1 7000
83.6 7400
90.4 8000
L Max
8307.9 cGy
Slice 47 / 81
Z 17.00 cm (-30.00)
L
S
A
P
X 6.88(cm)
A
R
L
Y -0.29(cm)
I

Dose Volume Histogram



Treatment

1. Surgery
2. Radiation only
3. **Chemo-radiation therapy**
4. Observation

Case 3

- 62/M

- Cough, sputum
- FVC 3.90 101%, FEV1 2.97 107%, FEV1/FVC 76%
- No smoking Hx.
- ECOG 1

Image study

Treatment

1. Surgery
2. Radiation only
3. Chemo-radiation therapy
4. Induction chemotherapy + CCRT
5. Chemotherapy only

Induction chemotherapy

- Breast cancer
- Down staging -> increased breast conserving rate
- Systemic control
- But local control -> sl. decreased local control

- Lung cancer?

Induction Chemotherapy Followed by Chemoradiotherapy Compared With Chemoradiotherapy Alone for Regionally Advanced Unresectable Stage III Non–Small-Cell Lung Cancer: Cancer and Leukemia Group B

Everett E. Vokes, James E. Herndon II, Michael J. Kelley, M. Giulia Cicchetti, Nithya Ramnath, Harvey Neill, James N. Atkins, Dorothy M. Watson, Wallace Akerley, and Mark R. Green

A B S T R A C T

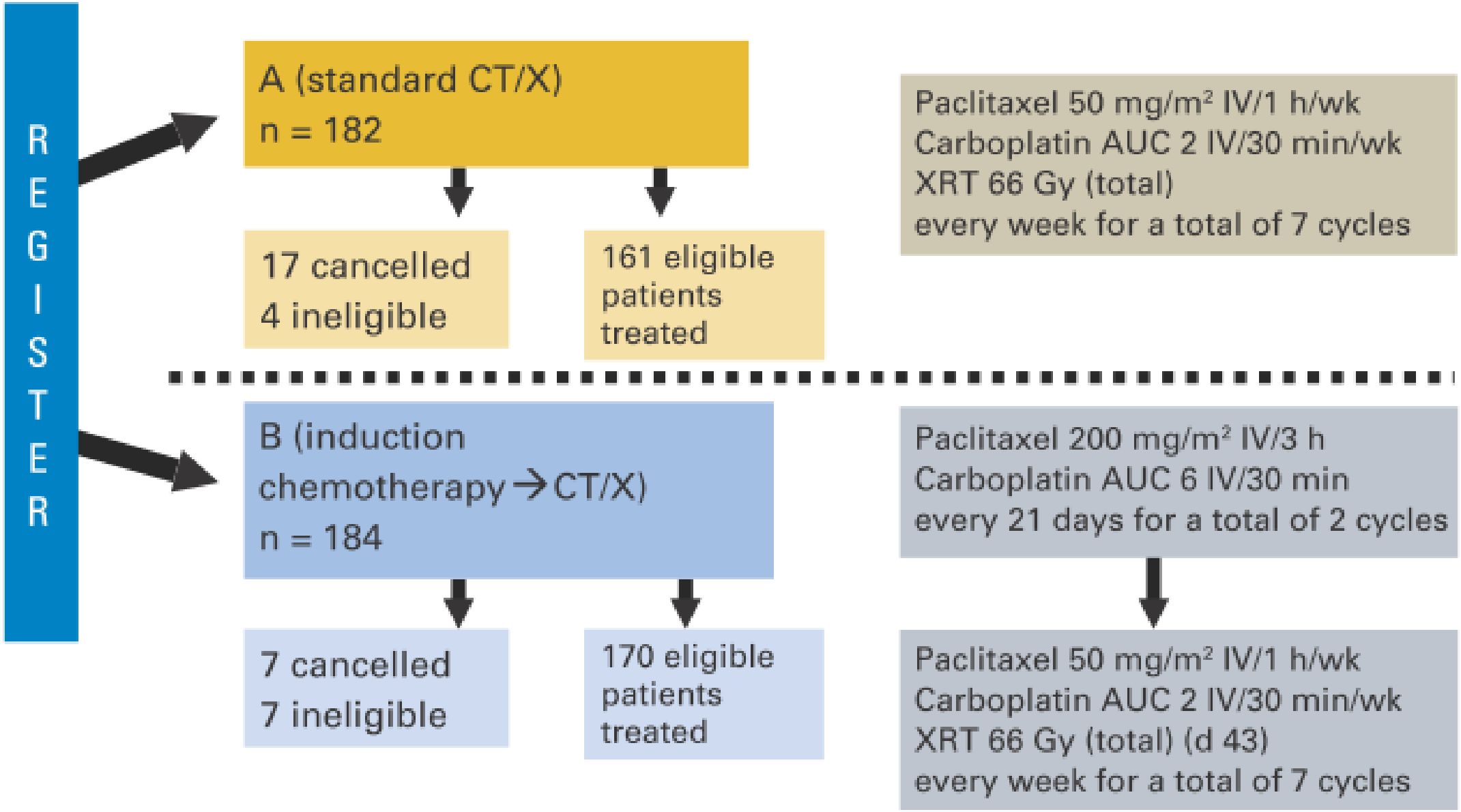
Purpose
Standard therapy for unresectable stage III non–small-cell lung cancer includes concomitant chemoradiotherapy. In Cancer and Leukemia Group B 39801, we evaluated whether induction chemotherapy before concurrent chemoradiotherapy would result in improved survival.

Patients and Methods
Between July 1998 and May 2002, 366 patients were randomly assigned to arm A, which involved immediate concurrent chemoradiotherapy with carboplatin area under the concentration-time curve (AUC) of 2 and paclitaxel 50 mg/m^2 given weekly during 66 Gy of chest radiotherapy, or arm B, which involved two cycles of carboplatin AUC 6 and paclitaxel 200 mg/m^2 administered every 21 days followed by identical chemoradiotherapy. The accrual goal was 360 patients.

Results
Thirty-four percent of patients were female, 66% were male, and the median age was 63 years. Grade 3 or 4 toxicities during induction chemotherapy on arm B consisted mainly of neutropenia (18% and 20%, respectively). During concurrent chemoradiotherapy, there was no difference in severity of in-field toxicities of esophagitis (grade 3 and 4 were, respectively, 30% and 2% for arm A *v* 28% and 8% for arm B) and dyspnea (grade 3 and 4 were, respectively, 11% and 3% for arm A *v* 15% and 4% for arm B). Survival differences were not statistically significant ($P = .3$), with a median survival on arm A of 12 months (95% CI, 10 to 16 months) versus 14 months (95% CI, 11 to 16 months) on arm B and a 2-year survival of 29% (95% CI, 22% to 35%) and 31% (95% CI, 25% to 38%). Age, weight loss before therapy, and performance status were statistically significant predictive factors.

Conclusion
The addition of induction chemotherapy to concurrent chemoradiotherapy added toxicity and provided no survival benefit over concurrent chemoradiotherapy alone. The median survival achieved in each of the treatment groups is low, and the routine use of weekly carboplatin and paclitaxel with simultaneous radiotherapy should be re-examined.

J Clin Oncol 25:1698-1704. © 2007 by American Society of Clinical Oncology


REGISTER
A (standard CT/X)
n = 182
17 cancelled
4 ineligible
161 eligible patients treated
Paclitaxel 50 mg/m² IV/1 h/wk
Carboplatin AUC 2 IV/30 min/wk
XRT 66 Gy (total)
every week for a total of 7 cycles
B (induction chemotherapy → CT/X)
n = 184
7 cancelled
7 ineligible
170 eligible patients treated
Paclitaxel 200 mg/m² IV/3 h
Carboplatin AUC 6 IV/30 min
every 21 days for a total of 2 cycles
Paclitaxel 50 mg/m² IV/1 h/wk
Carboplatin AUC 2 IV/30 min/wk
XRT 66 Gy (total) (d 43)
every week for a total of 7 cycles

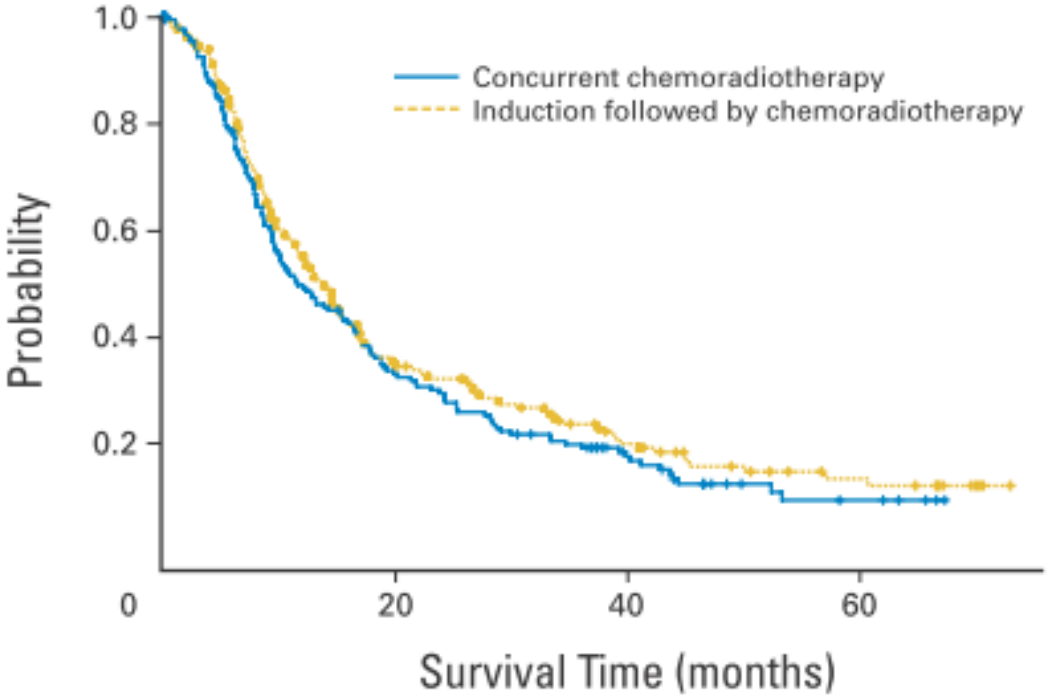


Table 3. CALGB 39801 Adverse Events (Concurrent CT/X)

Variable	Arm A (CT/X)		Arm B (Ind Followed by CT/X)	
	Grade 3 (%)	Grade 4 (%)	Grade 3 (%)	Grade 4 (%)
ANC	11	4	24	7*
WBC	32	4	38	6
HgB	5	0	12	0
Lymphopenia	55	8	47	9
Febrile neutropenia	2	0	4	0
Fatigue	19	1	17	4
Anorexia	15	5	11	8
Dysphagia-esophageal	30	2	28	8
Dyspnea	11	3	15	4
Pneumonitis	3	1	8	2†
Maximum toxicity	58	26	55	30‡

NOTE. Overall, there are five grade 5 events: A: 1% (n = 2); B: 2% (n = 3).
Abbreviations: CALGB, Cancer and Leukemia Group B; Ind, induction; CT/X, concomitant chemoradiotherapy; ANC, absolute neutrophil count; HgB, hemoglobin.
*$P < .0001$.
†One fatal event.
‡$P = .004$.

Randomized Controlled Trial of Resection Versus Radiotherapy After Induction Chemotherapy in Stage IIIA-N2 Non–Small-Cell Lung Cancer

Jan P. van Meerbeeck, Gijs W. P. M. Kramer, Paul E. Y. Van Schil, Catherine Legrand, Egbert F. Smit, Franz Schramel, Vivianne C. Tjan-Heijnen, Bonne Biesma, Channa Debruyne, Nico van Zandwijk, Ted A. W. Splinter, Giuseppe Giaccone

On behalf of the European Organisation for Research and Treatment of Cancer-Lung Cancer Group

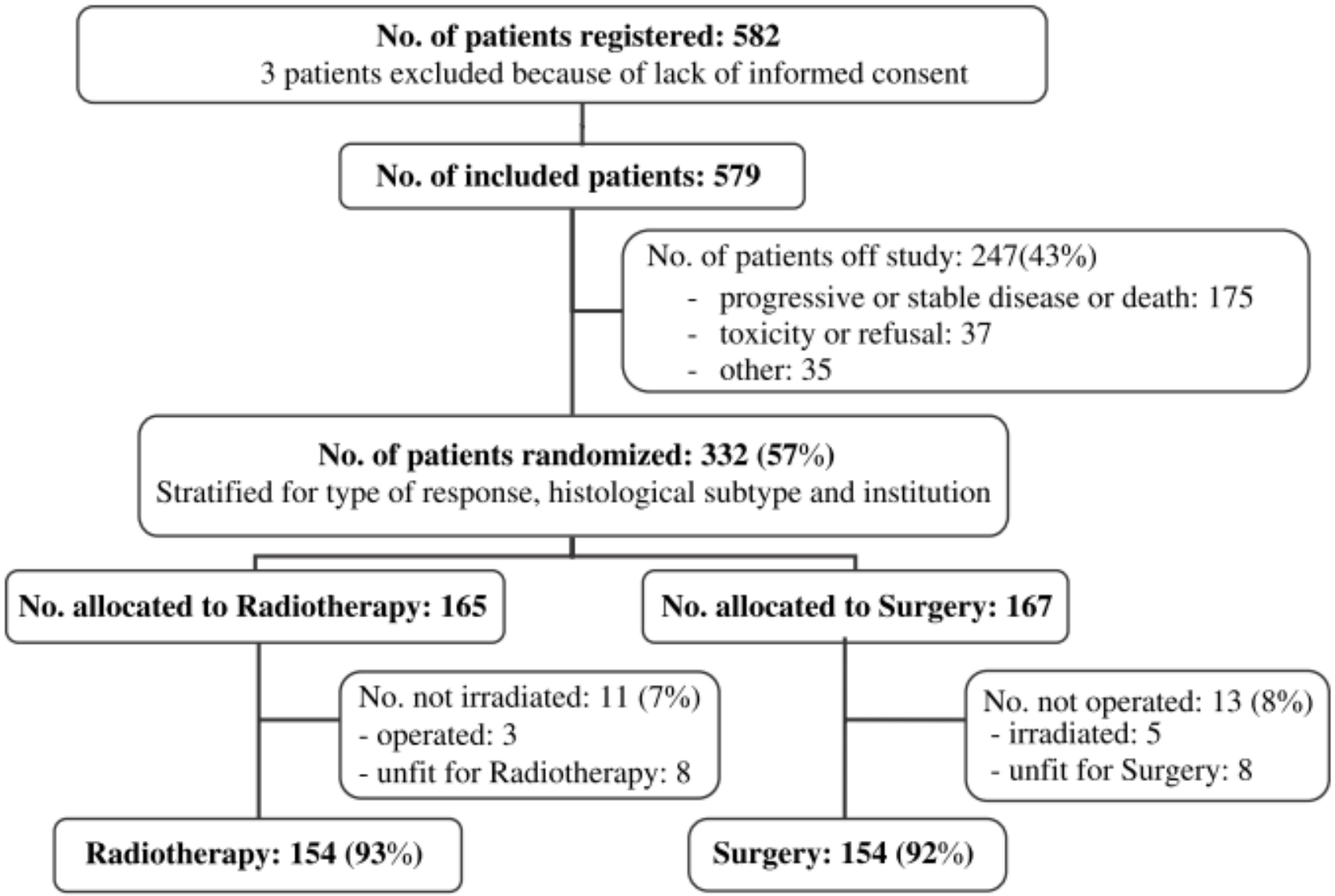
Background Induction chemotherapy before surgical resection increases survival compared with surgical resection alone in patients with stage IIIA-N2 non–small-cell lung cancer (NSCLC). We hypothesized that, following a response to induction chemotherapy, surgical resection would be superior to thoracic radiotherapy as locoregional therapy.

Methods Selected patients with histologic or cytologic proven stage IIIA-N2 NSCLC were given three cycles of platinum-based induction chemotherapy. Responding patients were subsequently randomly assigned to surgical resection or radiotherapy. Survival curves were estimated using Kaplan–Meier analyses from time of randomization.

Results Induction chemotherapy resulted in a response rate of 61% (95% confidence interval [CI] = 57% to 65%) among the 579 eligible patients. A total of 167 patients were allocated to resection and 165 to radiotherapy. Of the 154 (92%) patients who underwent surgery, 14% had an exploratory thoracotomy, 50% a radical resection, 42% a pathologic downstaging, and 5% a pathologic complete response; 4% died after surgery. Postoperative radiotherapy was administered to 62 (40%) of patients in the surgery arm. Among the 154 (93%) irradiated patients, overall compliance to the radiotherapy prescription was 55%, and grade 3/4 acute and late esophageal and pulmonary toxic effects occurred in 4% and 7%; one patient died of radiation pneumonitis. Median and 5-year overall survival for patients randomly assigned to resection versus radiotherapy were 16.4 versus 17.5 months and 15.7% versus 14%, respectively (hazard ratio = 1.06, 95% CI = 0.84 to 1.35). Rates of progression-free survival were also similar in both groups.

Conclusion In selected patients with pathologically proven stage IIIA-N2 NSCLC and a response to induction chemotherapy, surgical resection did not improve overall or progression-free survival compared with radiotherapy. In view of its low morbidity and mortality, radiotherapy should be considered the preferred locoregional treatment for these patients.

J Natl Cancer Inst 2007;99:442–50


No. of patients registered: 582
3 patients excluded because of lack of informed consent
No. of included patients: 579
No. of patients off study: 247(43%)
- progressive or stable disease or death: 175
- toxicity or refusal: 37
- other: 35
No. of patients randomized: 332 (57%)
Stratified for type of response, histological subtype and institution
No. allocated to Radiotherapy: 165
No. allocated to Surgery: 167
No. not irradiated: 11 (7%)
- operated: 3
- unfit for Radiotherapy: 8
No. not operated: 13 (8%)
- irradiated: 5
- unfit for Surgery: 8
Radiotherapy: 154 (93%)
Surgery: 154 (92%)

Mediastinal Lymph Node Clearance After Docetaxel-Cisplatin Neoadjuvant Chemotherapy Is Prognostic of Survival in Patients With Stage IIIA pN2 Non–Small-Cell Lung Cancer: A Multicenter Phase II Trial

Daniel C. Betticher, Shu-Fang Hsu Schmitz, Martin Tötsch, Eva Hansen, Christine Joss, Christian von Briel, Ralph A. Schmid, Miklos Pless, James Habicht, Arnaud D. Roth, Anastase Spiliopoulos, Rolf Stahel, Walter Weder, Roger Stupp, Fritz Egli, Markus Furrer, Hanspeter Honegger, Martin Wernli, Thomas Cerny, and Hans-Beat Ris

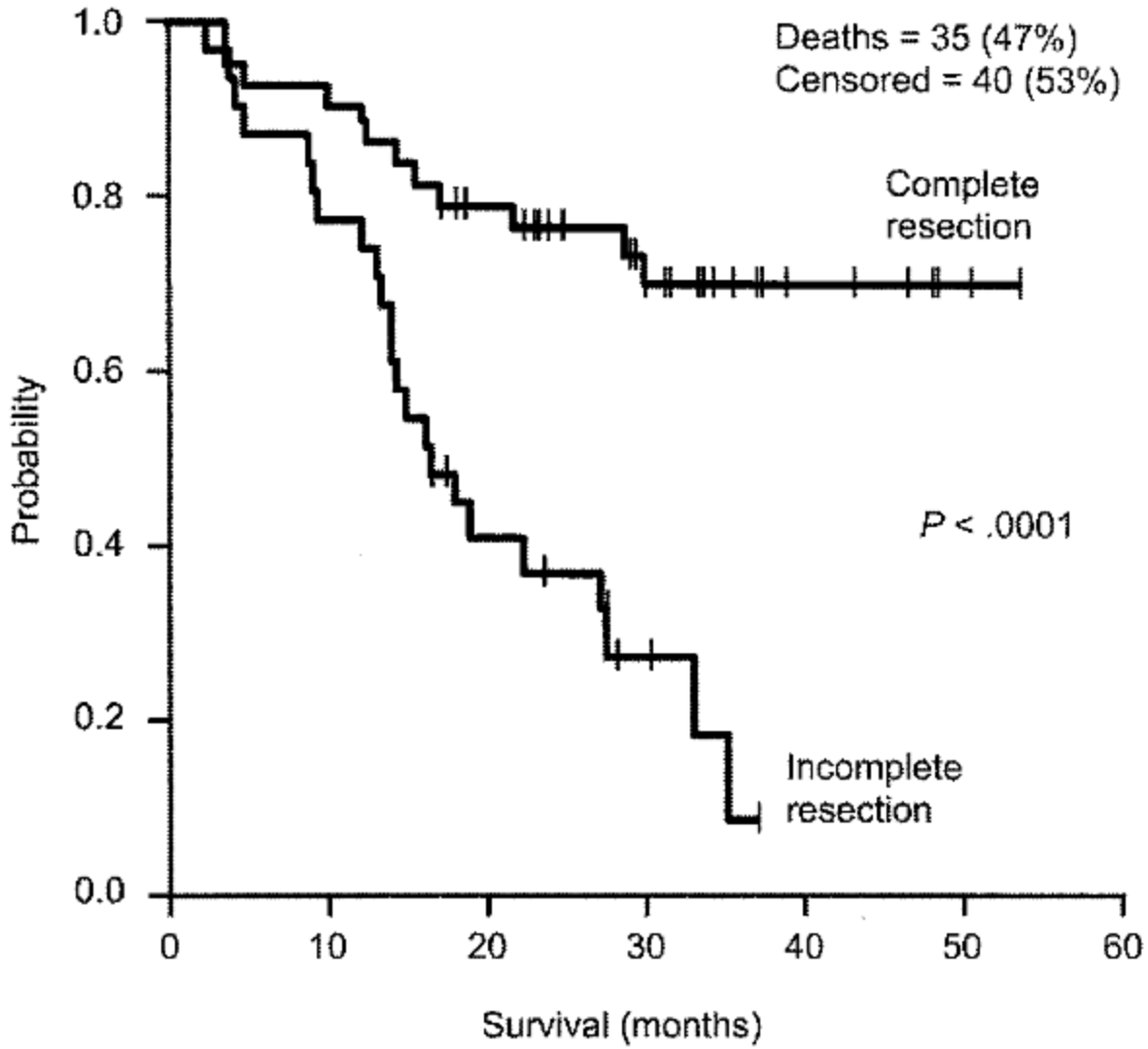
Purpose: **A multicenter, phase II trial investigated the efficacy and toxicity of neoadjuvant docetaxel-cisplatin in locally advanced non–small-cell lung cancer (NSCLC) and examined prognostic factors for patients not benefiting from surgery.**

Patients and Methods: **Ninety patients with previously untreated, potentially operable stage IIIA (mediastinoscopically pN2) NSCLC received three cycles of docetaxel 85 mg/m² day 1 plus cisplatin 40 mg/m² days 1 and 2, with subsequent surgical resection.**

Results: **Administered dose-intensities were docetaxel 85 mg/m²/3 weeks (range, 53 to 96) and cisplatin 95 mg/m²/3 weeks (range, 0 to 104). The 265 cycles were well tolerated, and the overall response rate was 66% (95% confidence interval [CI], 55% to 75%). Seventy-five patients underwent tumor resection with positive resection margin and involvement of the uppermost mediastinal lymph node in 16% and 35% of patients, respectively (perioperative mortality, 3%; morbidity, 17%). Pathologic complete response occurred in 19% of patients with tumor resection. In patients with tumor resection, downstaging to N0–1 at surgery was prognostic and significantly prolonged event-free survival (EFS) and overall survival (OS; *P* = .0001). At median follow-up of 32 months, the median EFS and OS were 14.8 months (range, 2.4 to 53.4) and 33 months (range, 2.4 to 53.4), respectively. Local relapse occurred in 27% of patients with tumor resection, with distant metastases in 37%. Multivariate analyses identified mediastinal clearance (hazard ratio, 0.22; *P* = .0003) and complete resection (hazard ratio, 0.26; *P* = .0006) as strongly prognostic for increased survival.**

Conclusion: **Neoadjuvant docetaxel-cisplatin is effective and tolerable in stage IIIA pN2 NSCLC. Resection is recommended only for patients with mediastinal downstaging after chemotherapy.**

J Clin Oncol 21:1752-1759.


Deaths = 35 (47%)
Censored = 40 (53%)
Complete resection
P < .0001
Incomplete resection
Probability
1.0
0.8
0.6
0.4
0.2
0.0
0
10
20
30
40
50
60
Survival (months)

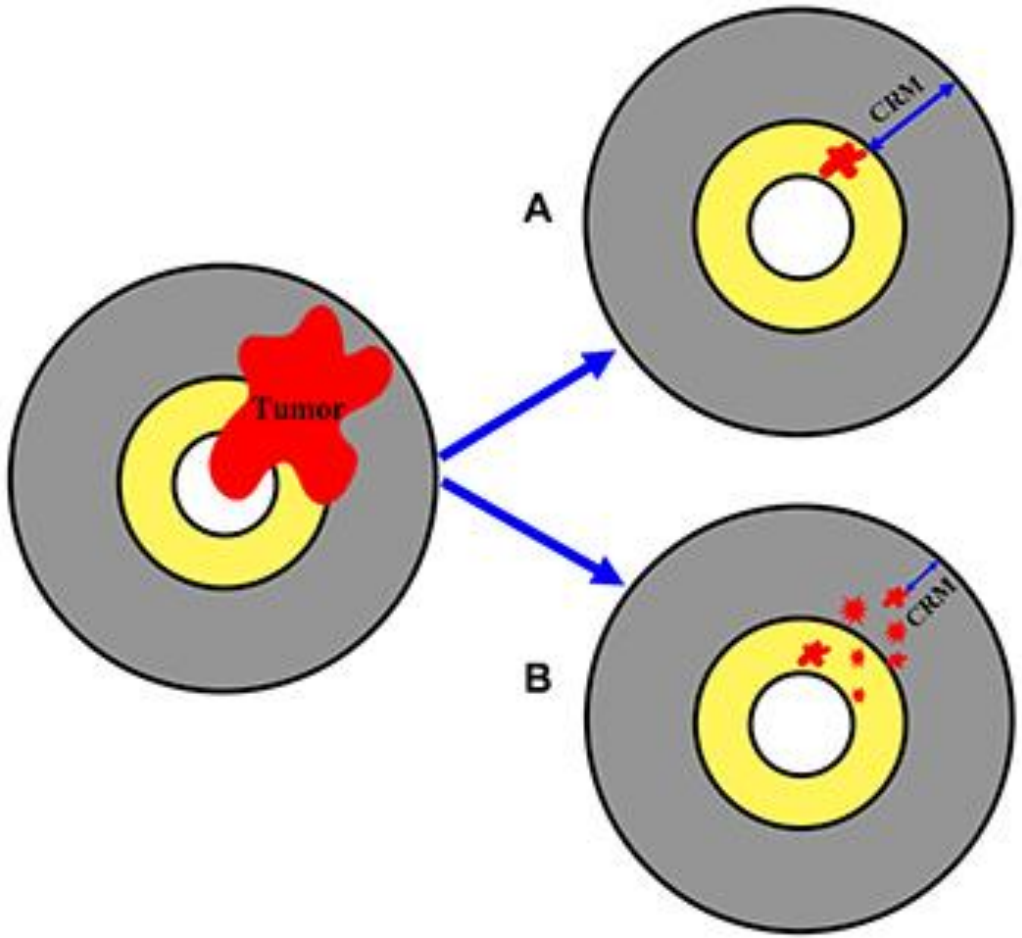
Induction chemotherapy

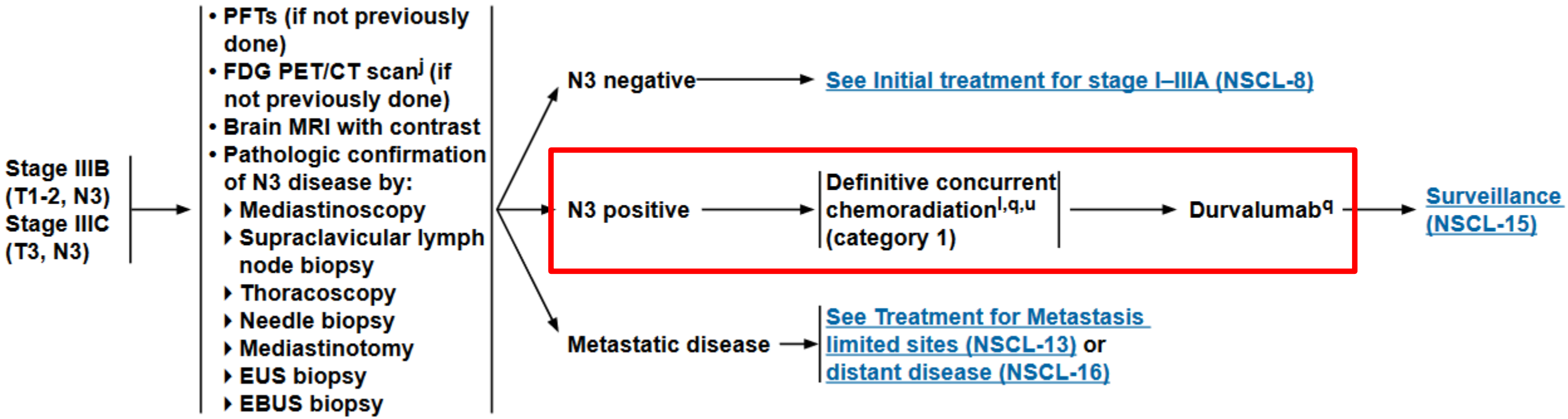
- Surgery compared with Radiotherapy?

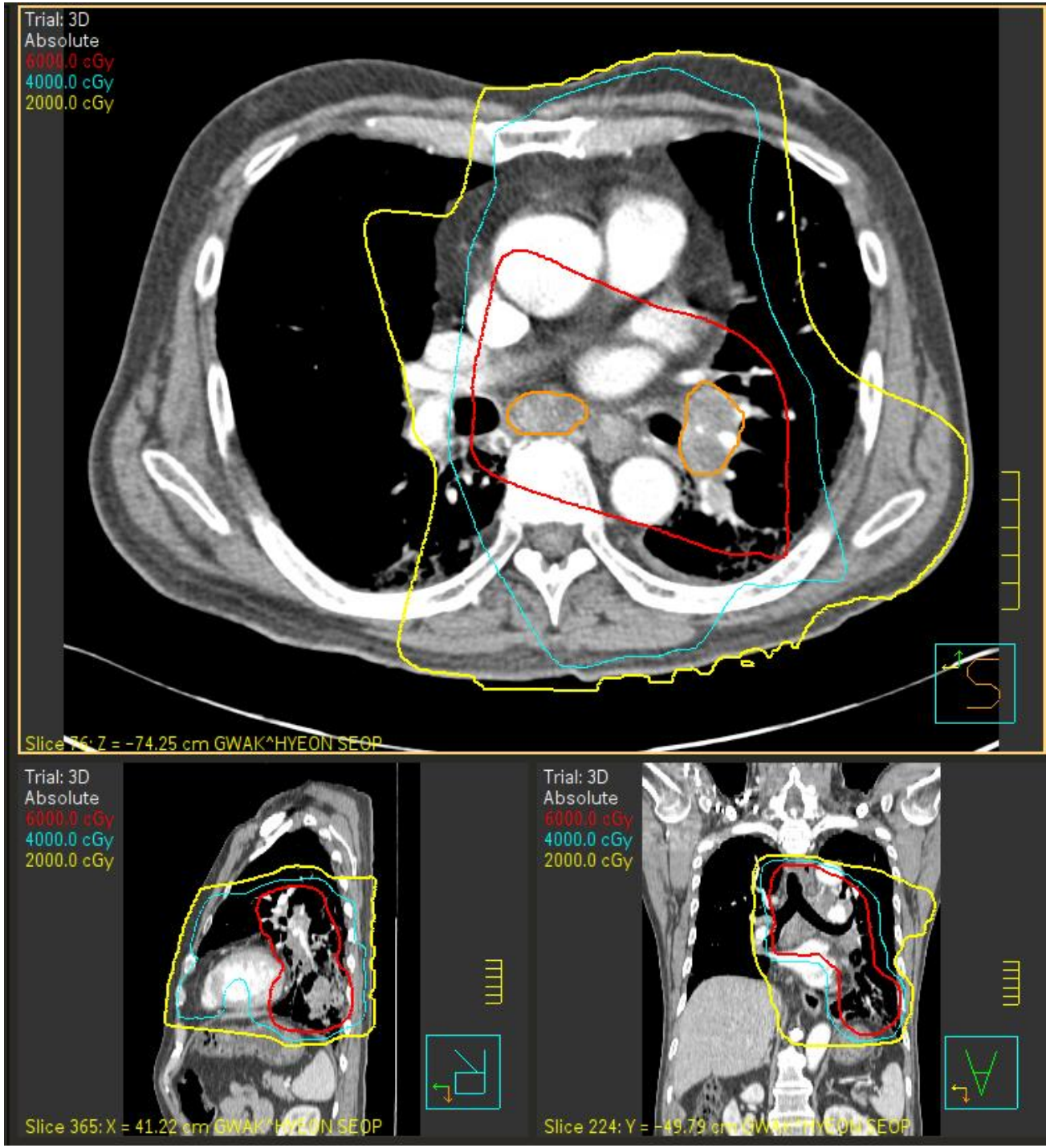
- Not clearly identified !

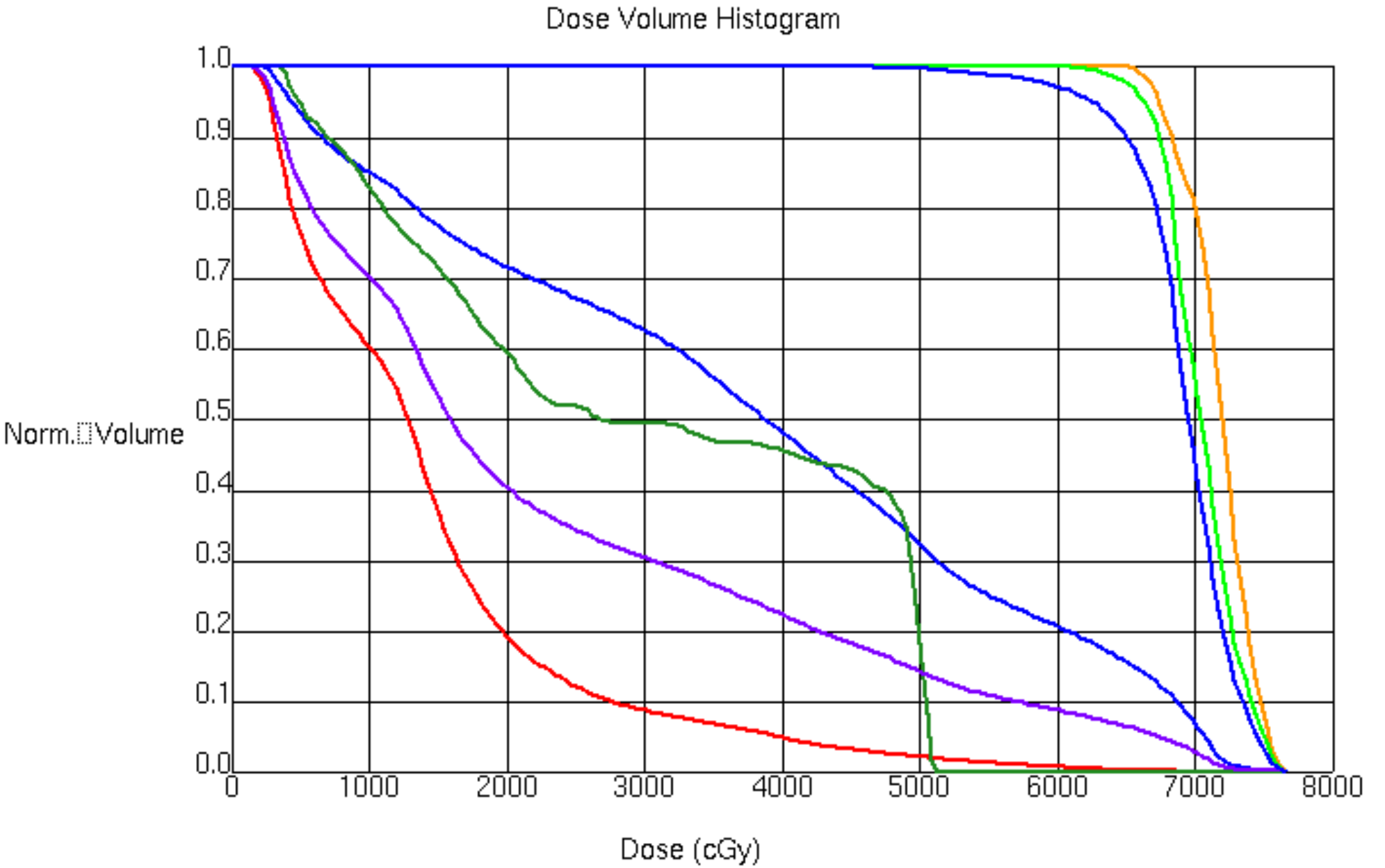
- If large tumor or lower lobe tumor?
  -> Large RT field
  -> increased complication risk
  -> downstaging or reduction of tumor size
  -> more small RT field -> decreased complication risk

Shrinkage or scatter?




Stage IIIB (T1-2, N3)
Stage IIIC (T3, N3)
• PFTs (if not previously done)
• FDG PET/CT scan[j] (if not previously done)
• Brain MRI with contrast
• Pathologic confirmation of N3 disease by:
Mediastinoscopy
Supraclavicular lymph node biopsy
Thoracoscopy
Needle biopsy
Mediastinotomy
EUS biopsy
EBUS biopsy
N3 negative
See Initial treatment for stage I–IIIA (NSCL-8)
N3 positive
Definitive concurrent chemoradiation[l,q,u] (category 1)
Durvalumab[q]
Surveillance (NSCL-15)
Metastatic disease
See Treatment for Metastasis limited sites (NSCL-13) or distant disease (NSCL-16)

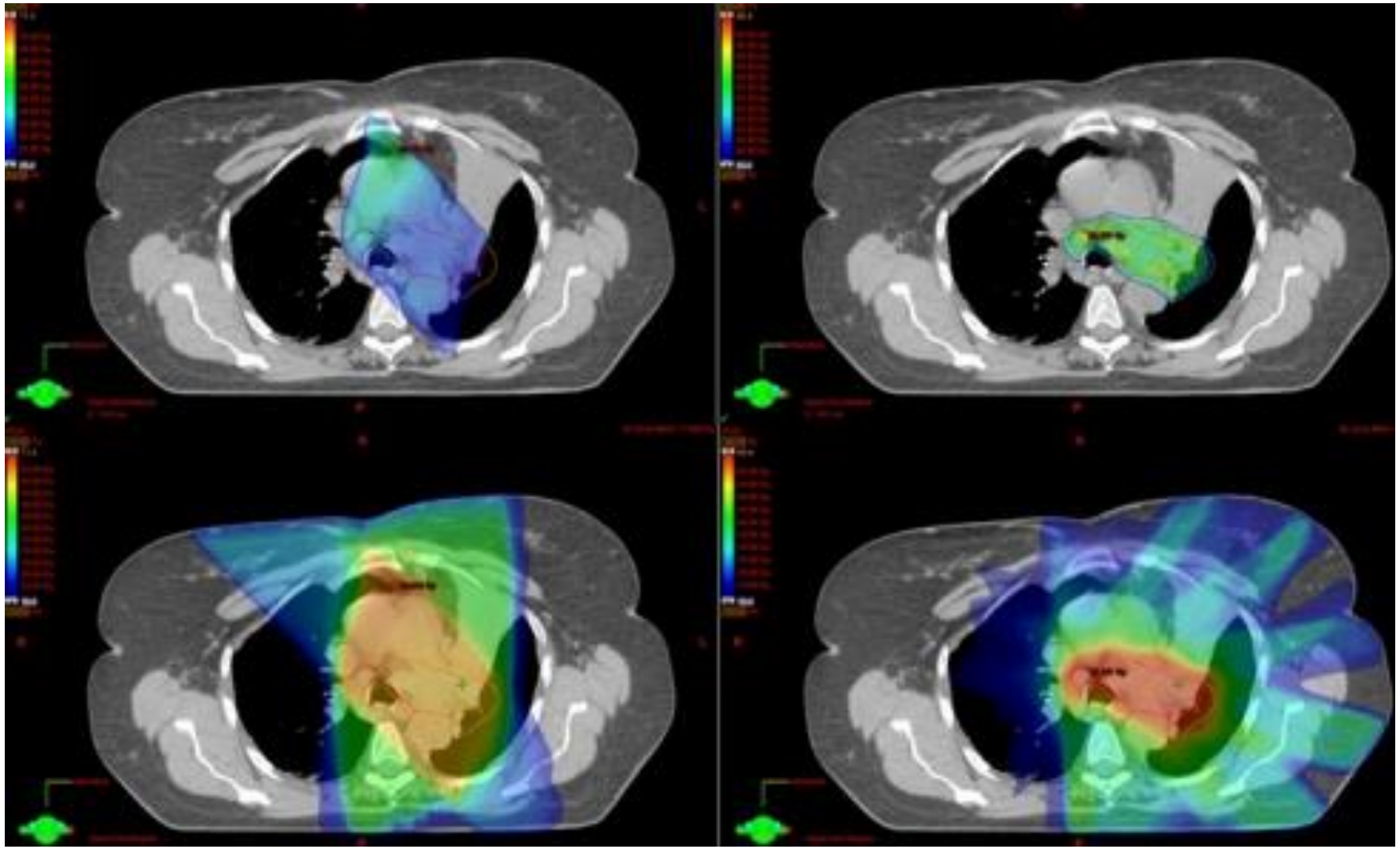

Trial: 3D
Absolute
6000.0 cGy
4000.0 cGy
2000.0 cGy
Slice 76: Z = -74.25 cm GWAK^HYEON SEOP
Trial: 3D
Absolute
6000.0 cGy
4000.0 cGy
2000.0 cGy
Slice 365: X = 41.22 cm GWAK^HYEON SEOP
Trial: 3D
Absolute
6000.0 cGy
4000.0 cGy
2000.0 cGy
Slice 224: Y = -49.79 cm GWAK^HYEON SEOP


Dose Volume Histogram
Norm. Volume
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
0
1000
2000
3000
4000
5000
6000
7000
8000
Dose (cGy)

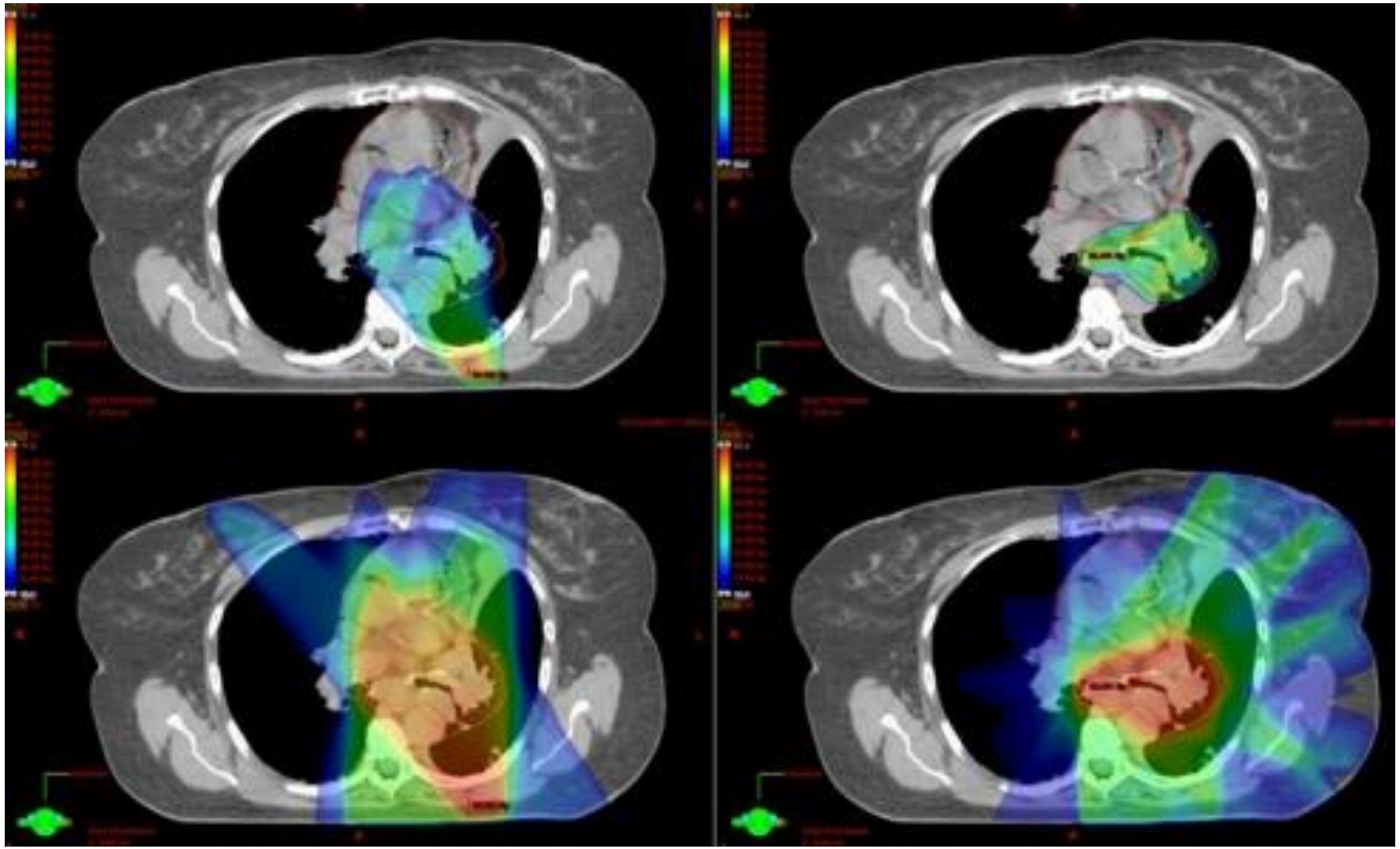
Radiation complication

- RT pneumonitis
- Spinal cord myelopathy
- High risk

Intensity modulated RT (IMRT)



Intensity modulated RT (IMRT)



DOSE AND VOLUME REDUCTION FOR NORMAL LUNG USING INTENSITY-MODULATED RADIOTHERAPY FOR ADVANCED-STAGE NON–SMALL-CELL LUNG CANCER

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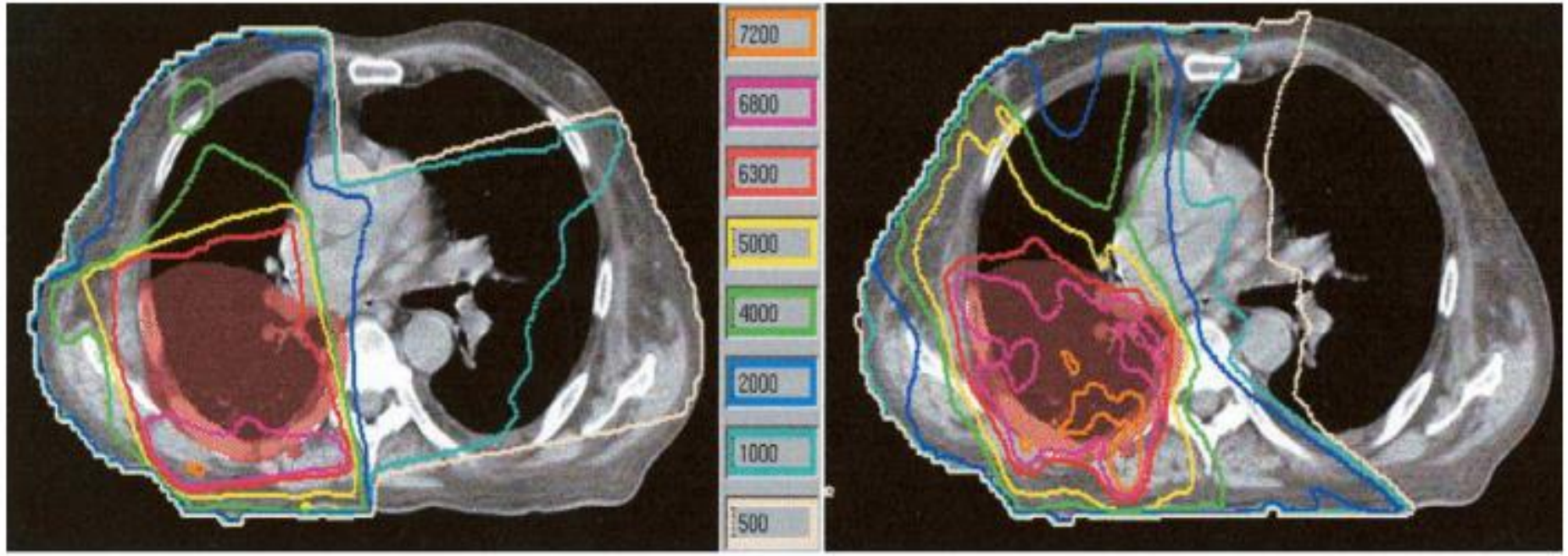
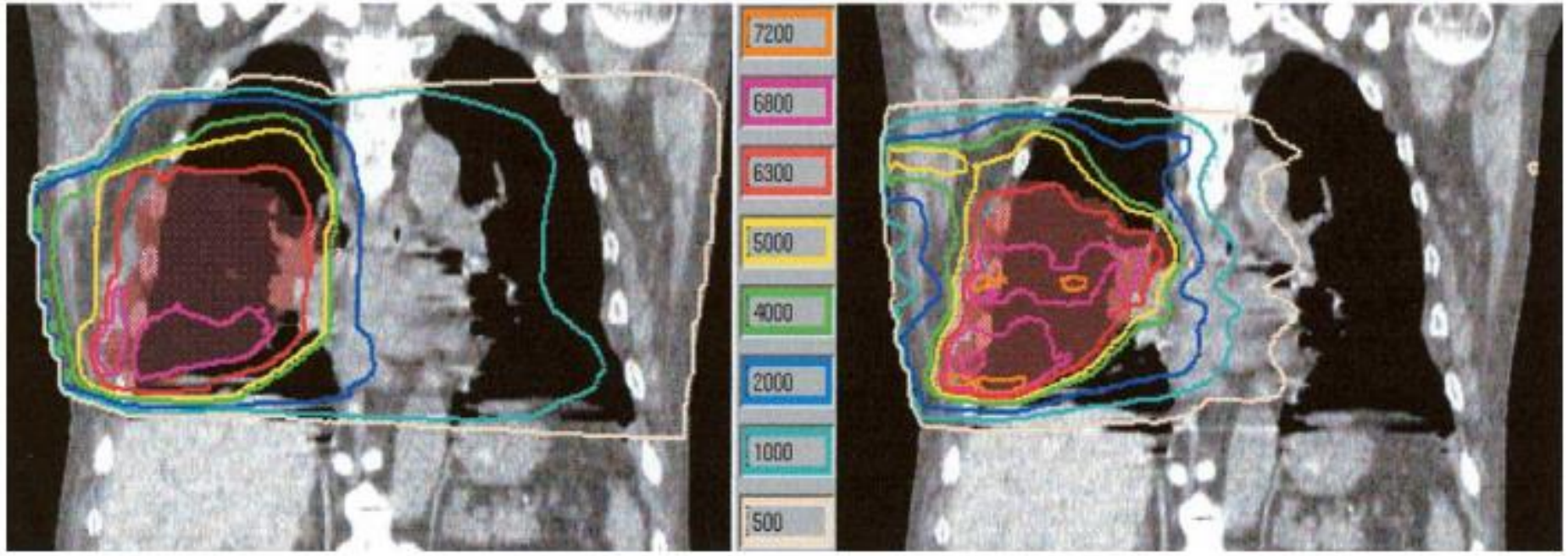

7200
6800
6300
5000
4000
2000
1000
500


7200
6800
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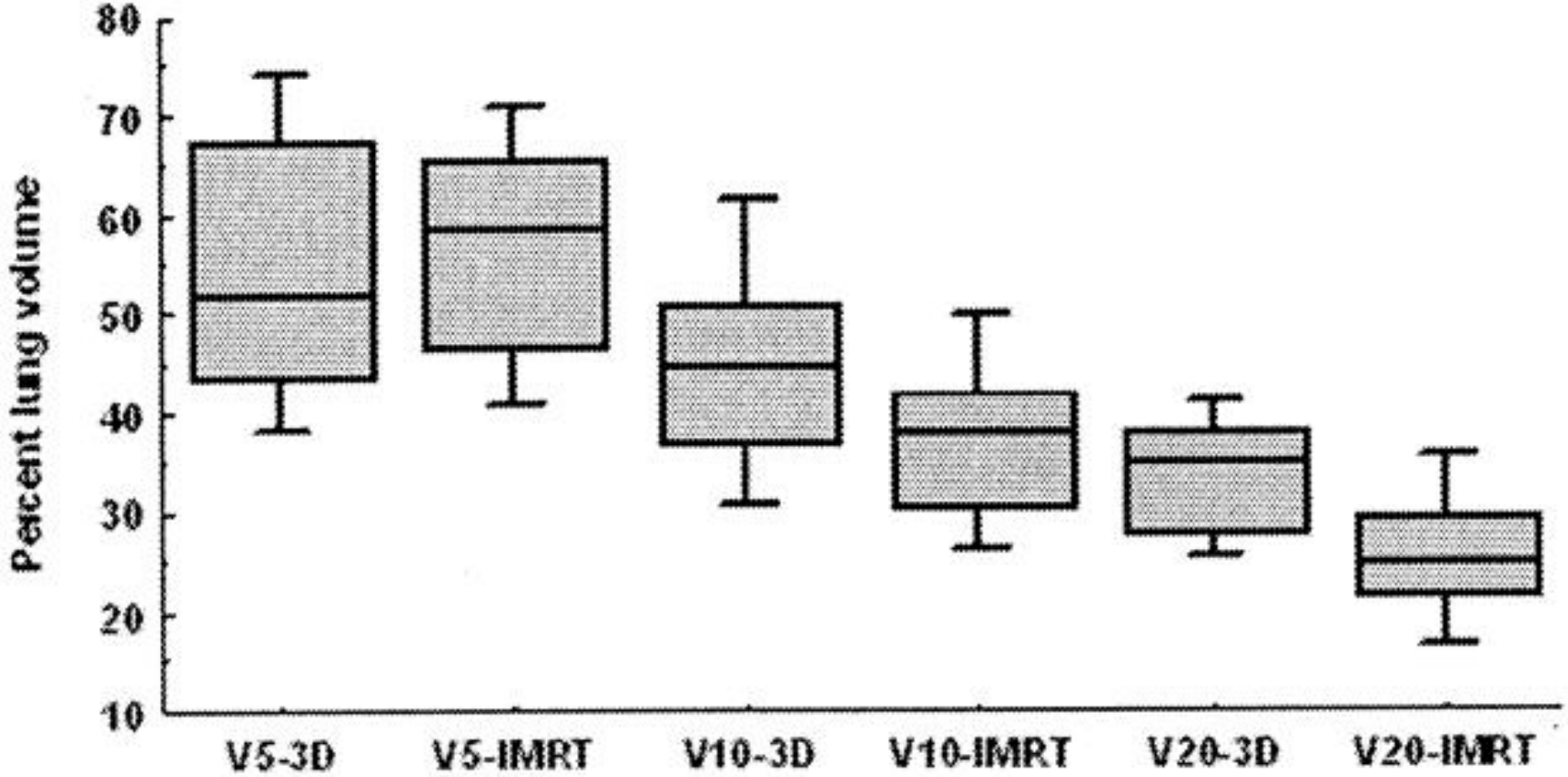
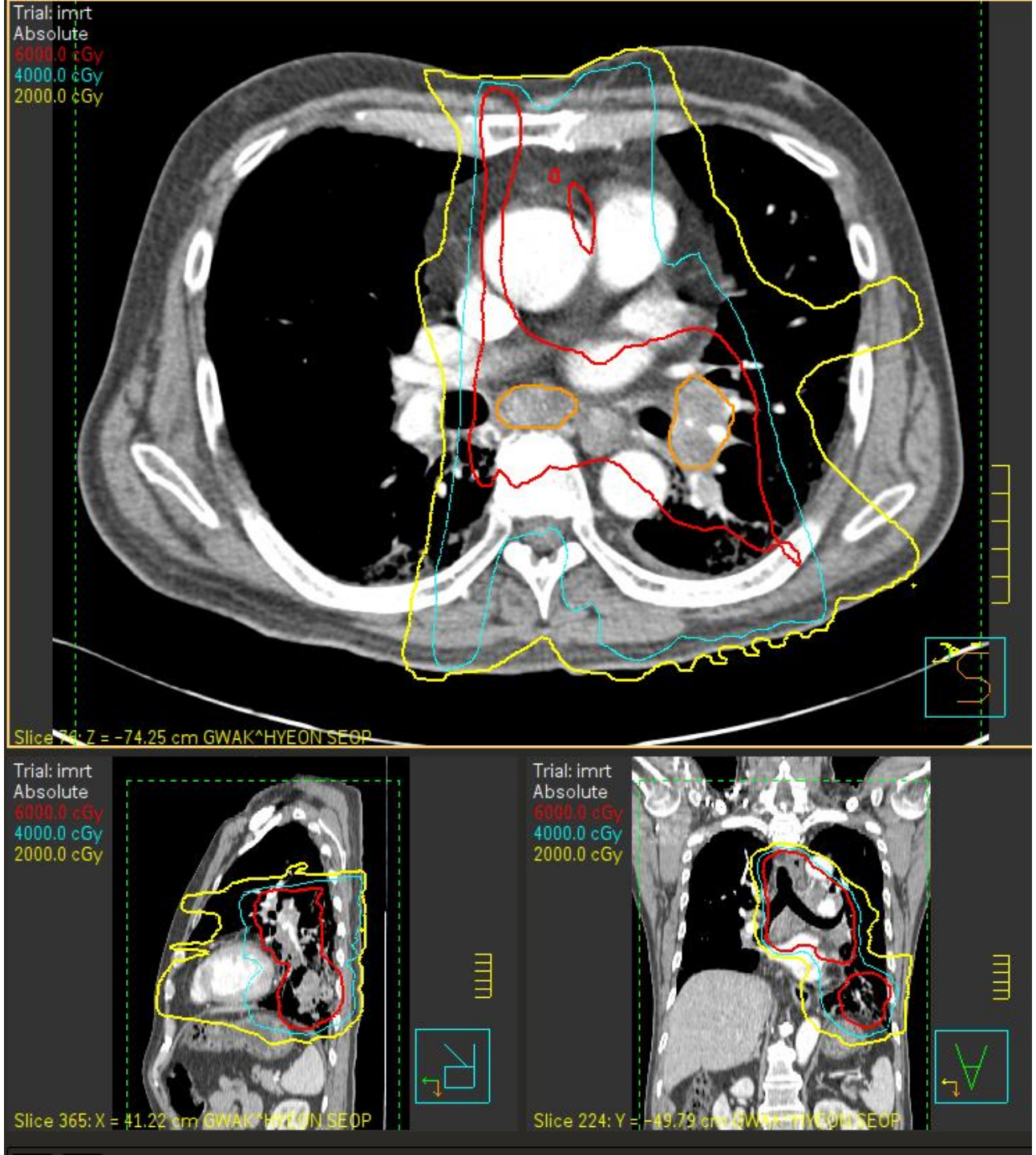
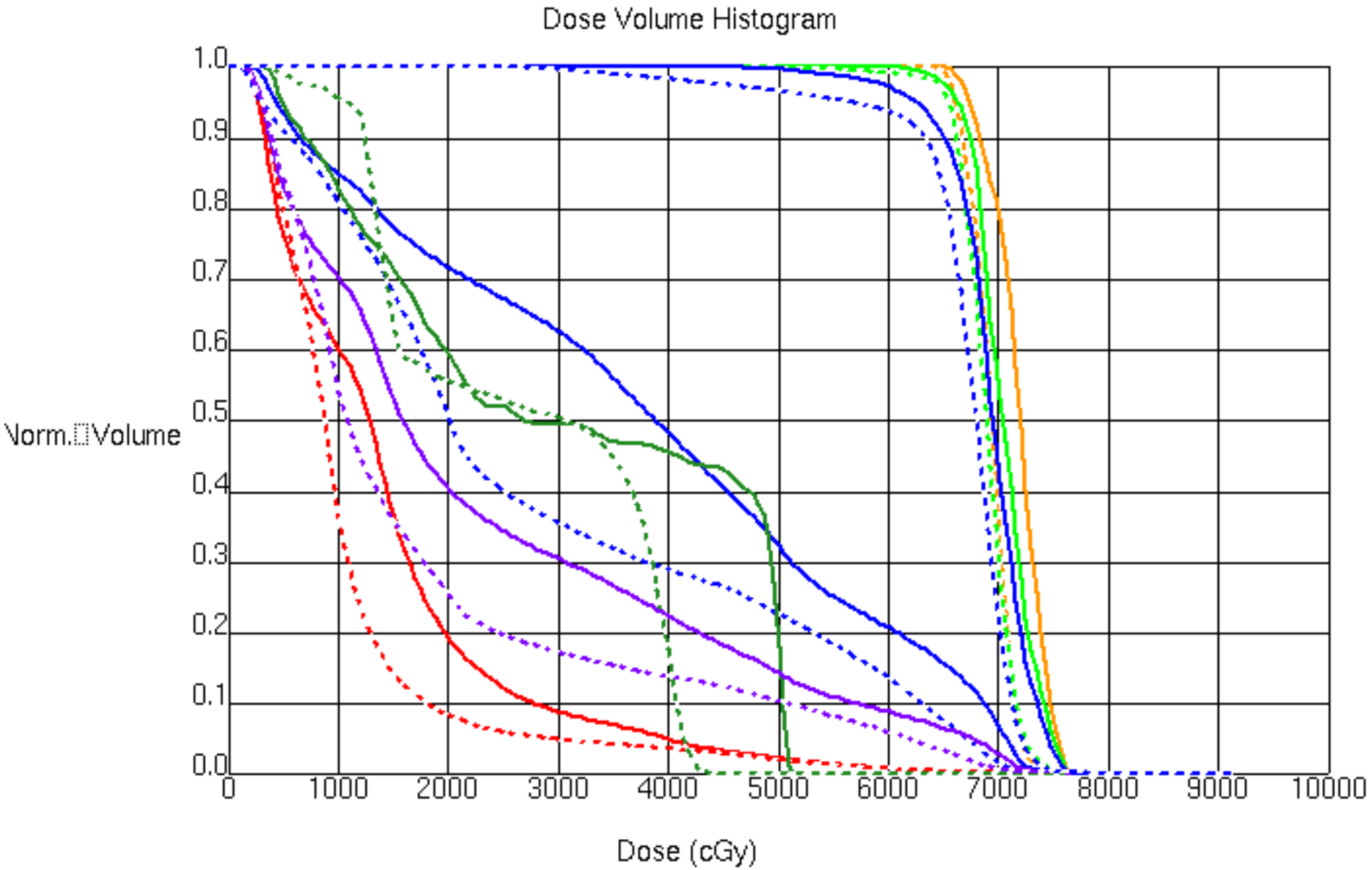


Fig. 3. Summary of total lung V_5, V_{10}, and V_{20} with three-dimensional conformal radiotherapy (3D-CRT) and intensity-modulated radiotherapy (IMRT) plans.


Trial: imrt
Absolute
6000.0 cGy
4000.0 cGy
2000.0 cGy
Slice 74: Z = -74.25 cm GWAK^HYEON SEOP
Trial: imrt
Absolute
6000.0 cGy
4000.0 cGy
2000.0 cGy
Slice 365: X = 41.22 cm GWAK^HYEON SEOP
Trial: imrt
Absolute
6000.0 cGy
4000.0 cGy
2000.0 cGy
Slice 224: Y = -49.79 cm GWAK^HYEON SEOP


Dose Volume Histogram
Norm. Volume
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
0
1000
2000
3000
4000
5000
6000
7000
8000
9000
10000
Dose (cGy)

Treatment

1. Surgery
2. Radiation only
3. **Chemo-radiation therapy**
4. Induction chemotherapy + CCRT
5. Chemotherapy only

Conclusions

- N2, N3 patients
  -> concurrent CCRT

- RT complication (RT pneumonitis, esophagitis etc)

- Benefit >> Risk

- if ambiguous, plz consult to Radiation oncologist.