N2 positive NSCLC

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Survival rates after CT-RT (in trials)

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Operable N2 disease

- INT 0139 [Albain K, 2009]: Median overall survival : 23.6 months (CT-RT-surgery) versus 22.2 months (CT-RT only)

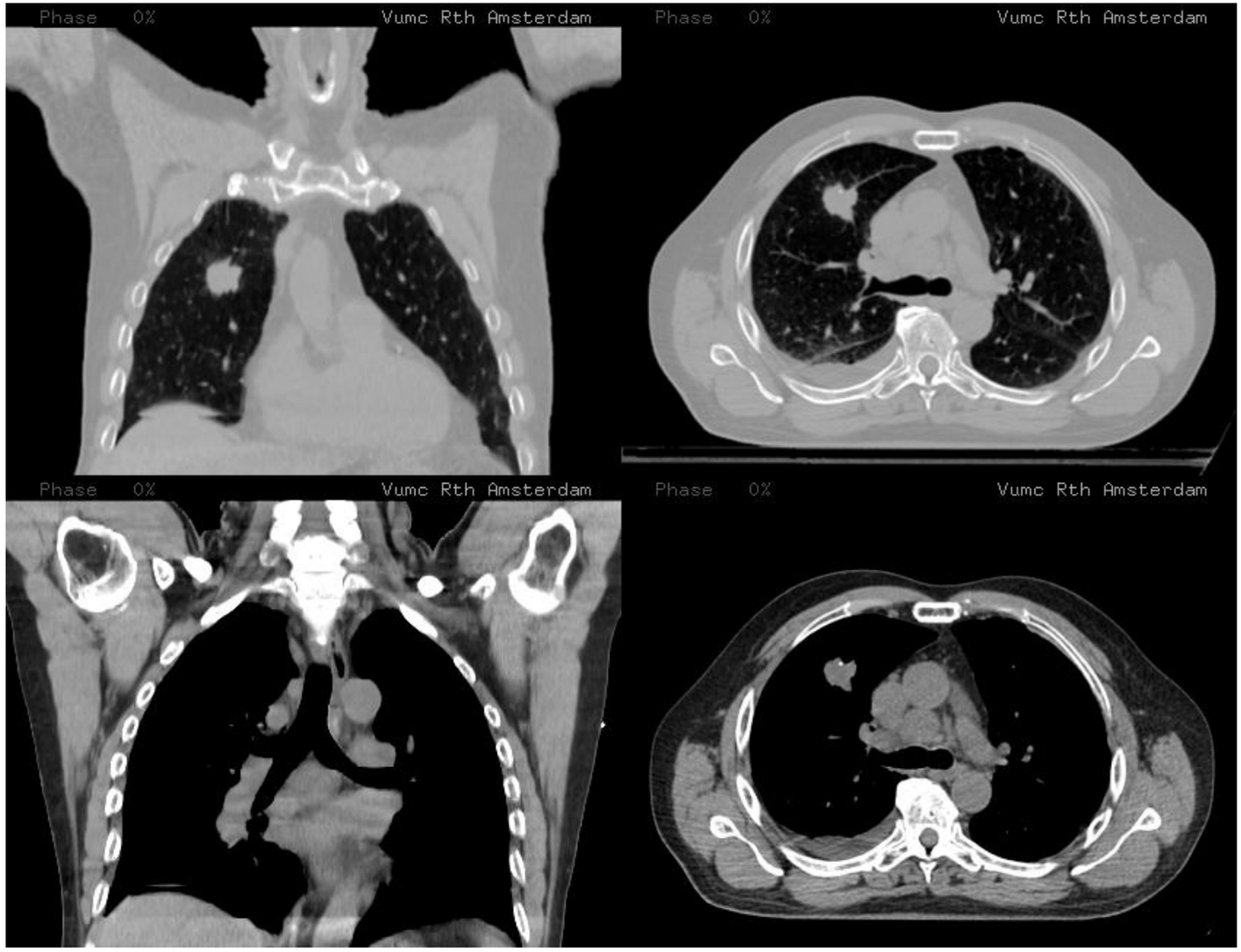
Inoperable N2/3 disease **

- RTOG 94-10 [Curran W, 2011]: Median overall survival 17 months

- RTOG 0617 [Bradley J, ASTRO 2011]: median survival ranging from 21.7 months - 20.7 months **

4-D imaging for planning

Differential 4D motion of primary tumors and nodes



Pantarotto JR, 2009

Imaging on treatment couch

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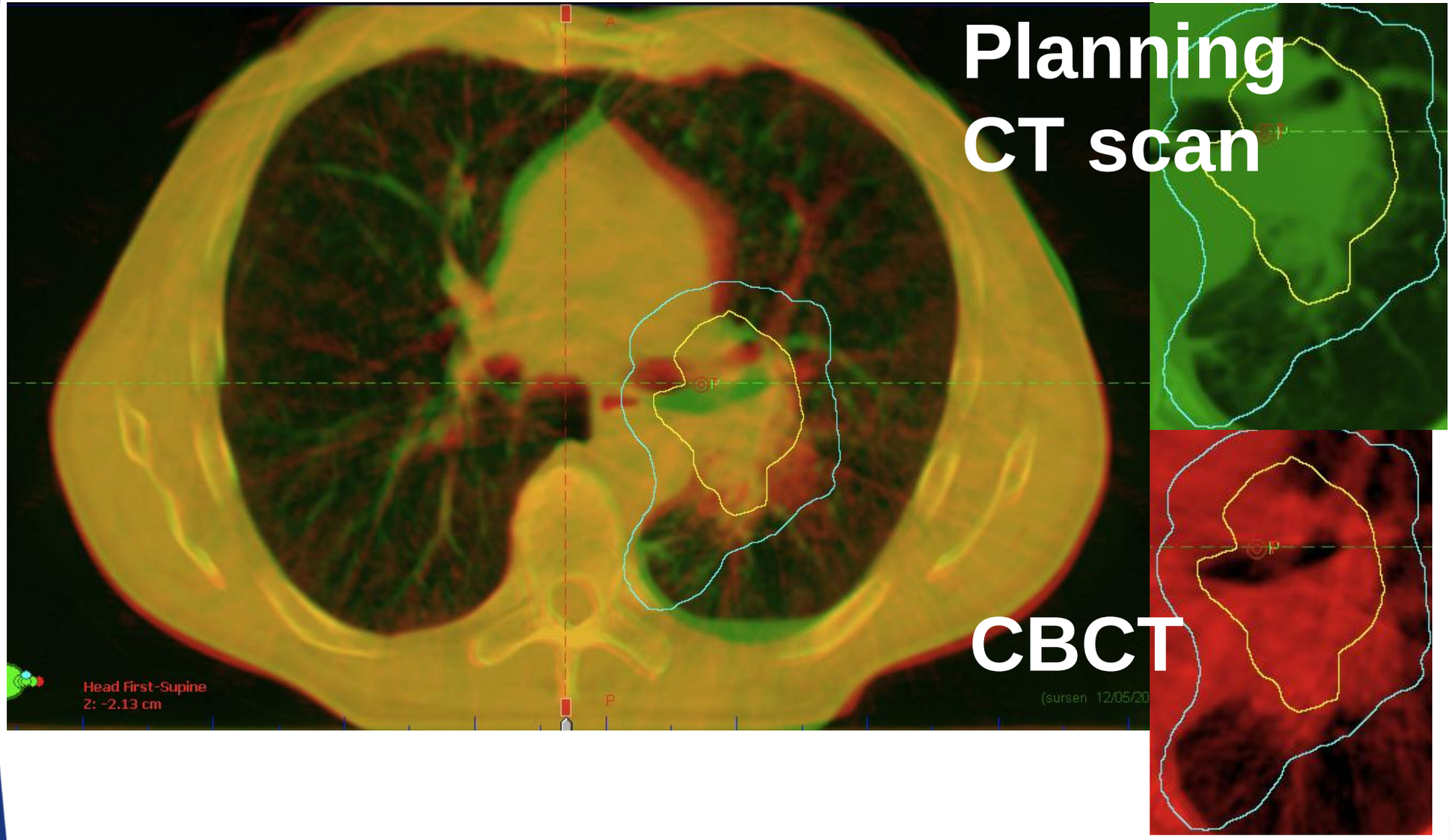
Cone-beam CT scan (CBCT)



Initiate NSCLC treatment quickly

- 40 patients with at least 2 CT-PET scans before treatment.
- Progression defined as any new lymph node involvement, site of disease, or stage change.

Table 2. Clinical progression rates at 4, 8, and 16 weeks from the initial staging scans

Event	Number of events	4 week	8 week	16 week	Median interval (range)
Any progression	19	13%	31%	46%	7.6 weeks (1.4–128.3)
Any new site	17	13%	31%	46%	7.1 weeks (1.4–25.0)
Overall stage change	10	3%	13%	21%	16.3 weeks (3.1–128.3)
Distant metastasis	4	3%	13%	13%	5.3 weeks (3.1–7.1)

Rapid progression possible; implement the most active treatment strategy as quickly as possible!

Treating large volume stage III tumors

VUmc

Concerns about excess toxicity and ‘radiocurability’

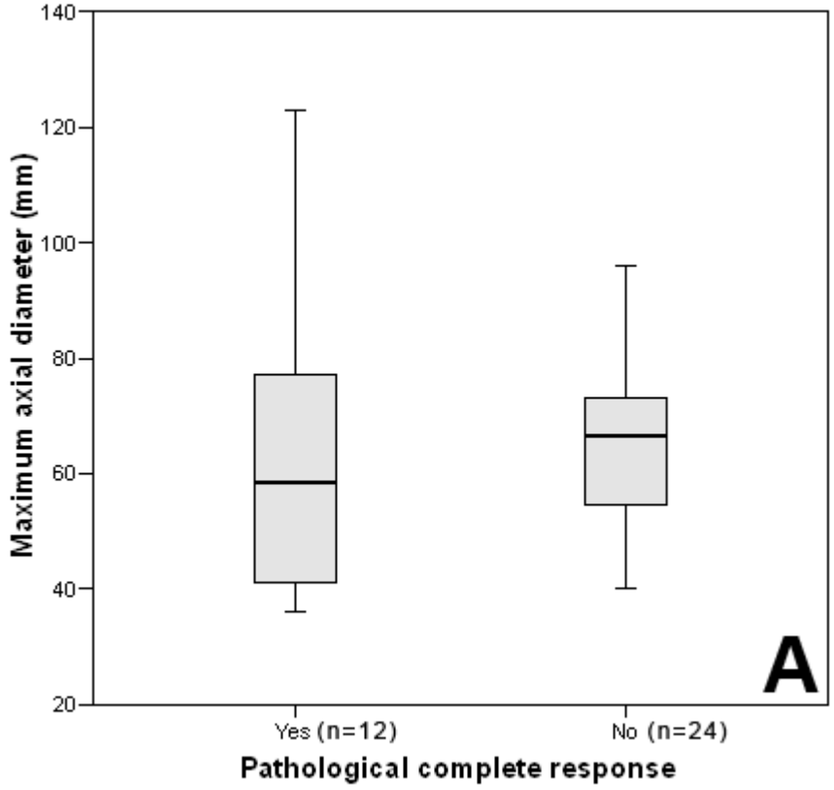
- Furuse K, 1999: fields for concurrent CT-RT <50% of 1 lung
- Cochrane Review, 2010: CT-RT only when disease can be “*encompassed within a radical radiotherapy volume*”
- Sundstrøm S, 2011: tumours >8-10 cm considered by *most clinicians* to be treated with a palliative intent
- Zwitter M, 2012: >80% of stage III NSCLC have bulky disease and/or have significant comorbidity, and are “*best treated by RT alone or with induction chemotherapy followed by RT*”

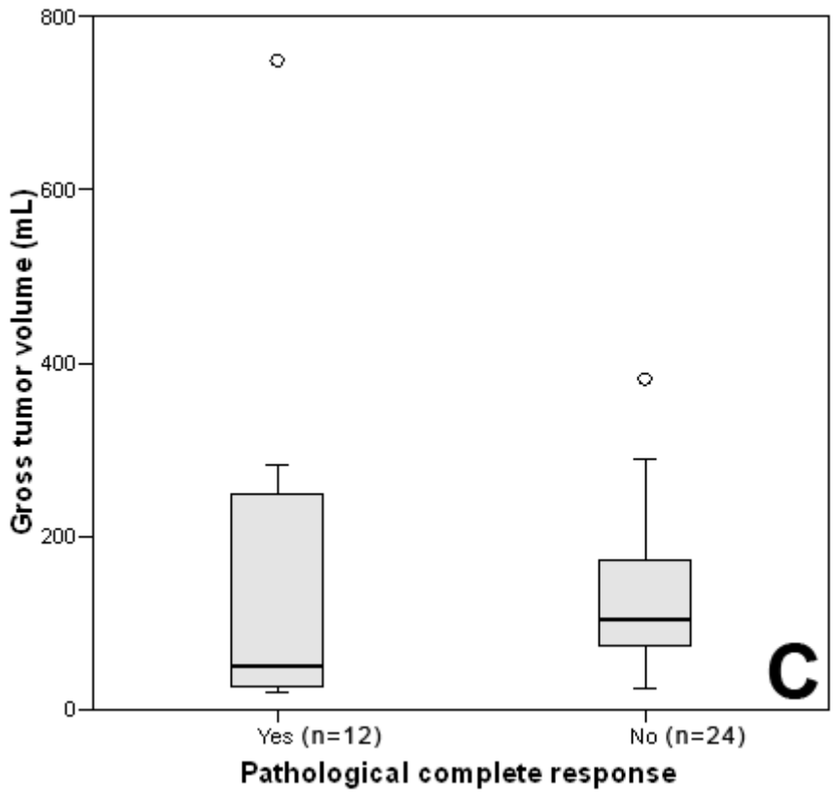
Large tumors can achieve a CR

36 superior sulcus tumors, pre-op CT-RT to 46-50 Gy

Maximal axial diameter: 4 cm –12.3 cm (volume: 20-750 mL)

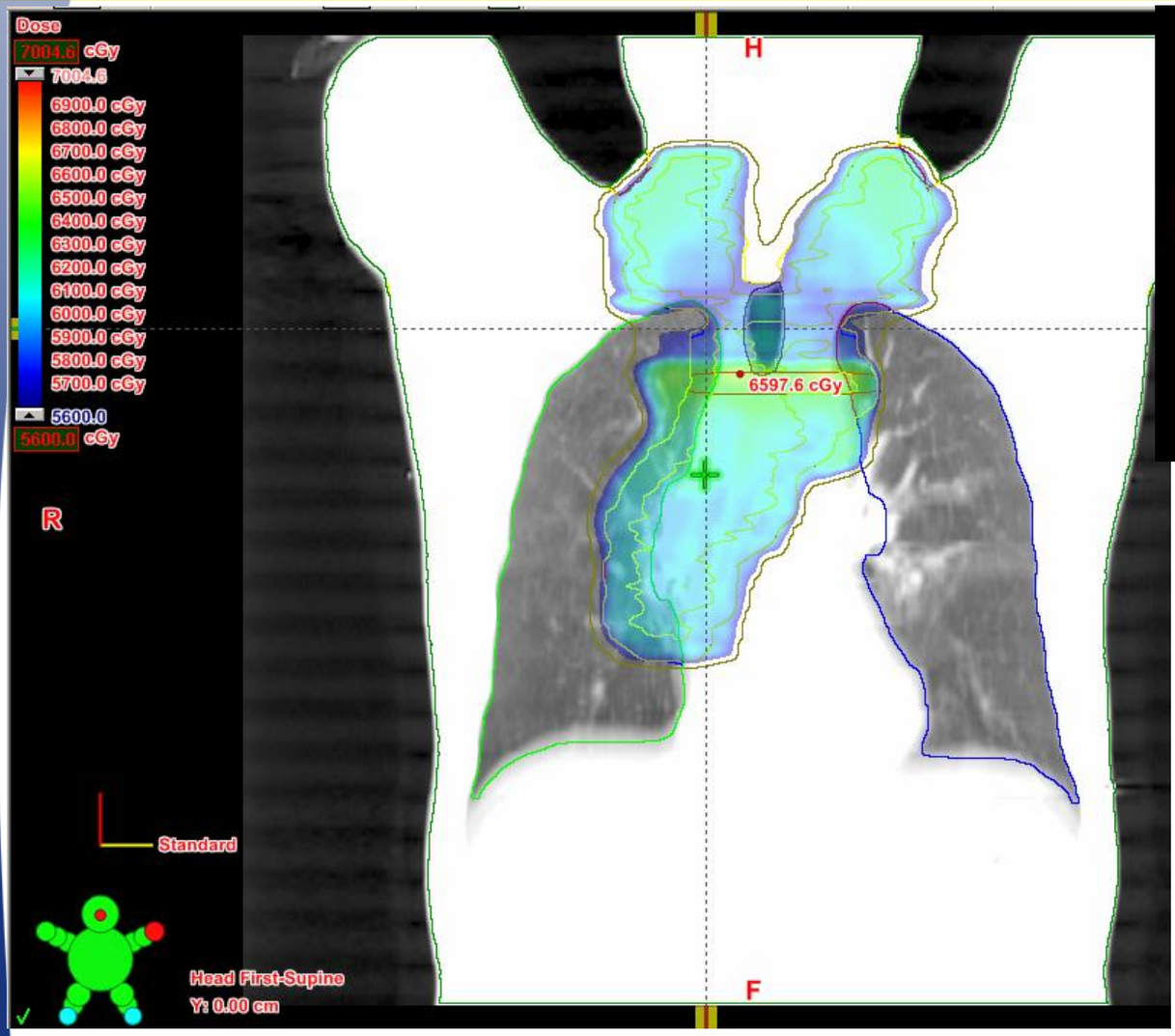
33% of patients achieved a pathological complete remission

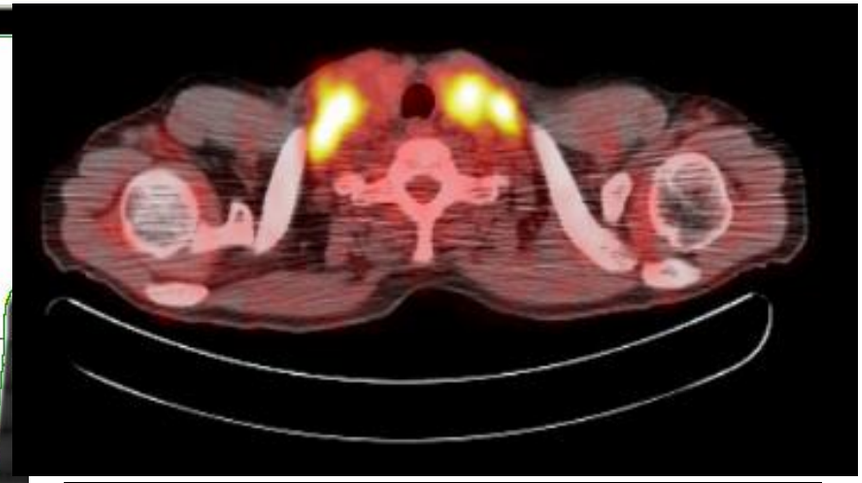


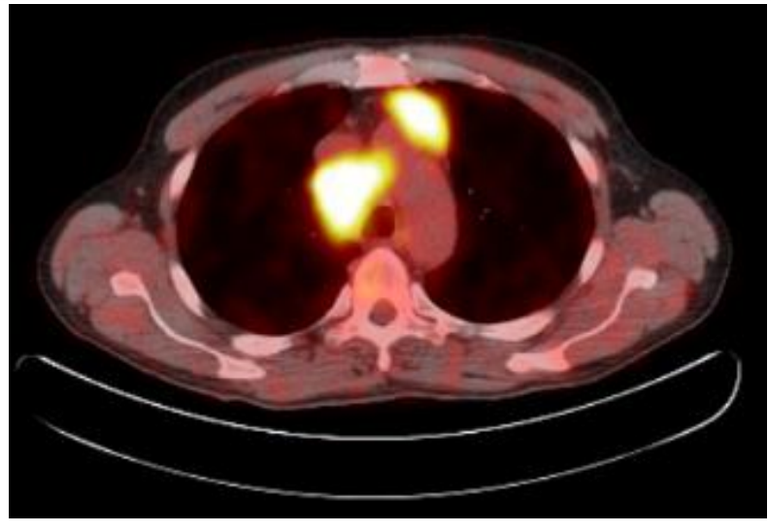


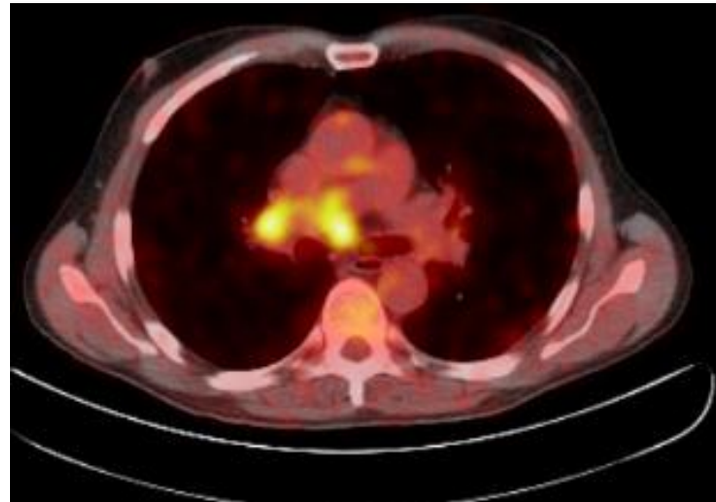
Vos CG, *in press*

T1N3M0 after induction chemo









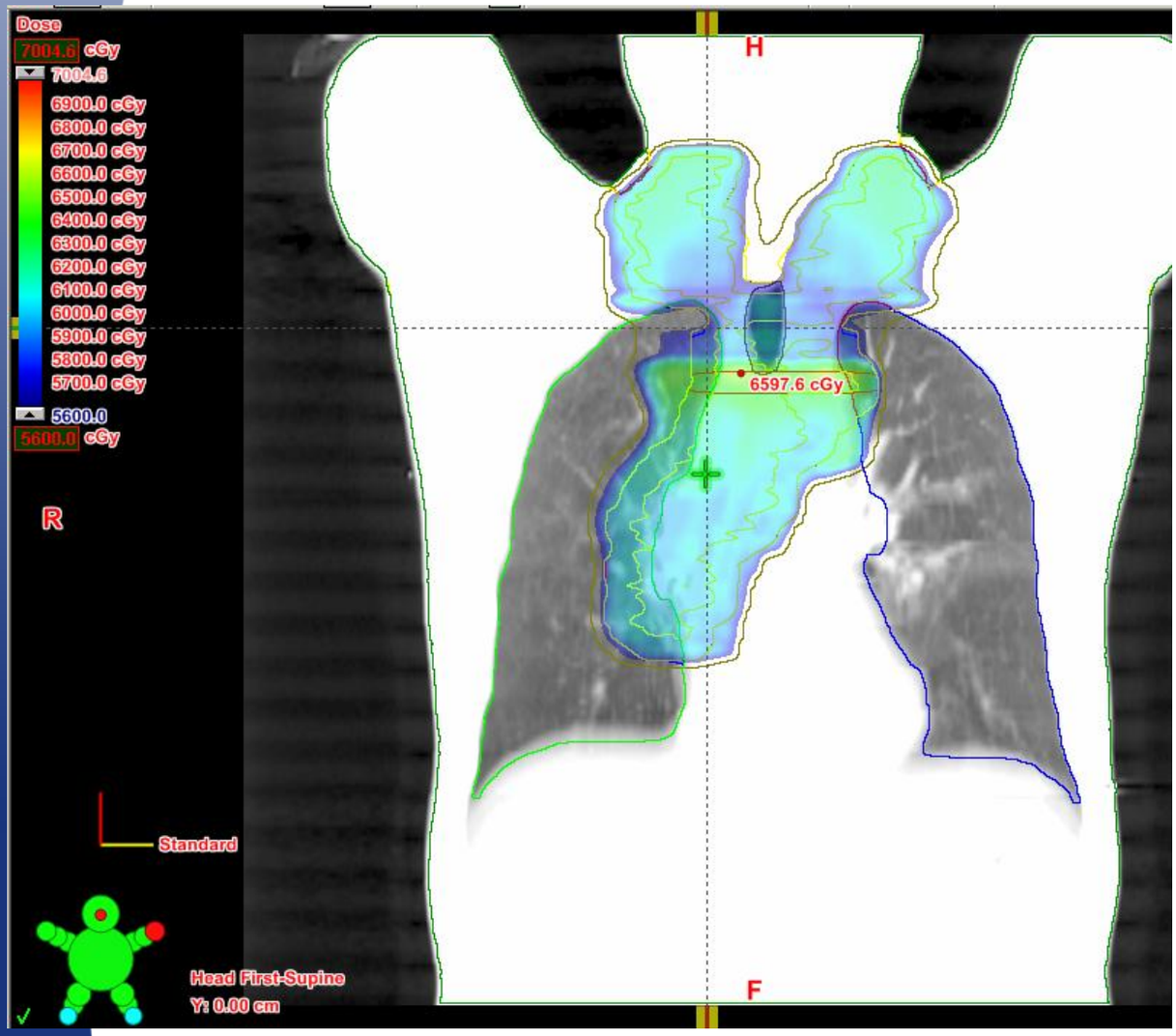
Which treatment would you advise this patient?

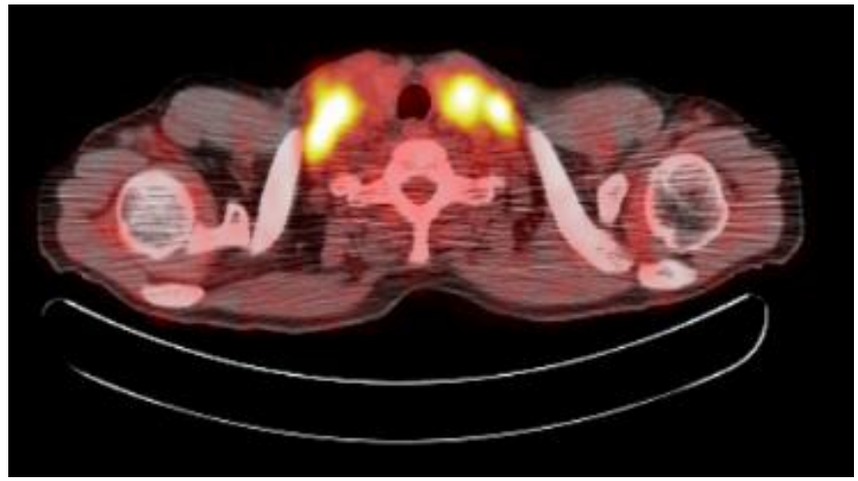
A. palliative radiotherapy

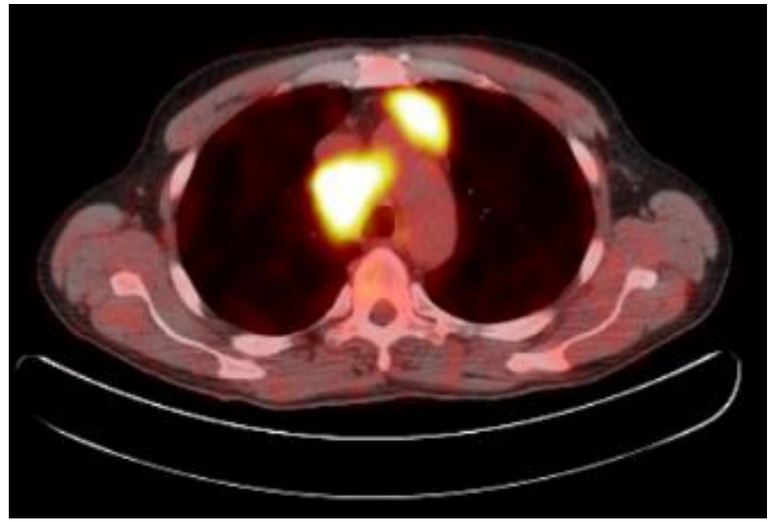
B. radical radiotherapy

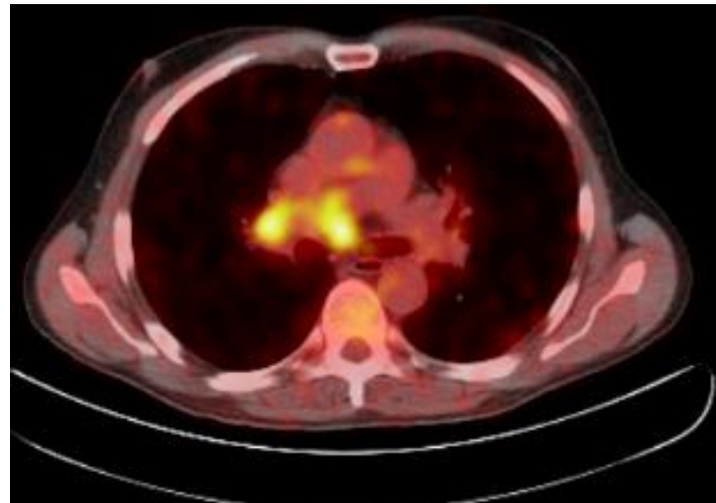
C. concurrent chemo-radiotherapy

T1N3M0 after induction chemo



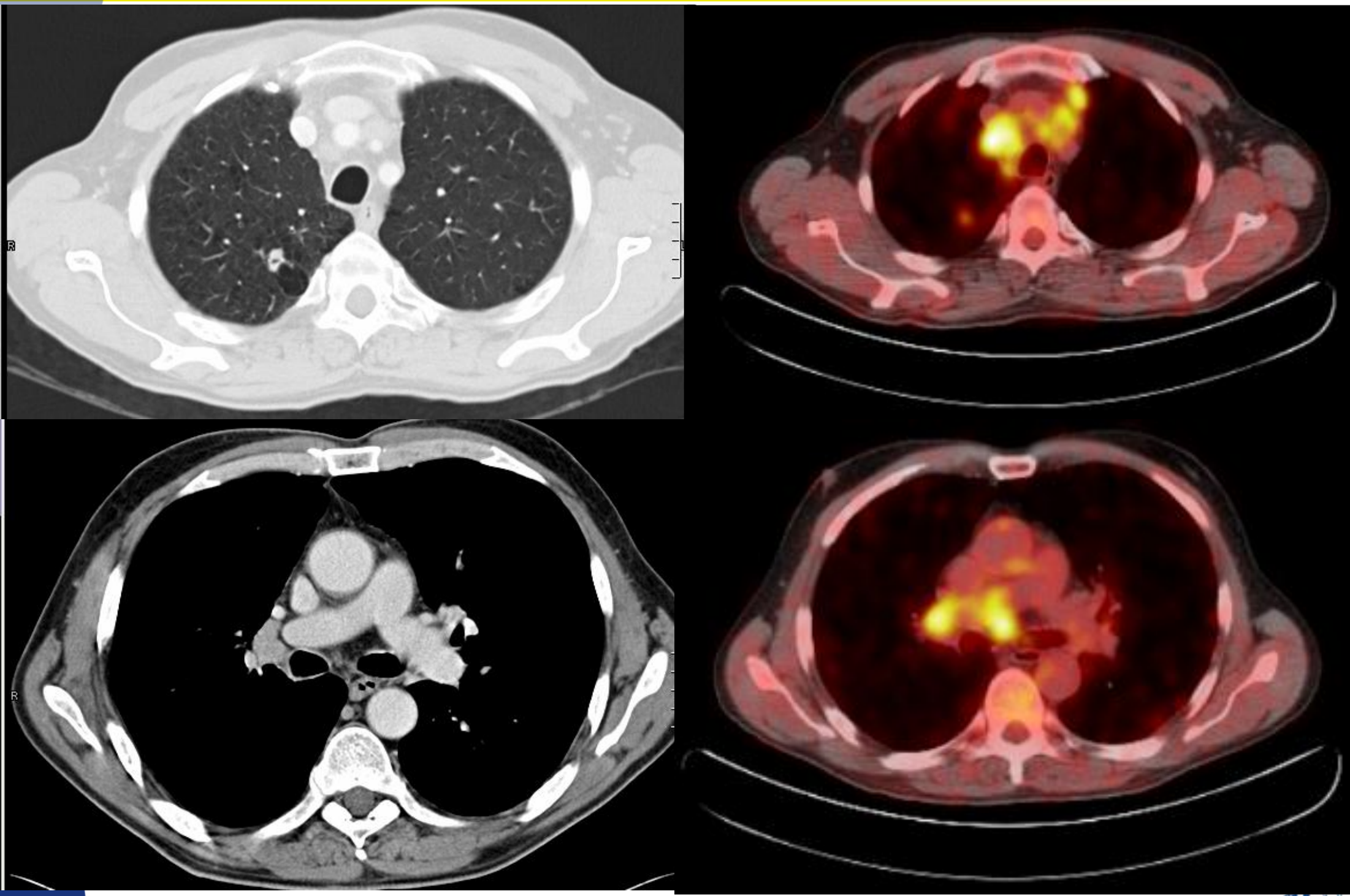






- WHO Performance Score 0
- 19 cm oesophagus in field
- Planning Target Volume = 1371 cc

T1N3M0 after induction chemo



When is a RT plan acceptable?

IMRT planning objectives used at VUMC, Amsterdam

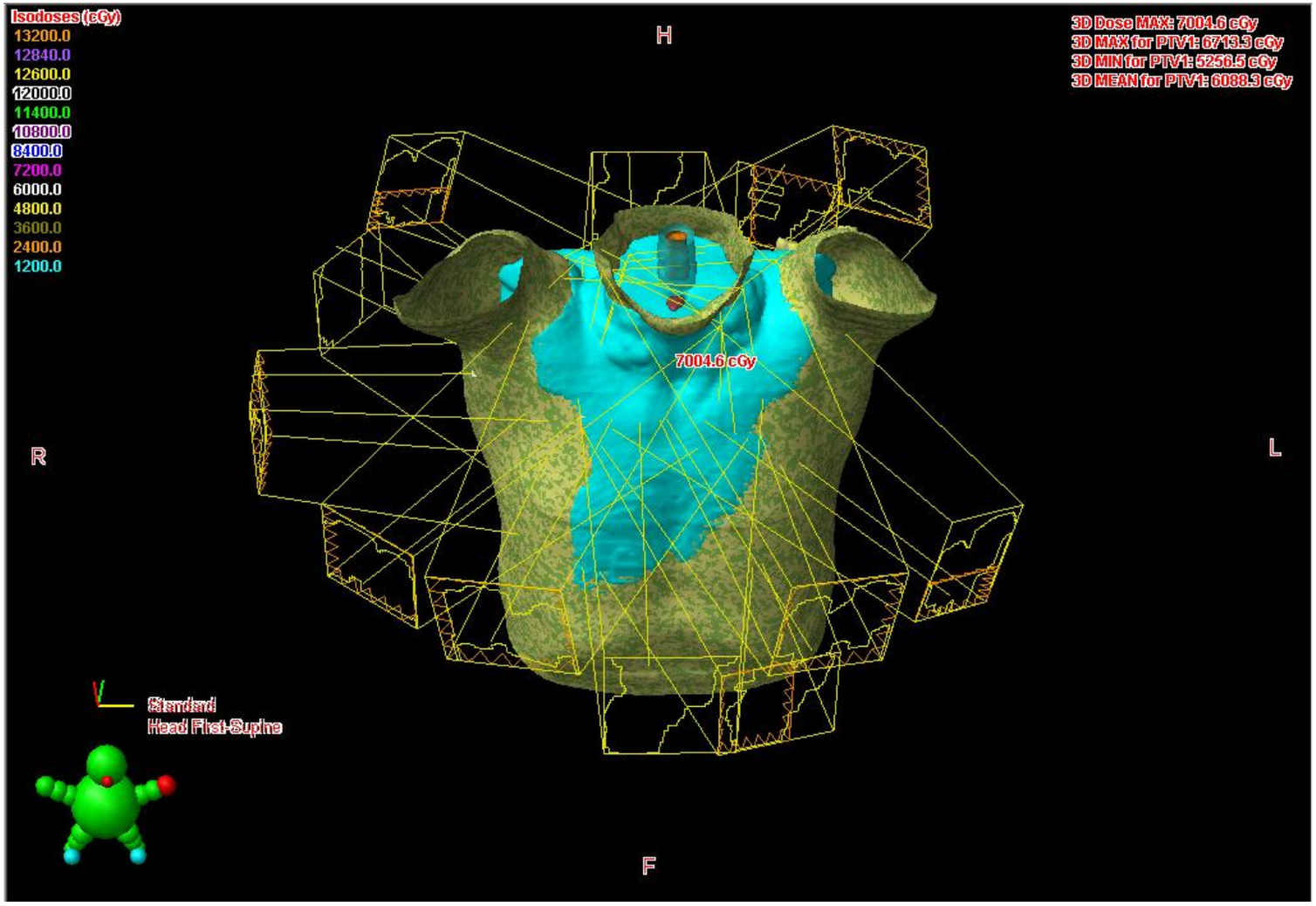
PTV $V_{95\%}$	>97%
PTV $V_{107\%}$	< 5%
Total body $V_{107\%}$	< 10 cm^3
Spinal cord D_{max}	< 50 Gy
Total lung V_{20}	**< 35%**
Total lung V_5	**< 60%**

Verbakel W, 2012

T1N3M0 after induction chemo

VUmc

Hybrid-IMRT: 13 fields (3 open, 9 IMRT fields)

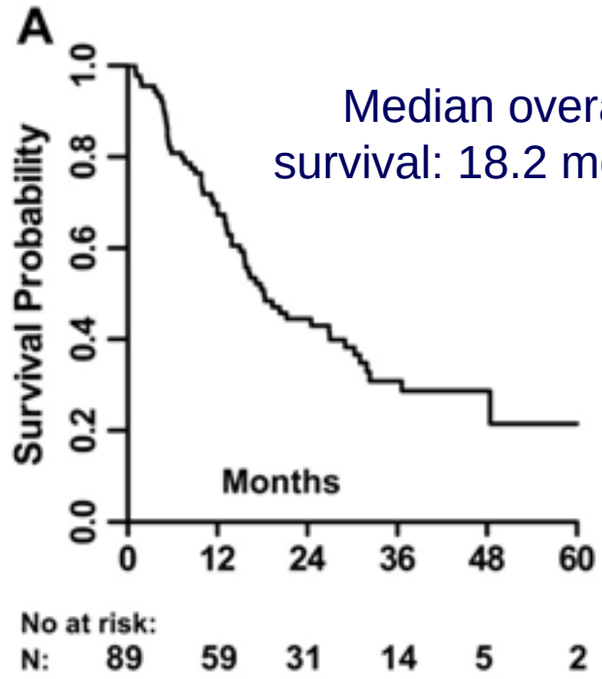


- Treated to 60 Gy (30 x 2Gy) until Oct 2010
- V_{20} = 34%, V_5 = 65%, cord dose = 49 Gy
- No evidence of disease (2012)

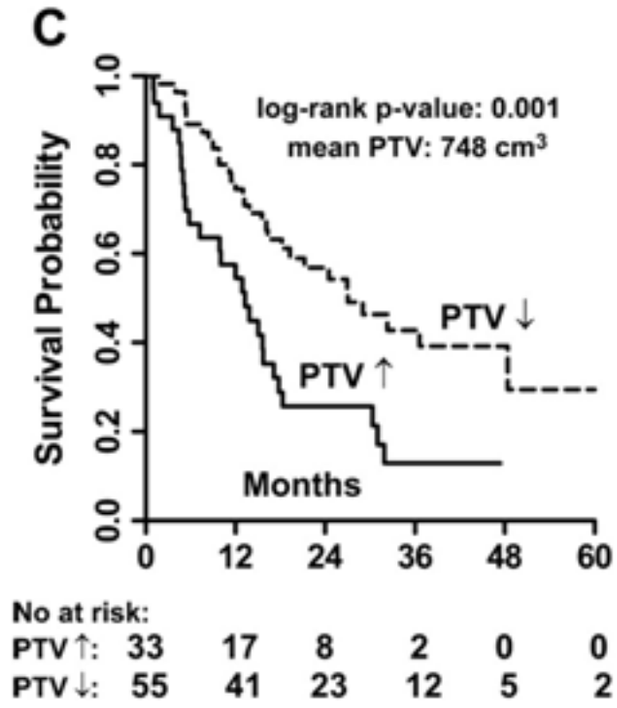
CT-RT in stage III NSCLC

Single institution, non-trial patients (2003-2008)

Tumor volume (PTV) and median OS: 13.3 months versus 27 months for PTV greater or less than **mean** of **748 cm³**



Median overall survival: 18.2 months

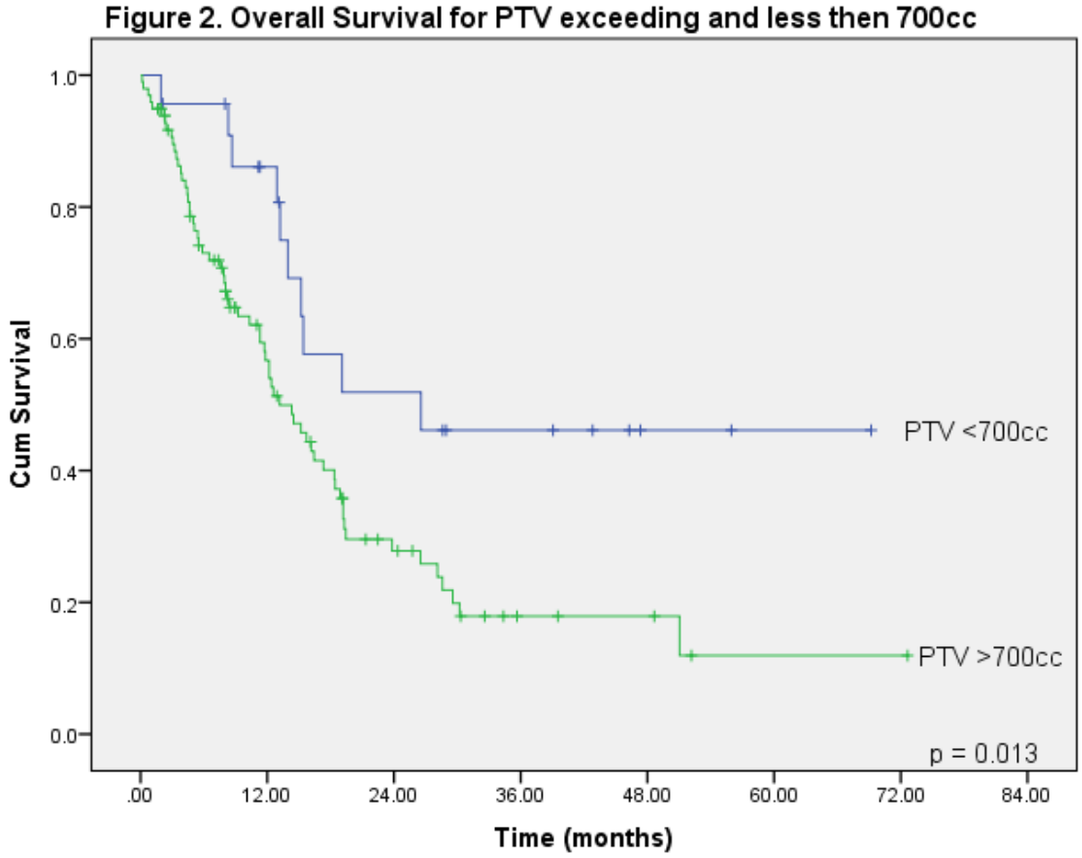


Phernambucq E, 2011

CT-RT in ‘large’ stage III NSCLC

121 patients with a PTV >700cc (± N3 nodal disease) or a PTV <700cc and N3 disease;

Gr ≥3 esophagitis – 34%; Gr ≥3 pneumonitis - 4%



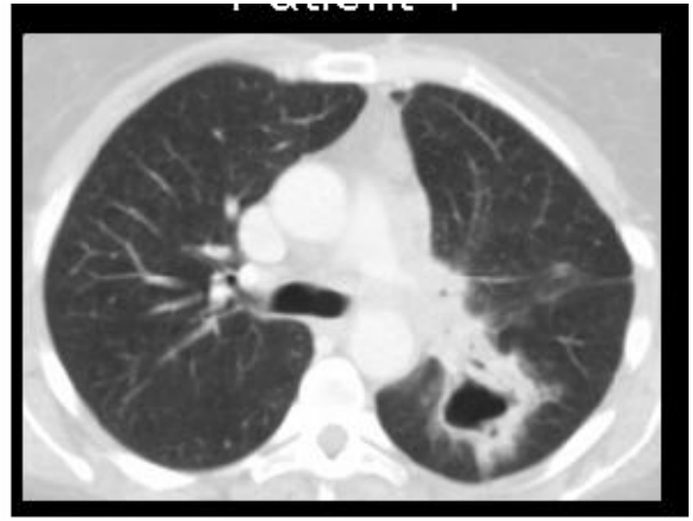
Wiersma T, *submitted*

No. at risk PTV>700cc	98	60	40	35	35	34	34	-
No. at risk PTV<700cc	23	20	14	13	13	13	-	-

Case for discussion

62 year old male with a stage III-N2 squamous cell carcinoma (biopsy-proven nodes at 4L and 7**)**

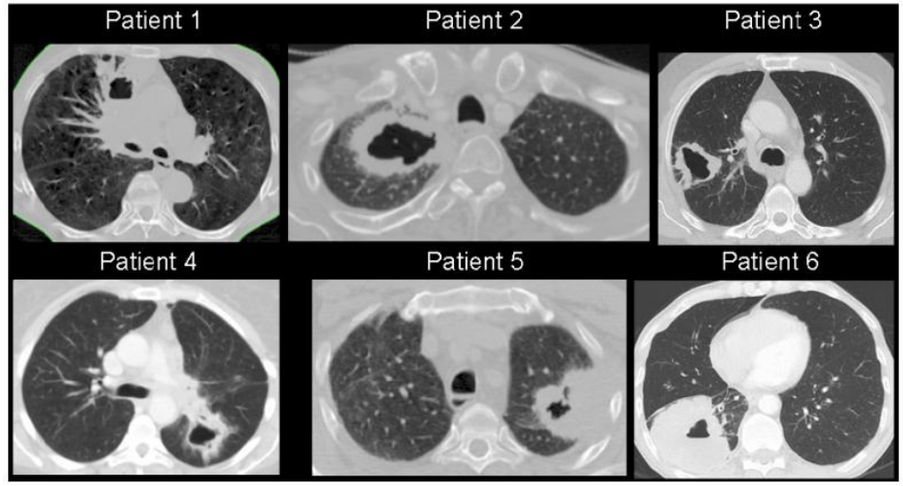
Afebrile, ECOG PS 1



Question: What treatment would you suggest?

- Concurrent CT-RT
- Concurrent CT-RT, followed by surgery
- Sequential CT-RT
- Surgery + adjuvant therapy
- RT alone
- Other options?

Cavitation in stage III NSCLC



- 87 patients treated with CT-RT)
- Cavitation on baseline CT scans in 16 patients (18%) squamous cell (n=14), adenocarcinoma (n=1), large cell (n=1)
- In 8 patients developing enlarging cavities, complications included tumor abscess (n=5), fatal hemorrhage (n=2) and fatal lung embolism (n=1). Two required open-window thoracostomy following CT-RT

Phernambucq E, 2012

Cavitation in stage III NSCLC

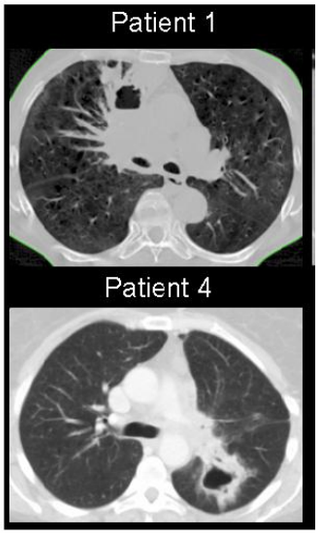
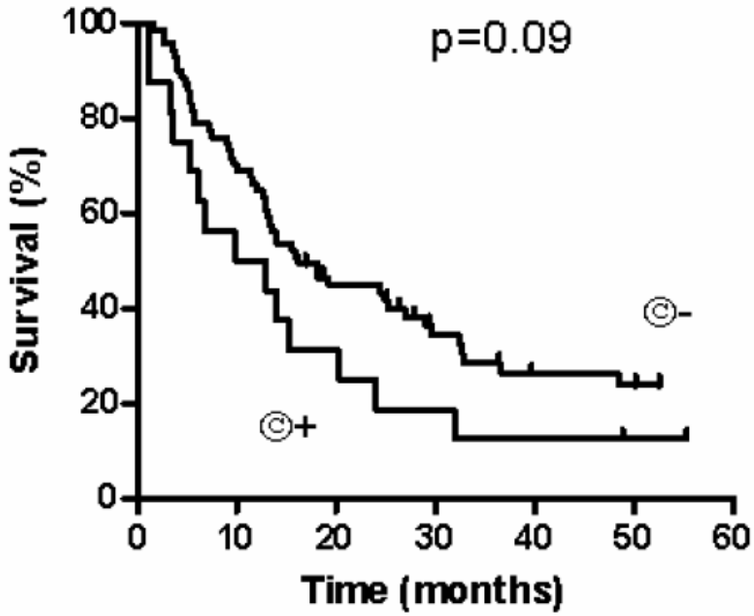


Figure 1. Overall survival for patients with or without tumor cavitation



©+, patients with cavitated tumors; ©-, patients with non-cavitated tumors

Median OS for patients with, or without, tumor cavitation was 9.9 and 16.3 months, respectively (p=0.09)

Phernambucq E, 2012

Chemotherapy choice in CT-RT

National Comprehensive Cancer Network®

NCCN Guidelines™ Version 1.2011
Non-Small Cell Lung Cancer

NCCN Guidelines Index
NSCLC Table of Contents
Discussion

CHEMOTHERAPY REGIMENS USED WITH RADIATION THERAPY

Concurrent Chemotherapy/RT Regimens*
Cisplatin 50 mg/m^2 on day 1, 8, 29, and 36 Etoposide 50 mg/m^2 days 1-5, 29-33 Concurrent thoracic RT[a] (preferred)
Cisplatin 100 mg/m^2 day 1, 29 Vinblastine 5 mg/m^2/weekly x 5 Concurrent thoracic RT[b] (preferred)
Paclitaxel 45-50 mg/m^2 weekly over 1 hour Carboplatin AUC = 2 mg/mL/min over 30 min weekly Concurrent thoracic RT[c] (category 2B)

Sequential Chemotherapy/RT Regimens
Cisplatin 100 mg/m^2 on day 1, 29 Vinblastine 5 mg/m^2/weekly on days 1, 8, 15, 22, 29 followed by RT[b]
Paclitaxel 200 mg/m^2 every 3 weeks over 3 hours, 2 cycles Carboplatin AUC 6, 2 cycles followed by thoracic RT[c]

NCCN guidelines (v 3.2012): "There are data that support full-dose cisplatin over carboplatin-based regimens. Carboplatin regimens have not been adequately tested (www.nccn.com)

Symptomatic radiation pneumonitis (RP): a meta-analysis

- Individual patient meta-analysis in 836 patients treated with concurrent CT-RT; Median dose 60 Gy; median FU 2.3 years
- Cisplatin/etoposide (38%), carboplatin/paclitaxel (26%).
- Overall rate of RP 30% (n=249), fatal RP in 1.9% (n=16)

Table 4 Multivariable analysis of factors predictive of symptomatic radiation pneumonitis in the validation dataset (n = 279)

	Multivariable analysis		
Factor	OR	95% CI	*P* value
Age (per 10-y increase)	1.38	0.95-2.01	.089
Chemotherapy regimen			<.001
Cisplatin-etoposide	1	Reference	
Carboplatin-paclitaxel	5.52	2.25-13.55	
Other	3.39	1.50-7.68	
Volume of lung receiving ≥20 Gy (V_{20})	1.07	1.03-1.11	<.001

Abbreviations: CI = confidence interval; OR = odds ratio.

Palma D, 2012

Symptomatic radiation pneumonitis (RP): a meta-analysis

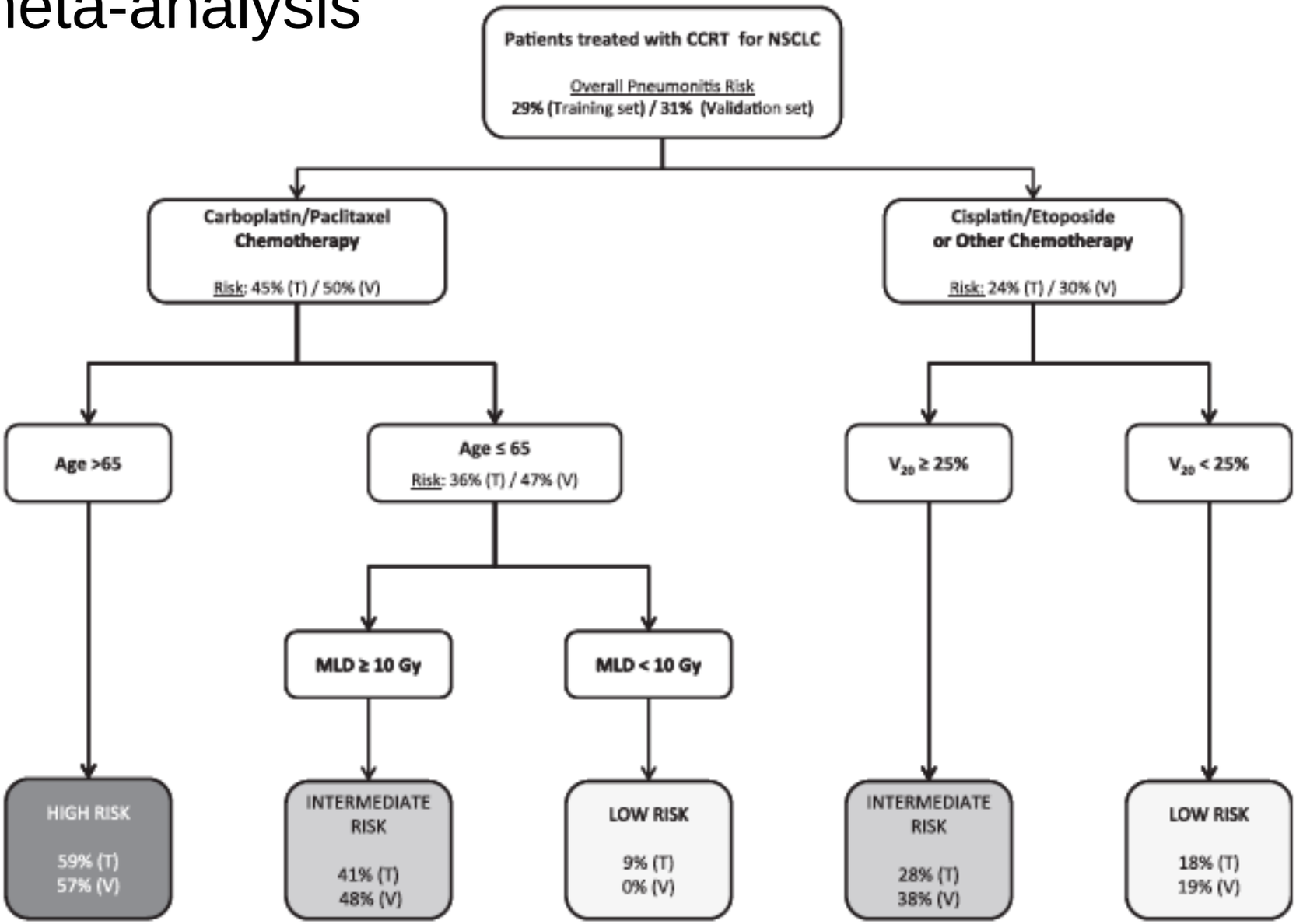


Fig. Recursive partitioning analysis of radiation pneumonitis risk in patients undergoing concurrent chemoradiation therapy (CCRT) for non-small-cell lung cancer (NSCLC). Patients were randomly divided into a training set (T) and validation set (V). MLD, mean lung dose; V_{20}, volume of lung receiving ≥20 Gy.

Palma D, 2012

N2 positive NSCLC: Conclusions (1)

- Histological or cytological confirmation of N2 disease is mandatory
- Subsets of N2 disease determine prognosis, as well as the feasibility of some treatment strategies
- An expert multi-disciplinary team is essential
- Response evaluation after induction and definitve chemo-radiotherapy can be difficult

N2 positive NSCLC: Conclusions (2)

- Concurrent chemo-radiotherapy (CT-RT) is the standard of care in multi-level N2 disease
- With modern image-guided radiotherapy, large tumors are eligible for routine concurrent CT-RT
- Optimal treatment of cavitating N2 tumors unclear
- Use of carboplatin-paclitaxel for CT-RT increases risk of radiation pneumonitis in elderly patients