Hypofractionation for Primary and Metastatic Lung Tumors

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The Story of Lung Cancer

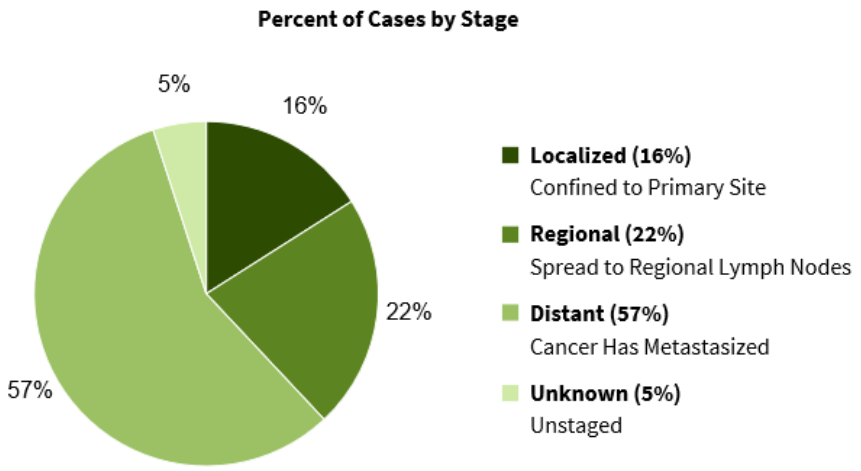
- **The Beginning:** Prevention
  - Smoking cessation (combined pharmacologic and behavioral therapy is most effective)
  - Low-dose CT screening (age 50, ≥ 20 pack-years, cessation < 15 years ago)

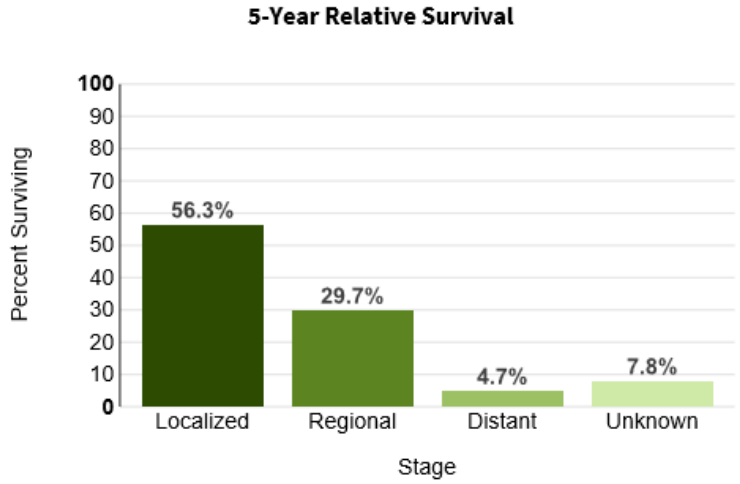
- **The Middle:** Diagnosis and Treatment
  - Integration of multidisciplinary care provided by various oncologists
  - Monitoring for recurrence
  - Survivorship care

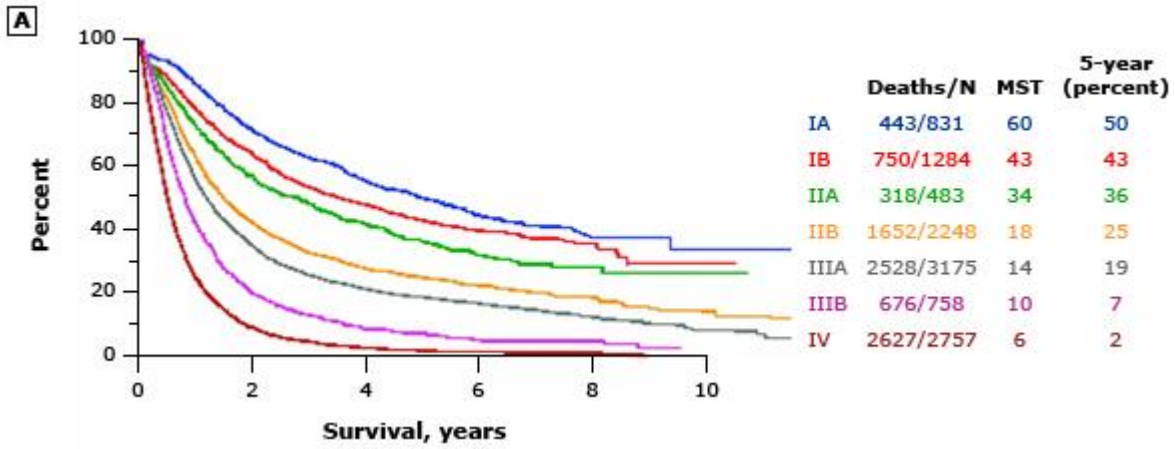
- **The End:** Palliation
  - Early palliative care involvement
  - Effective symptom management
  - Appropriate advance care planning and use of hospice

Lung Cancer Incidence and Prognosis

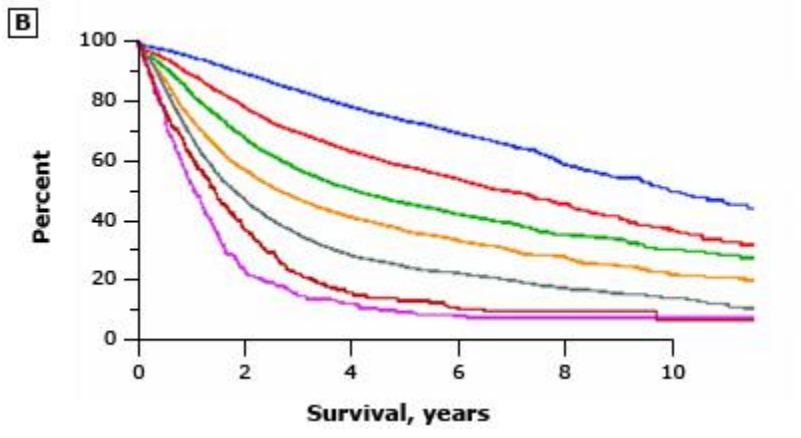
T/M	Subcategory	N0	N1	N2	N3
T1	T1a	IA1	IIB	IIIA	IIIB
	T1b	IA2	IIB	IIIA	IIIB
	T1c	IA3	IIB	IIIA	IIIB
T2	T2a	IB	IIB	IIIA	IIIB
	T2b	IIA	IIB	IIIA	IIIB
T3	T3	IIB	IIIA	IIIB	IIIC
T4	T4	IIIA	IIIA	IIIB	IIIC
M1	M1a	IVA	IVA	IVA	IVA
	M1b	IVA	IVA	IVA	IVA
	M1c	IVB	IVB	IVB	IVB







	Deaths/N	MST	5-year (percent)
IA	443/831	60	50
IB	750/1284	43	43
IIA	318/483	34	36
IIB	1652/2248	18	25
IIIA	2528/3175	14	19
IIIB	676/758	10	7
IV	2627/2757	6	2



	Deaths/N	MST	5-year (percent)
IA	1168/3666	119	73
IB	1450/3100	81	58
IIA	1485/2579	49	46
IIB	1502/2252	31	36
IIIA	2896/3792	22	24
IIIB	263/297	13	9
IV	224/266	17	13

Overall survival, expressed as median survival time (MST) and five-year survival, using the seventh edition of TNM staging system by (A) clinical stage and (B) pathologic stage.

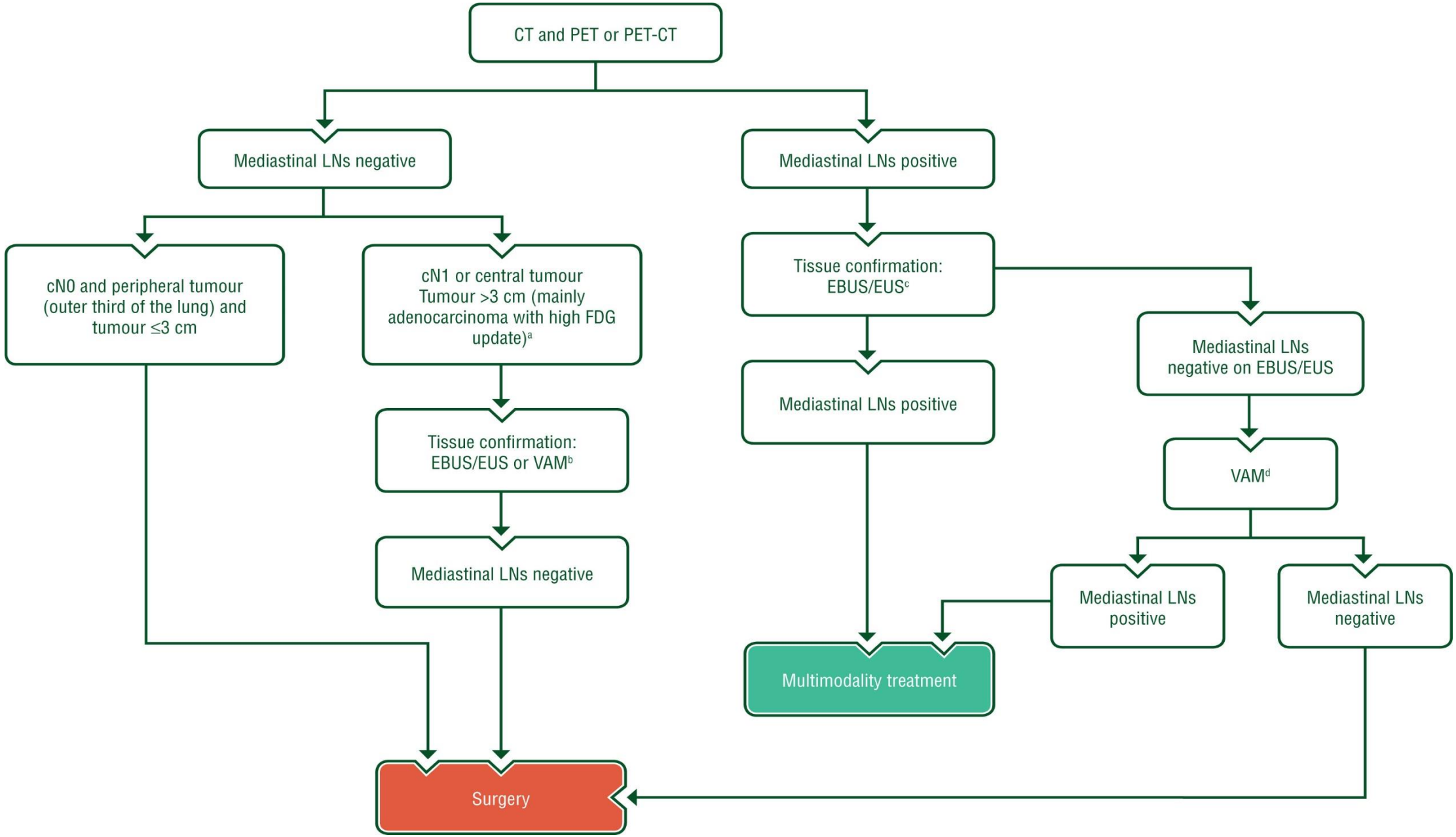
Recent trends you have observed?

- Lung cancer incidence?
- Smoking trends?
- Lung cancer in non-smokers?
- Stage of diagnosis – any change?
- Most common histology?
- Optimal staging investigations being done?

Management of NSCLC

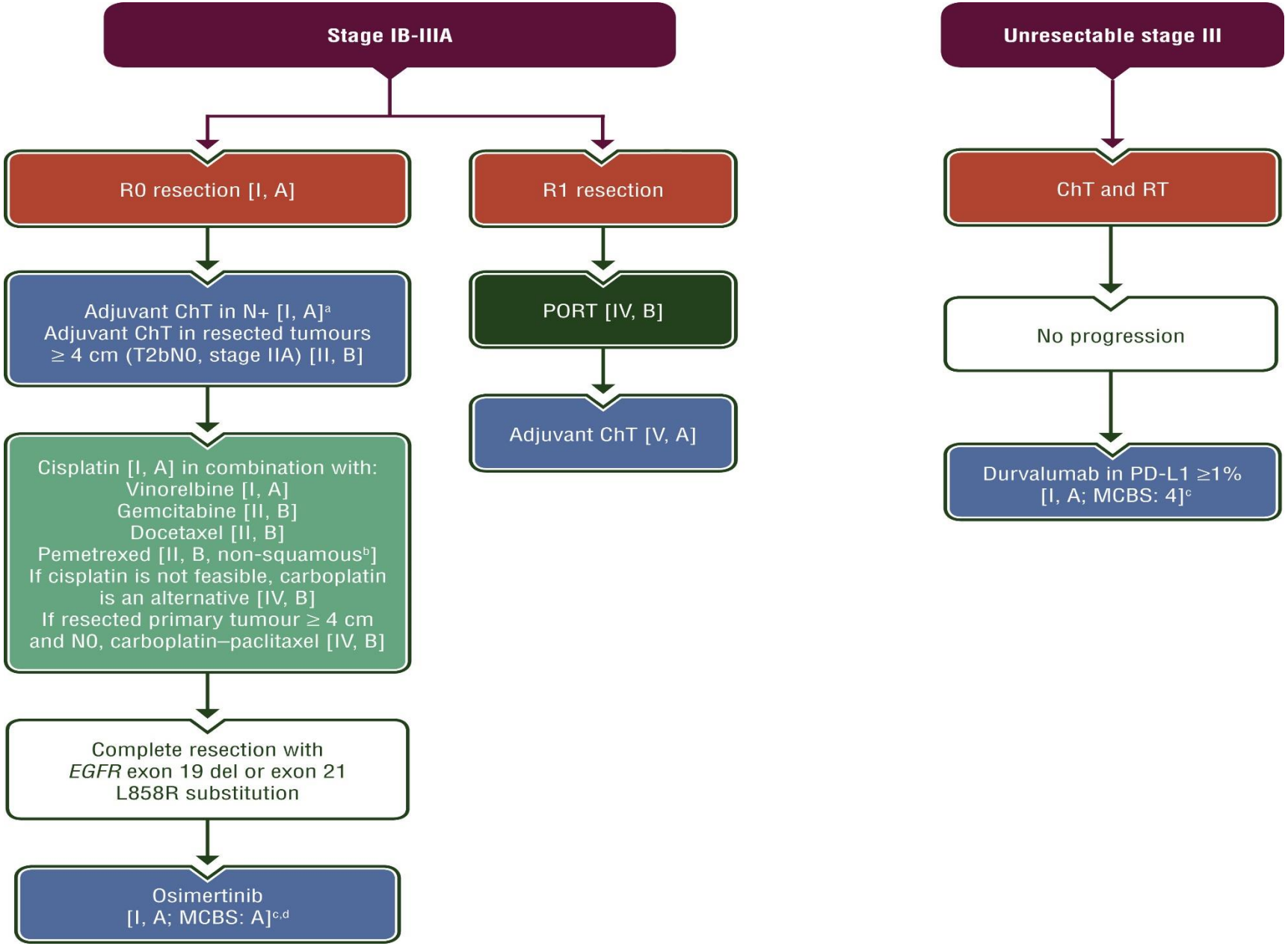
Work up

- Blood tests
- PFT
- Biopsy
- Molecular markers
- PET CT
- MRI Brain
- EBUS


CT and PET or PET-CT
Mediastinal LNs negative
Mediastinal LNs positive
cN0 and peripheral tumour (outer third of the lung) and tumour ≤3 cm
cN1 or central tumour Tumour >3 cm (mainly adenocarcinoma with high FDG update)[a]
Tissue confirmation: EBUS/EUS or VAM[b]
Mediastinal LNs negative
Tissue confirmation: EBUS/EUS[c]
Mediastinal LNs positive
Mediastinal LNs negative on EBUS/EUS
VAM[d]
Mediastinal LNs positive
Mediastinal LNs negative
Multimodality treatment
Surgery

Treatment Modalities

- **Surgery**
  - Open vs. VATS or Robotic-assisted Approaches
  - Lobectomy vs. Pneumonectomy vs. Sublobar Resection
- **Systemic Therapy**
  - Chemotherapy
  - Targeted Therapy
  - Immunotherapy
- **Radiation**
  - External Beam Radiation Therapy
    - 3-Dimensional Conformal Radiation Therapy (3-D CRT)
    - Intensity Modulated Radiation Therapy (IMRT)
  - Stereotactic Body Radiation Therapy (SBRT/SABR)
  - Proton Therapy (PT)


Stage IB-IIIA
R0 resection [I, A]
R1 resection
Adjuvant ChT in N+ [I, A][a]
Adjuvant ChT in resected tumours ≥ 4 cm (T2bN0, stage IIA) [II, B]
PORT [IV, B]
Adjuvant ChT [V, A]
Cisplatin [I, A] in combination with:
Vinorelbine [I, A]
Gemcitabine [II, B]
Docetaxel [II, B]
Pemetrexed [II, B, non-squamous[b]]
If cisplatin is not feasible, carboplatin is an alternative [IV, B]
If resected primary tumour ≥ 4 cm and N0, carboplatin–paclitaxel [IV, B]
Complete resection with *EGFR* exon 19 del or exon 21 L858R substitution
Osimertinib [I, A; MCBS: A][c,d]
Unresectable stage III
ChT and RT
No progression
Durvalumab in PD-L1 ≥1% [I, A; MCBS: 4][c]

Basic Principles of Surgical Selection

- **The definition of medically inoperable varies substantially between surgeons**
- PFTs that suggest a patient should tolerate surgery include:
  - Pre-op FEV_1 >1.8-2 L (or ≥80% predicted) if patient needs a pneumonectomy
  - Pre-op FEV_1 >1.2-1.5L if patient needs a lobectomy
  - Predicted post-op FEV_1 >800 mL (>40% predicted)
  - DLCO > 50-60%
  - Resection of tumor in a dominant area of emphysema may have less impact on post-op lung function
- Patients with cardiac risk factors should have a preoperative cardiologic evaluation
- Contemporary 30-day mortality rates are 1-3% for lobectomy or sublobar resection and 2-11% for pneumonectomy

Management of Stage I + II NSCLC

-*Surgery alone is the standard treatment choice !*

-Lobectomy: optimal procedure

-Wedge resection: 3x LR/ 30% more mortality (Ginsberg 1995) but newer series show no worse outcome with limited surgery (Lee 2003, El Sherif 2006)

-Wedge resection for small tumors (<3cm) and elderly patients

-No randomized trials, but excellent results (randomized trial 'Surgery- Radiotherapy' underway)

-Adjuvant Cisplatin-based ChT for stage II for stage IB data is conflicting

-No adjuvant radiotherapy after radical surgery (i.e. RO)

Definitive Radiotherapy for Stage I + II NSCLC

-Alternative for comorbid patients who are not fit for surgery
-For patients who refuse surgery

-60 - 66Gy to primary(+/- 50Gy to part of mediastinum, if feasible)

Review of 26 nonrandomized trials (Powell 2001)

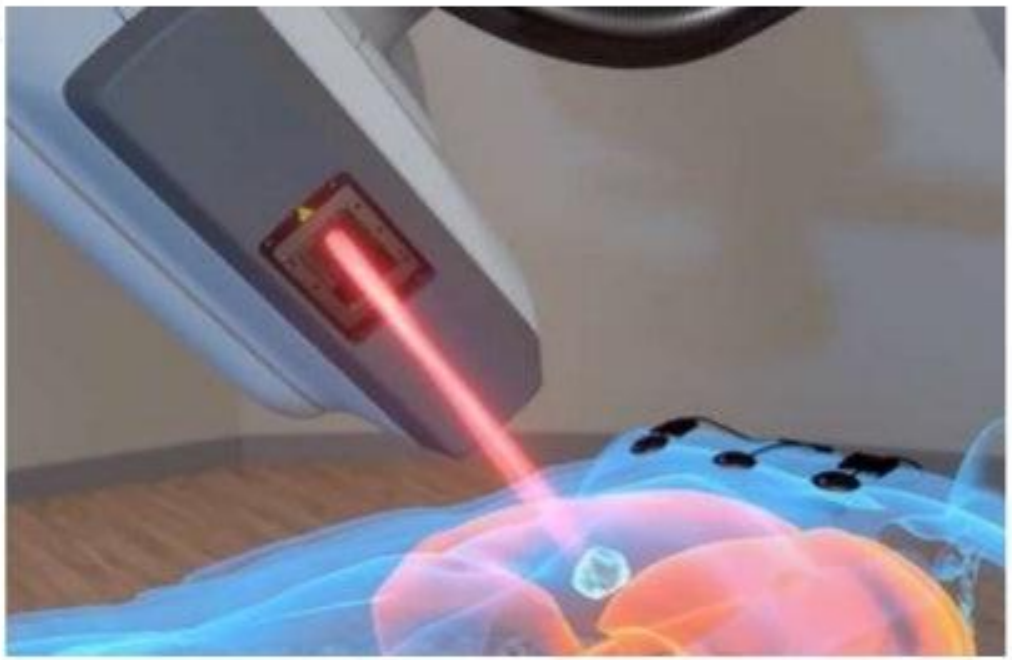
	Cancer-specific Survival	OS (RT)	OS (surgery)
2y	54-93%	22-72%	67%
3y	22-56%	17- 55%	
5y	13-39%	0-42%	47%

Non-cancer deaths following RT: 11 - 43%
(reflecting the poor health status of pts. treated in these studies)

-Clinical stage I only in 57% pathologic stage I (Lopez 2005)

Introduction

- SBRT (also known as SABR) uses short courses of very high (ablative), highly conformal, and dose-intensive RT precisely delivered to limited-size targets.
- Current standard-of-care for early-stage, nonoperative NSCLC is stereotactic body radiation therapy (SBRT)
- SBRT is a **noninvasive treatment** involving the **precise delivery** of ablative dose radiation
- Compared with fractionated radiation, SBRT achieves superior local control and survival

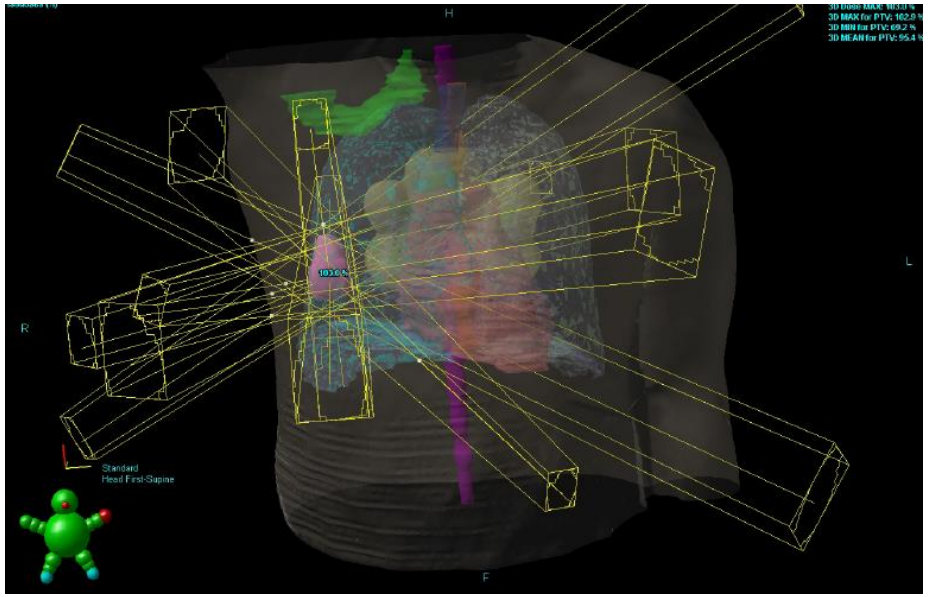


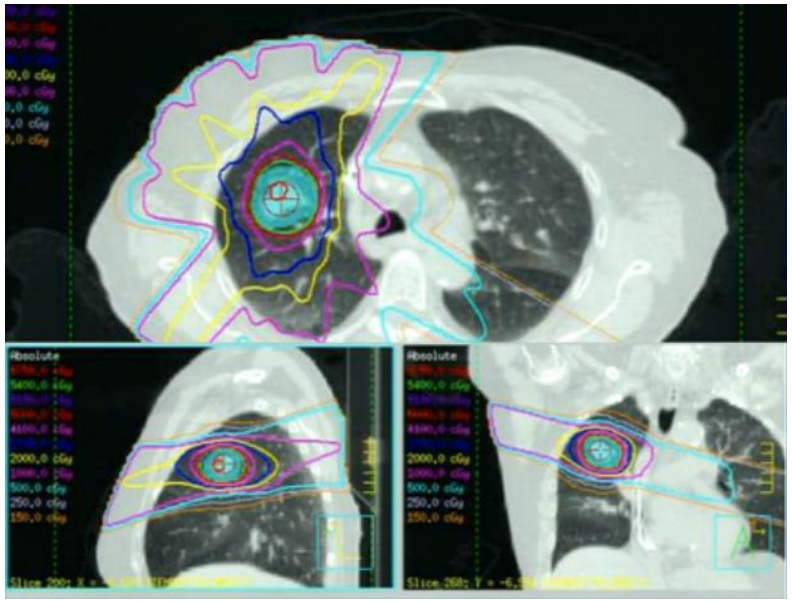
Definition of SBRT

- Method of Ext beam radiotherapy
- Accurately deliver
- High dose of irradiation
- One or few treatment fractions
- Extracranial target

Hypofractionation Using SBRT/SABR

- For early-stage NSCLC
  - Smaller target volume treated with highly conformal SBRT/SABR plan
- Risk-adapted dosing based on tumor location
  - Typically 10-18Gy/fraction in 3-5 fractions (total dose 48-54 Gy)
  - Ideally achieve Biologically Effective Dose (BED) > 100 Gy





Comparing 3-D CRT/IMRT to SBRT/SABR

	3DCRT/IMRT	SBRT/SABR
Target Type	≥1 target (e.g., primary + nodes) Any size Close proximity to (or overlapping) critical organs	Single well-defined target Small-medium size Sufficient distance from critical organs
Dose/Fraction	Low	High
# Fractions	30-35	1-5
Biologically Effective Dose	70-90 Gy	≥ 100 Gy
Dose Conformity	Moderate - High	Very High
Immobolization	Secure	Very Secure
Image-Guidance	Should be performed daily, especially IMRT/PT	Required Daily
5 Year Local/Lobar Control	50-75%	85-95%

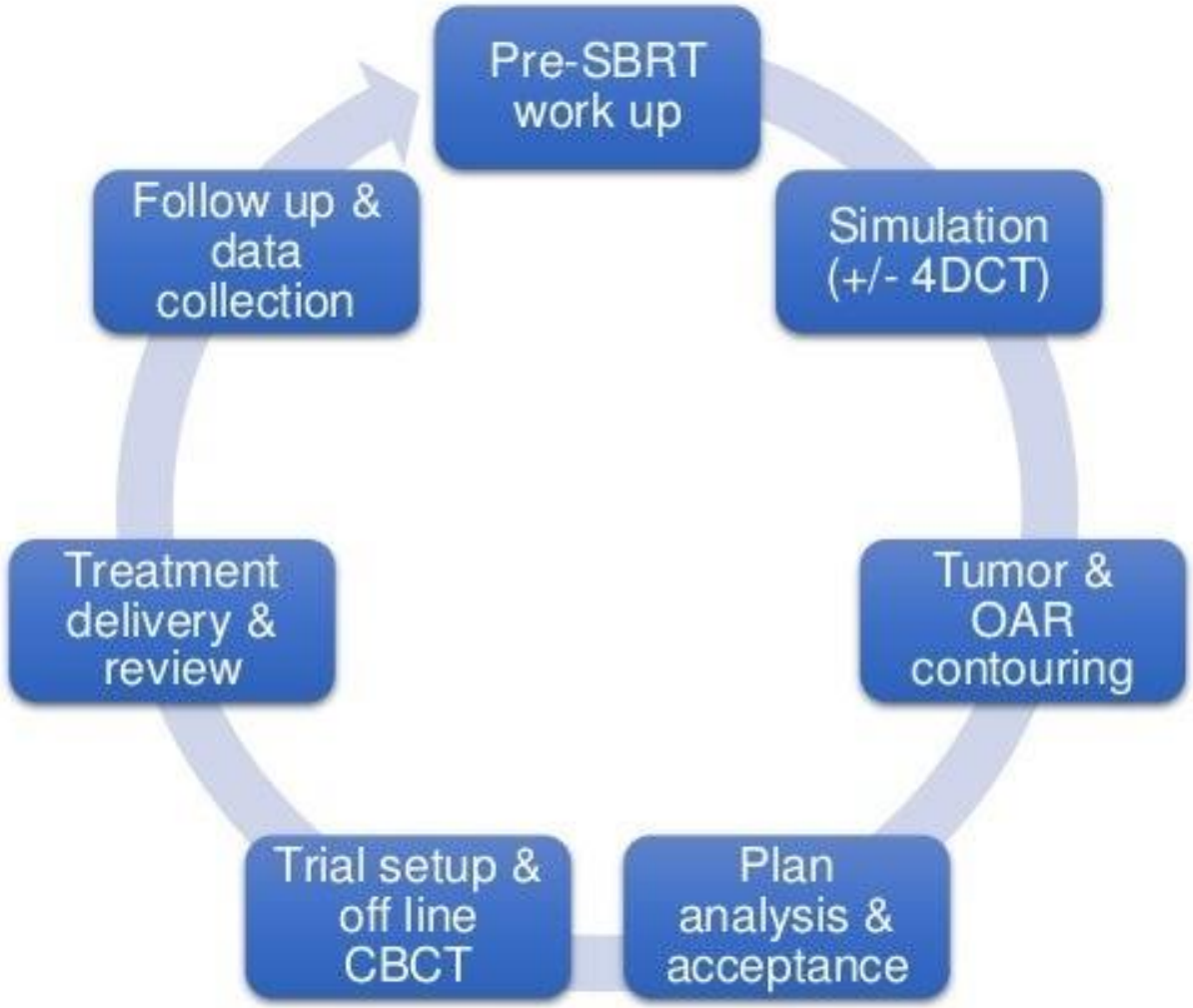
Stereotactic Body Radiation Therapy (SBRT)

-Ultra precise treatment planning (fixation, IGRT)
-High doses (e.g. 4x12Gy), but optimal dose /fx not known
-Dose response relationship: BED> lOOGy vs. <lOOGy

Results (Lagerwaard 2008):

ly-/ 2y-	OS:	81 / 64%	
ly-/ 2y-	DFS:	83 / 68%	(88 / 81% for stage IA)
Median OS:		34 months	
Local failure rate:		7%	
Regional failure:		9%	
Distant failure:		11%	
Severe late toxicities:		<3%	

The work flow



Pre requisites for SBRT

- Equipment
- Staff teaching and training
- Patient selection for SBRT
- Patient counselling
- Treatment planning
- Dose and fractionation
- Radiotherapy planning steps
- Inter- and intra-fraction image guidance
- Quality assurance
- Follow-up

TEAM

Equipment

Mandatory

- C-arm linear accelerator with volumetric in-room image guidance
- Respiration correlated 4D-CT

Recommended

- Dedicated C-arm stereotactic linear accelerator (more advanced IGRT, more precise accuracy)
- High-resolution MLC <10 mm

Patient selection for SBRT

SBRT is recommended in the NSCLC for patients with

- ✓ **Stage I and II (T1–3,N0,M0)**
- ✓ NSCLC who are **medically inoperable**
- ✓ **High risk- elderly**
- ✓ **Refuse surgery** after appropriate consultation

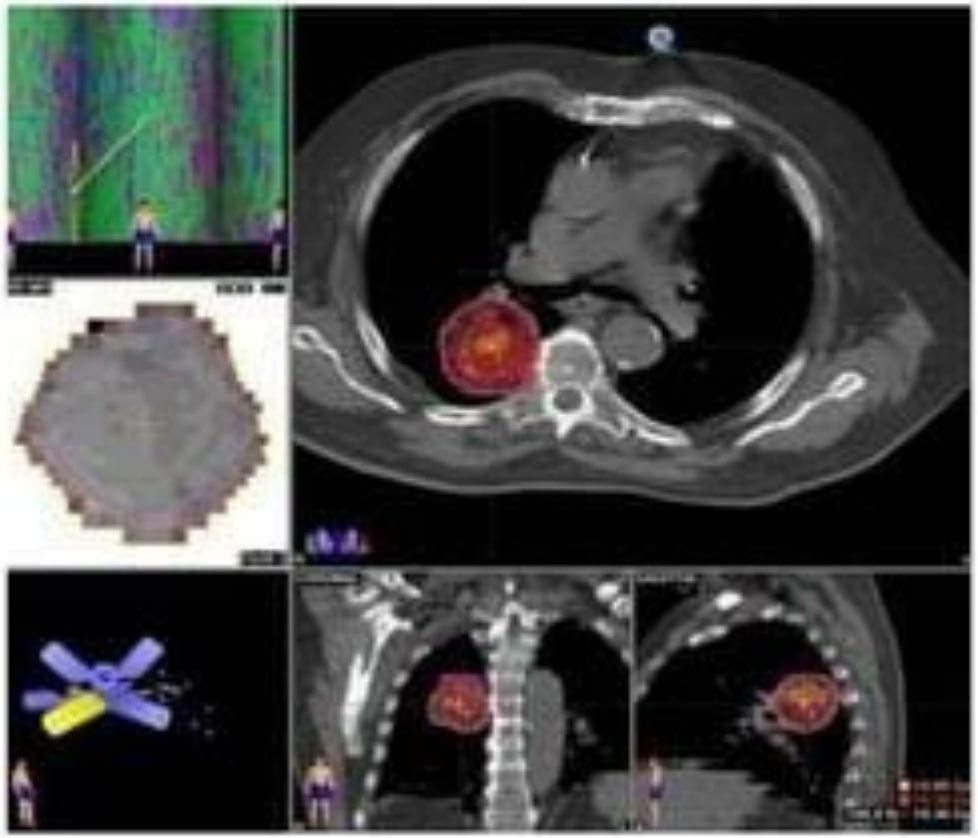
SBRT has **no established role in small cell lung cancer**

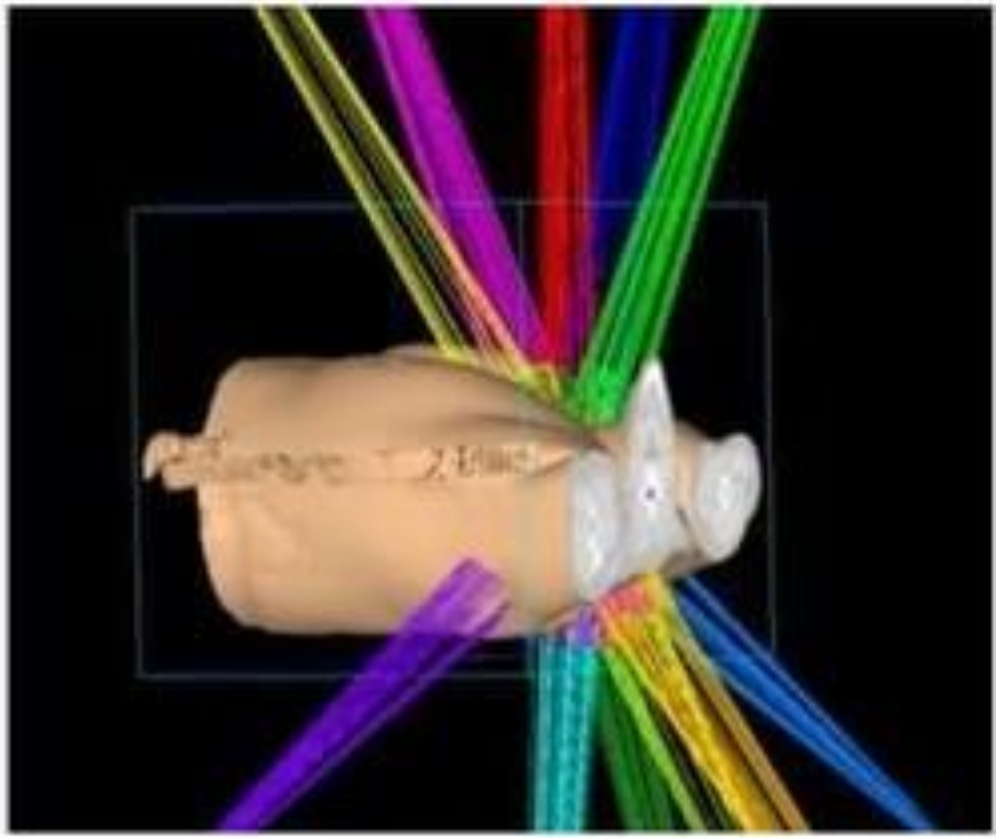
- ✓ PFT (FEV1 or DLCO < 40%)
- ✓ DM/CAD
- ✓ Cerebral disease
- ✓ Pul. HTN
- ✓ PS 0-2
- ✓ Able to lie flat for at least one hour

Patient Positioning and Immobilization

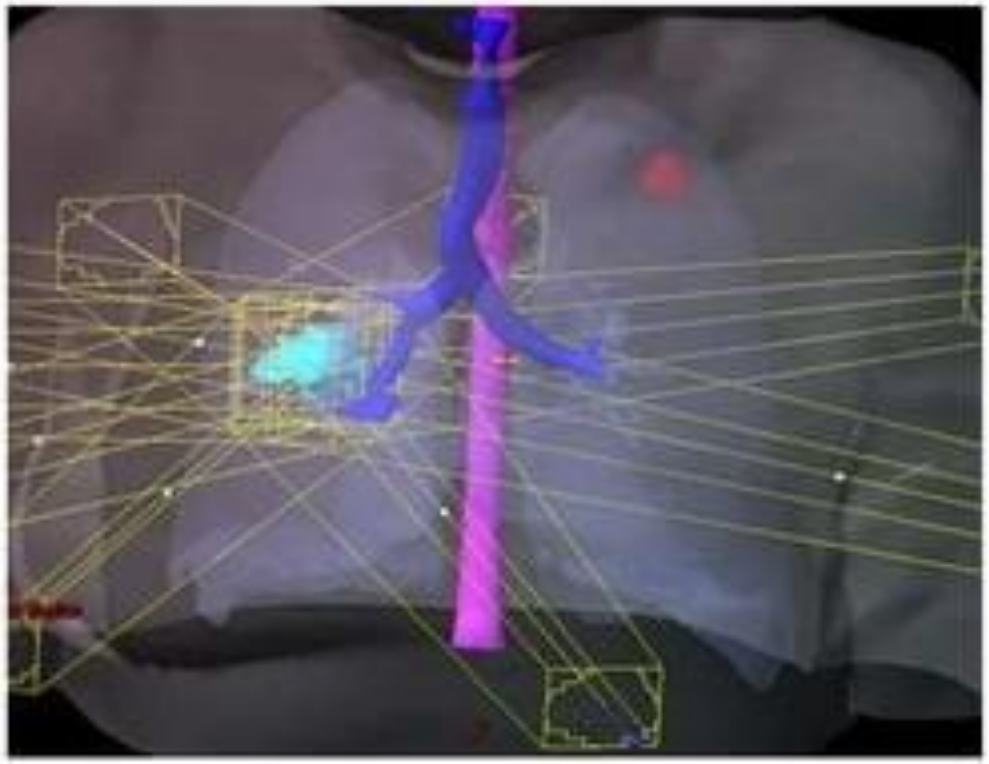
- Stable and reproducible patient positioning is essential. If possible, patients should be positioned with both arms above the head as this position permits a greater choice of beam positions.
- Reproducible setup can be achieved using a stable arm support, in combination with knee support to improve patient comfort.

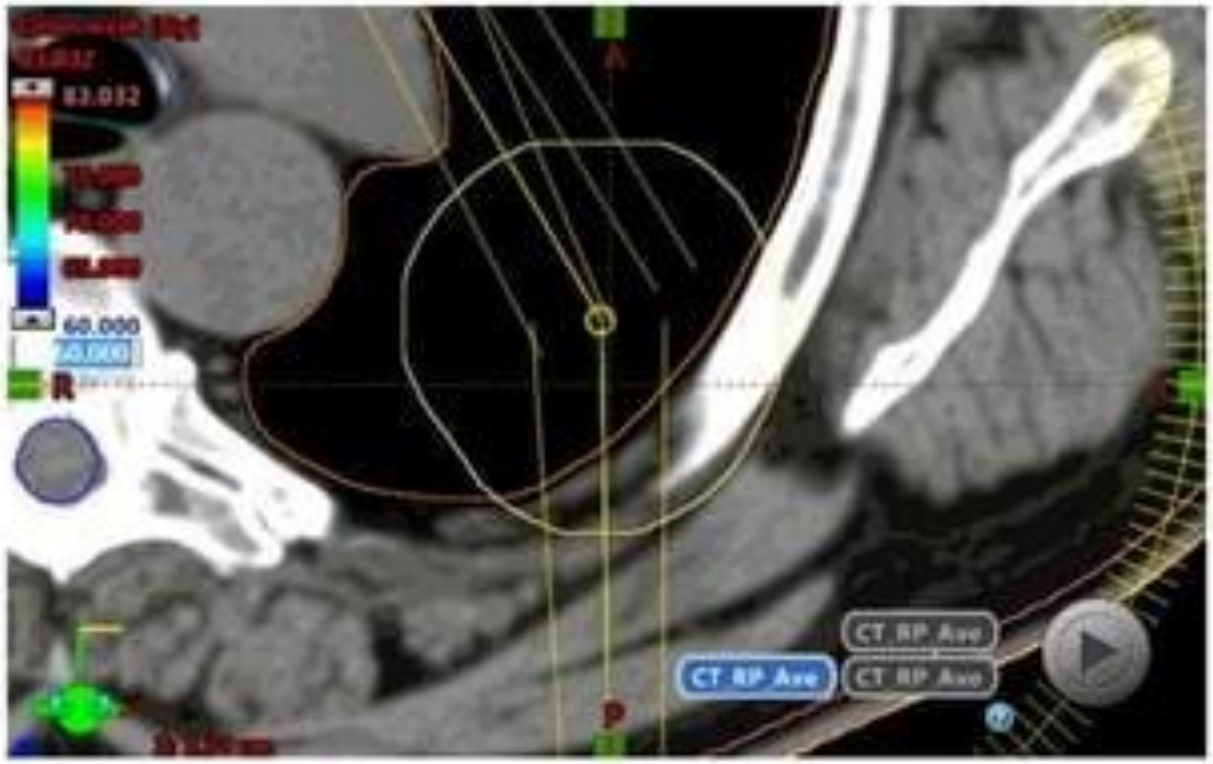
Beam Placement

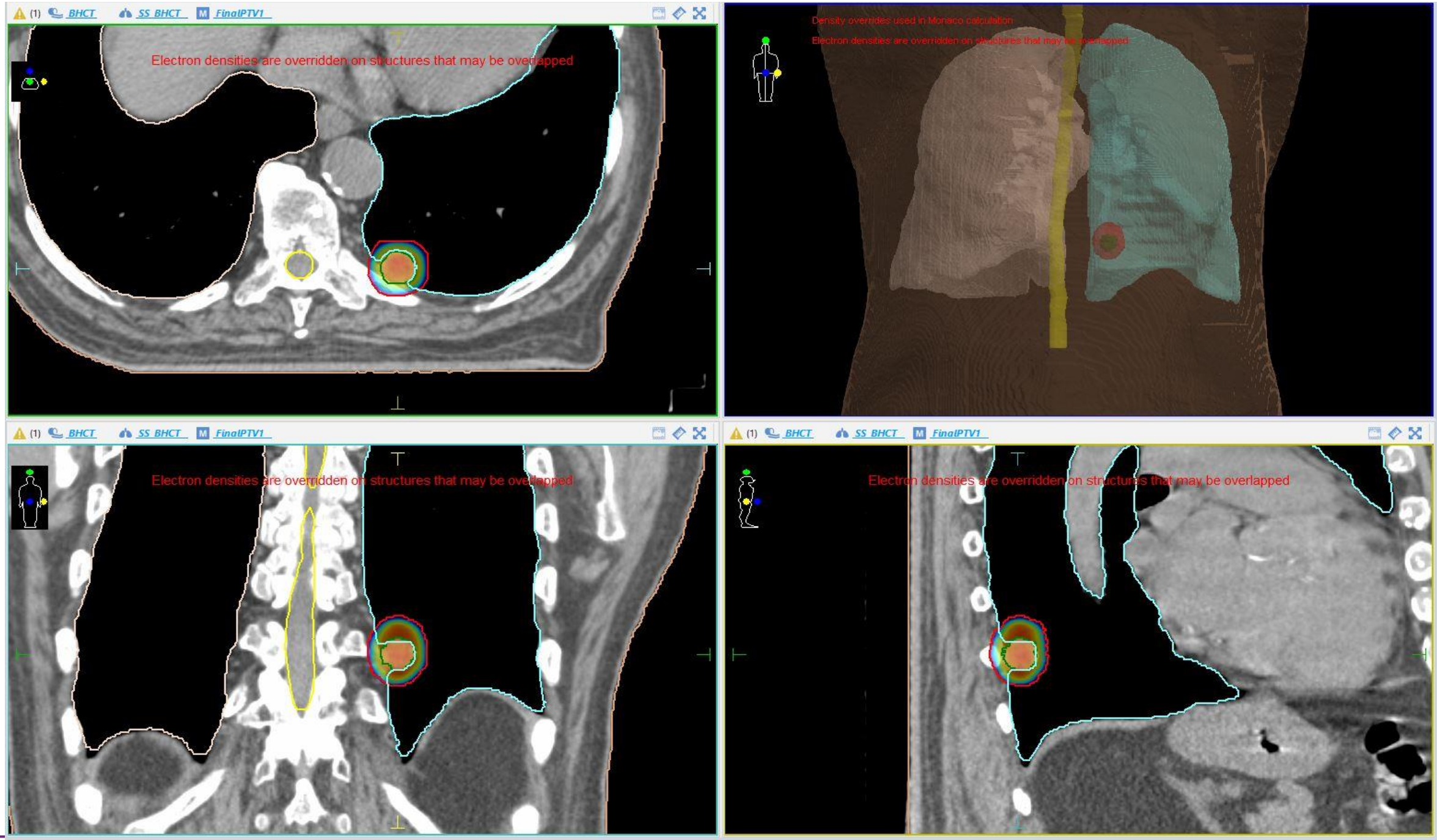




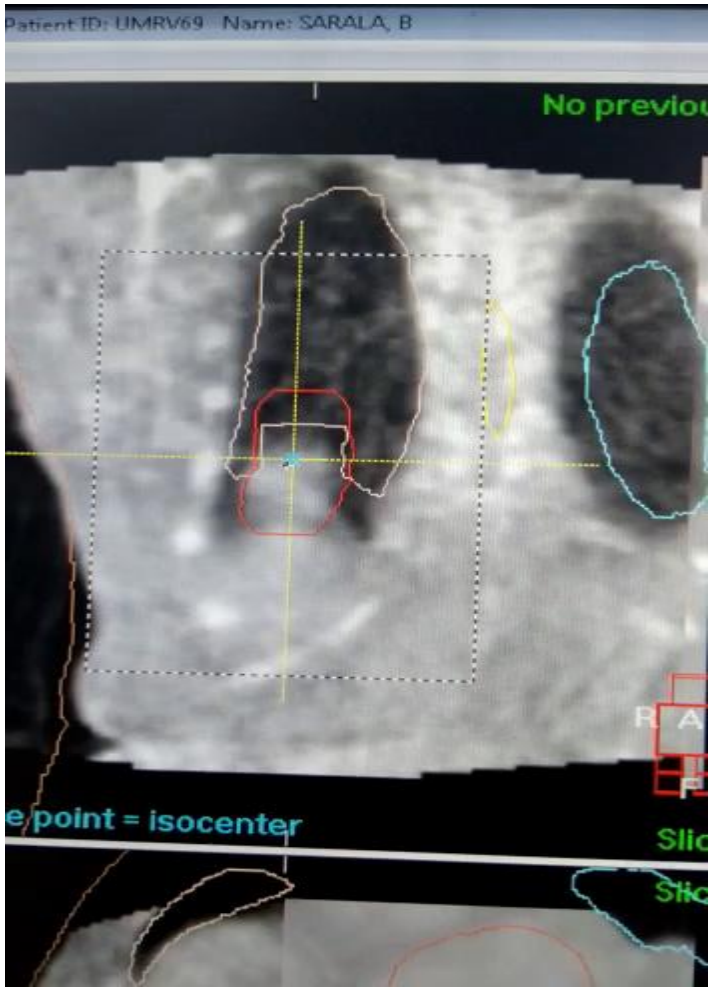
Beam Placement

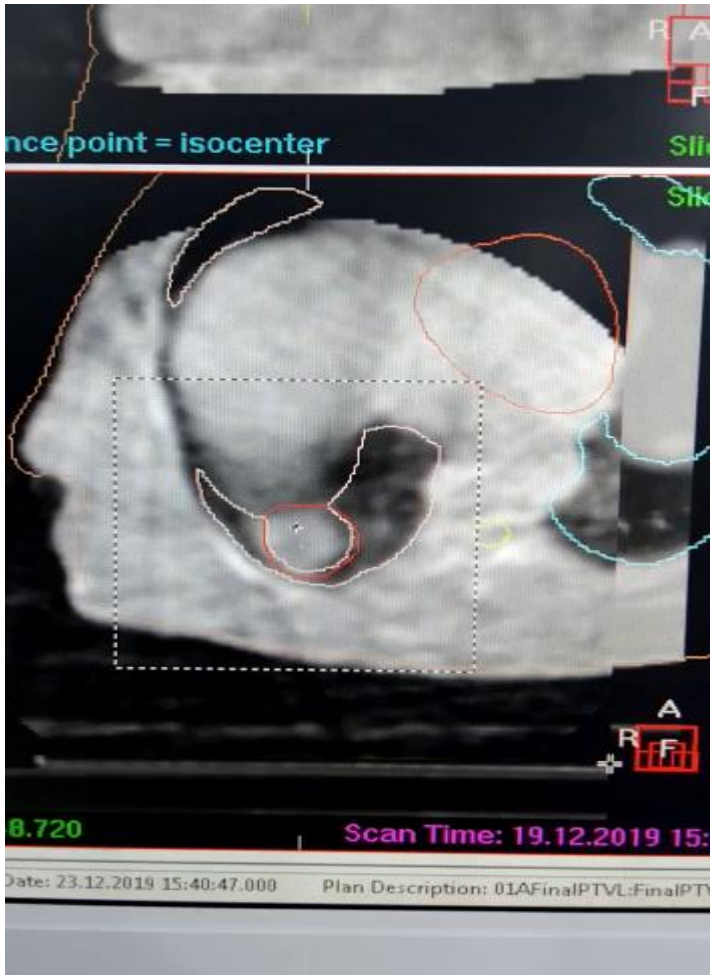





(1) BHCT SS BHCT FinalPTV1
Electron densities are overridden on structures that may be overlapped
Density overrides used in Monaco calculation
Electron densities are overridden on structures that may be overlapped
(1) BHCT SS BHCT FinalPTV1
Electron densities are overridden on structures that may be overlapped
(1) BHCT SS BHCT FinalPTV1
Electron densities are overridden on structures that may be overlapped

TECHNIQUES OF MOTION MANAGEMENT IN LUNG CANCER


Patient ID: UMRV69 Name: SARALA, B
No previou
e point = isocenter
Slic
Slic


nce point = isocenter
Slic
Slic
A
R
F
8.720
Scan Time: 19.12.2019 15:
Date: 23.12.2019 15:40:47.000
Plan Description: 01AFinalPTVL:FinalPTV

Respiratory Motion Management

Conventional (ITV-based)

- Contour and treat full tumor ROM

Accelerator beam gating

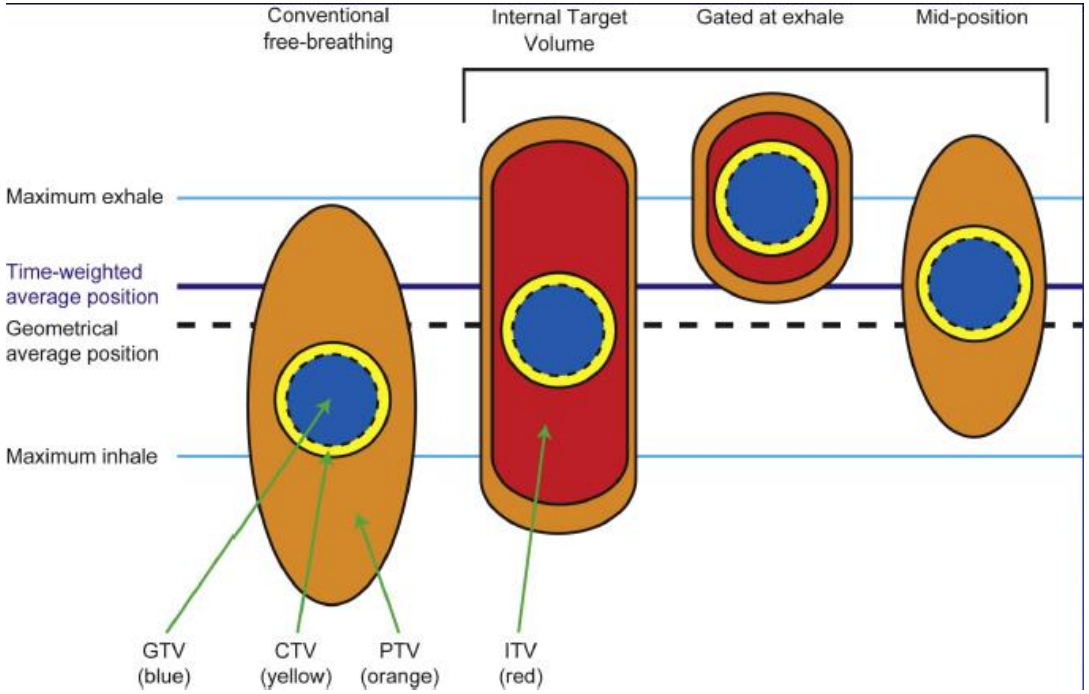
- Patient breathes normally; beam only on while patient is in a certain phase of the respiratory cycle

Active breathing control

- Patient holds breath in a certain position; beam only on in that phase of the respiratory cycle

Dynamic tumor tracking

- Patient breathes normally; tumor is tracked; beam always on and moves with tumor



Regardless of the motion management used, an additional “CTV/PTV” margin around our target is needed to ensure that we hit it.

METHODS OF ASSESSING LUNG TUMOR MOTION DURING RESPIRATION

- Four dimensional computerised tomography (4DCT) / respiratory gated CT scans

- Slow CT scans

METHODS TO CONTROL / COMPENSATE FOR LUNG MOTION DURING RESPIRATION

Free breathing methods:

- Internal Target Volume (ITV)-based treatment
- Gating
- Tracking

Breath-hold methods:

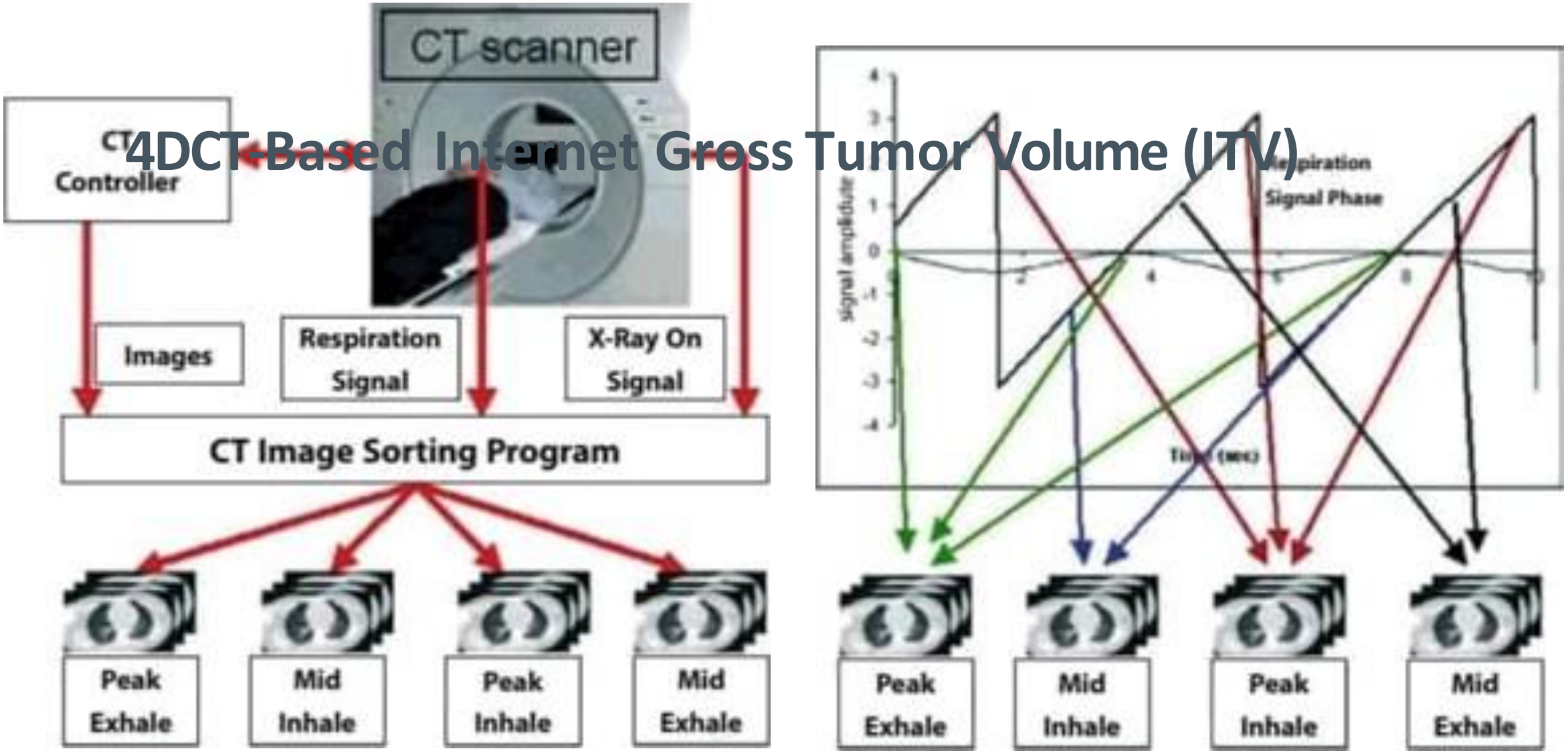
- Active Breathing Coordinator (ABC)

ITV-based treatment

Generates a **composite target volume** for lung tumors, taking into account the different shape, size and position of the tumor in each phase of respiration

Can be done on any LA with MLCs or on Tomotherapy , where there is no specialised motion management technology available for treatment delivery.

4DCT-Based Internet Gross Tumor Volume (ITV)



The breathing cycle is divided in to distinct bins eg (Peak exhale, mid inhale, peak inhale, mid exhale) images are sorted into these image bins depending on the phase of the breathing cycle in which they were aquired yielding a 4D data set

Gating

Treatment delivery is done in the phase of respiration where the tumor motion & resulting treatment volume is minimum, by **coupling the beam delivery with the phase of respiration**

Usually requires an internal fiducial, implanted within the tumor.

Tumor Tracking

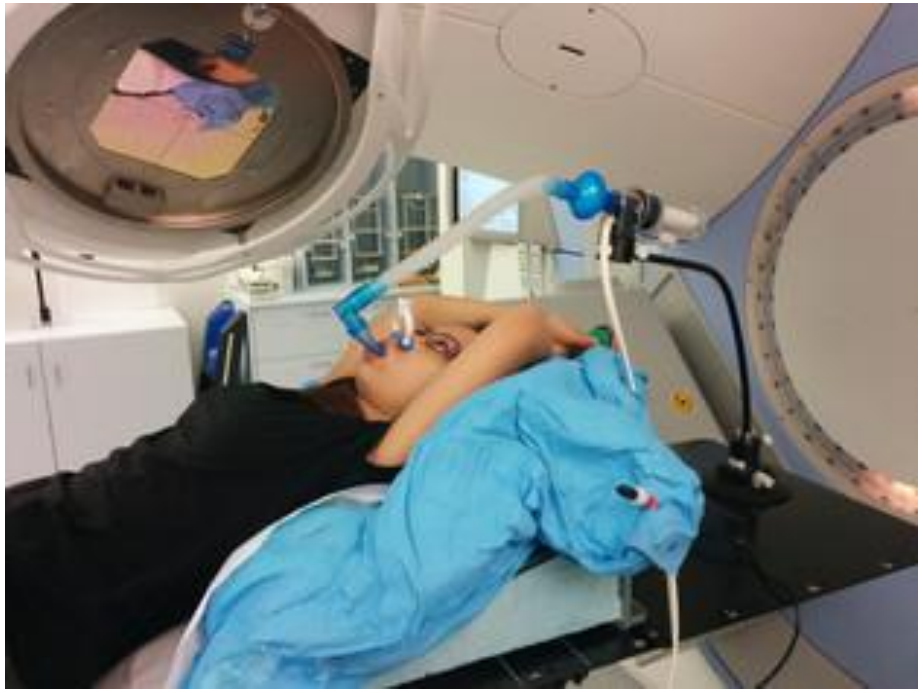
Imaging is used to **track the actual tumor motion** during treatment delivery and to **move the treatment beam** accordingly based on the varying position of the tumor.

Usually requires an internal fiducial, implanted within the tumor.

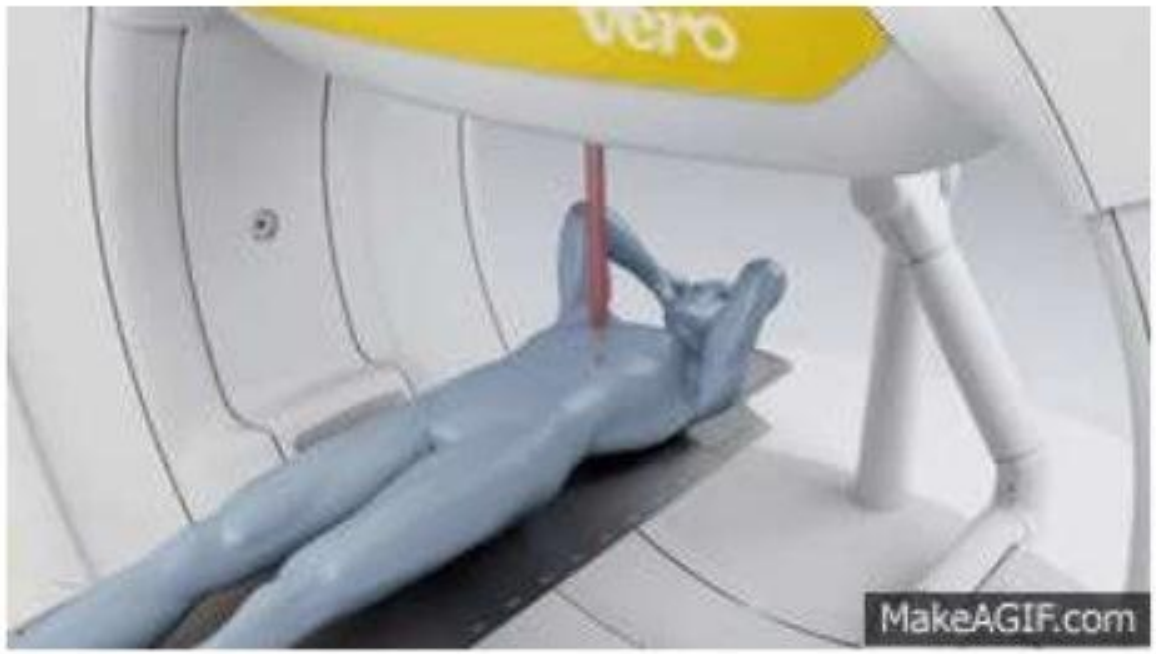
Can also be done non-invasively in some cases.

Active Breathing Coordinator

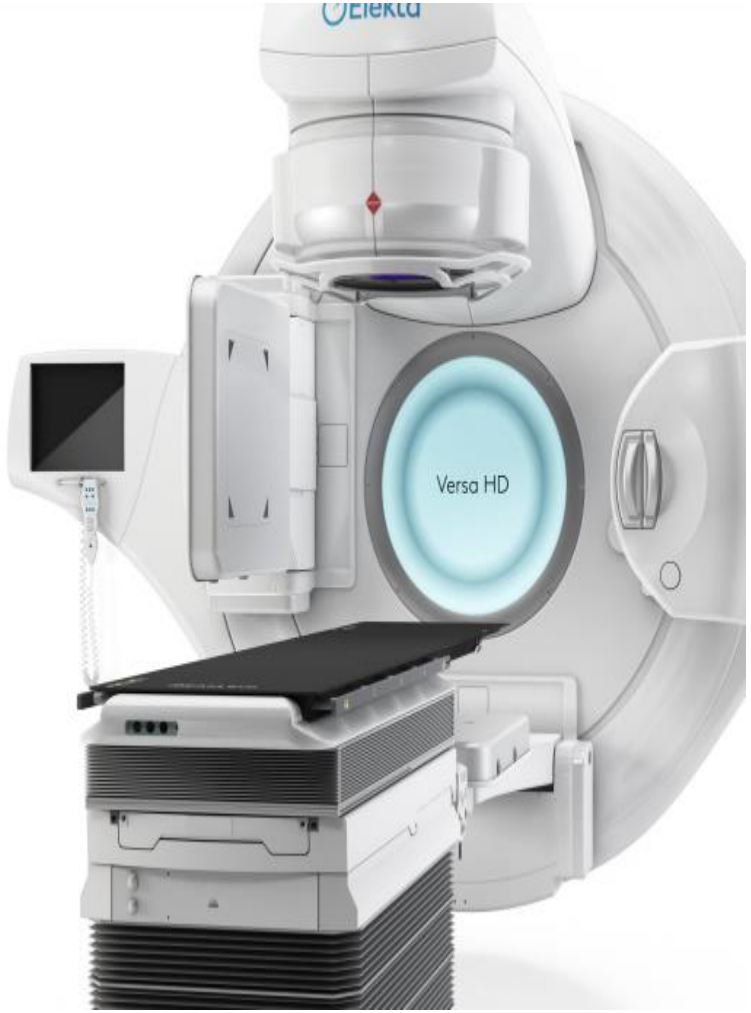
The patient is coached to **breath-hold** in inspiration, to **eliminate lung motion** & treatment is delivered only in this state.

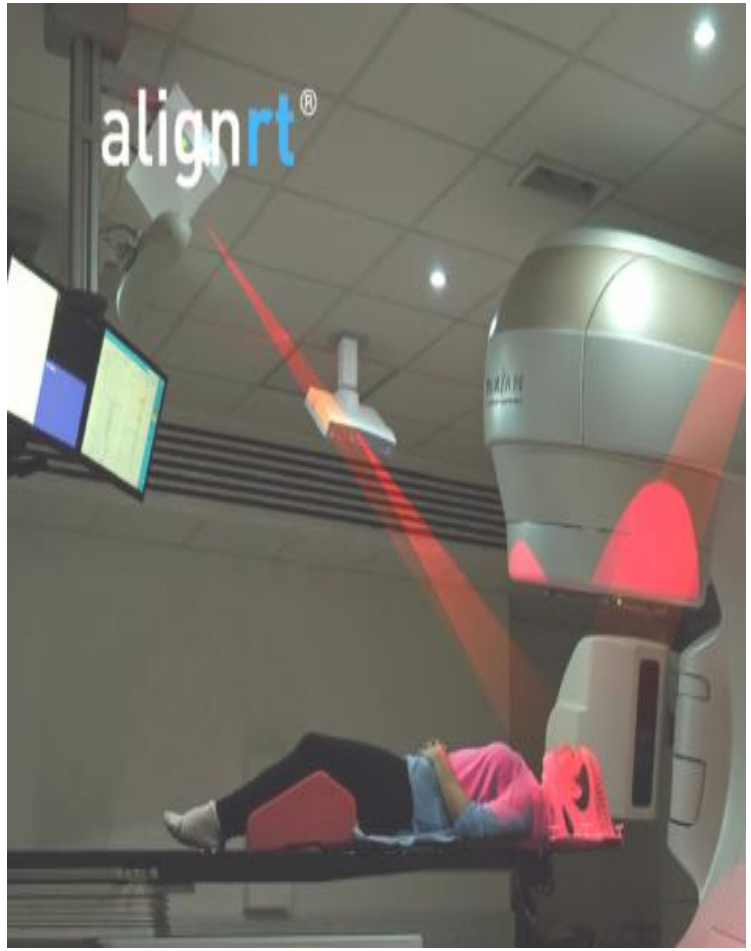


- Deep inspiration breath hold (DIBH) reduces tumour motion while increasing the lung volume, resulting in decreased doses to lung, and often also to the heart



Our Machine





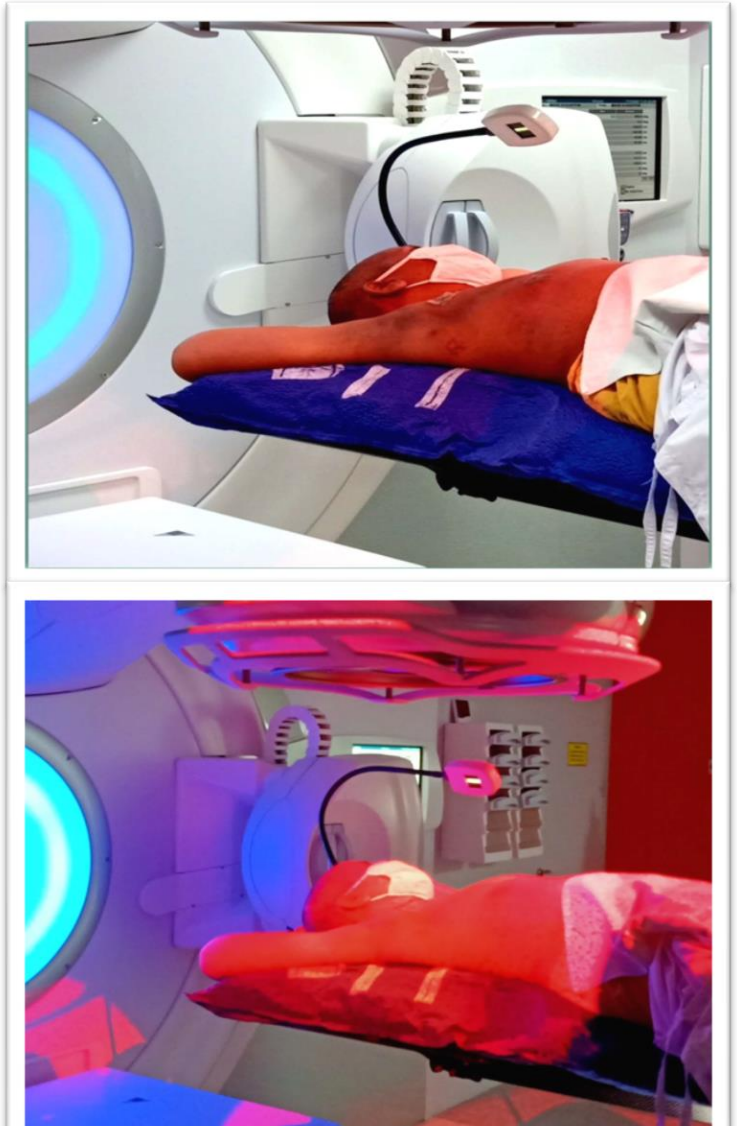
SGRT

DIBH for Lung Patients

For DIBH planning patient need to undergo both Free Breathing(FB) and Breath Hold(BH) CT.

FB CT's body structure will be used for patient positioning purpose

BH CT's body structure will be used for treatment purpose with proper well defined ROI and threshold



Outcomes of SBRT for Early Stage NSCLC

	RTOG 0236	RTOG 0915	RTOG 0813
Prospective Study Type	Single Arm Phase II	Randomized Phase II	Single Arm Phase I/II
# of patients	55	94	120
Medically Operable?	No	No	No
TNM Stage	cT1-2N0M0	cT1-2N0M0	cT1-2N0M0
Tumor Location	Peripheral	Peripheral	Central
RT Dose/Fx	54Gy/3fx	34Gy/1fx vs. 48Gy/4fx	50-60Gy/5fx
Local Control	93% @ 5 years	89-93% @ 5 years	88% @ 2 years
Overall Survival	40% @ 5 years	30-41%@ 5 years	70% @ 2 years

- **Most recurrences are distant** (~30%); **most deaths are not cancer related**
- Toxicity using risk-adapted dosing:
  - Grade 3 in 10-15%, grade 4 in 3-5%, and grade 5 in < 1%

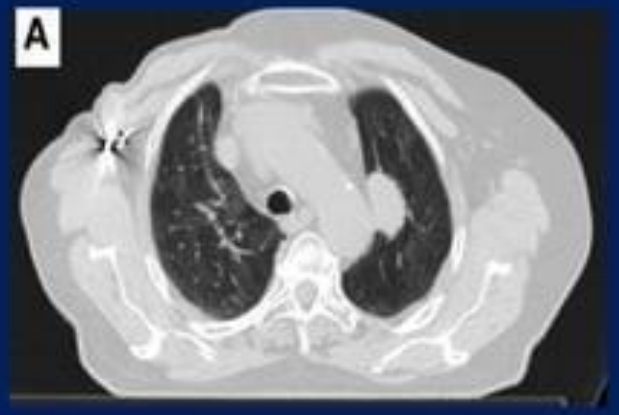
How Does SBRT Compare to Surgery?

- **No fully enrolled randomized trials**
- **Selection bias** when comparing survival numbers from non-randomized cohorts of patients are difficult to compare with surgery
  - Radiation patients are generally medically inoperable, or older with worse PS and often don't undergo full mediastinal staging

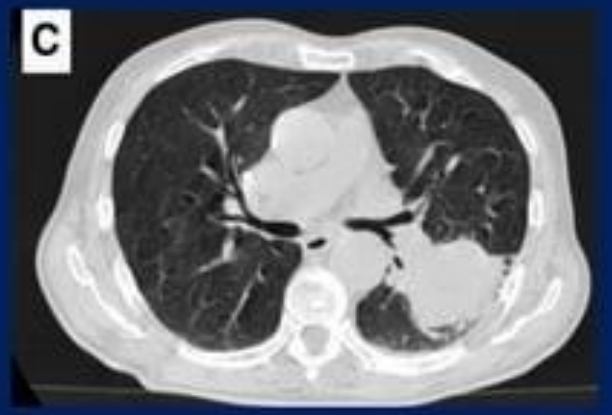
- **Pooled Analysis of STARS and ROSEL Randomized Trials (Chang, Lancet Oncol 2015)**
  - 58 pts, operable T1-2a (<4 cm) N0 M0 NSCLC randomized to lobectomy vs. SBRT
  - Results: SBRT → ↑ **3Y-OS** (79→95%) with no difference in RFS (~83%)
  - Why the difference?
    - Surgery has higher M&M (G3-5 toxicity (48% vs. 10%).
      - Grade 3+ toxicities SBRT were all Grade 3, i.e., no Grade 4 or 5
      - Surgery had 4% Grade 5 toxicity
    - Abscopal effect from RT?


CAUTION

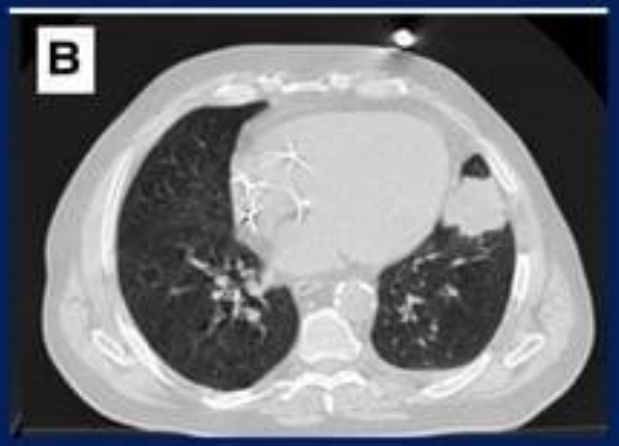
Central lung tumour



Tumour close to arch of aorta



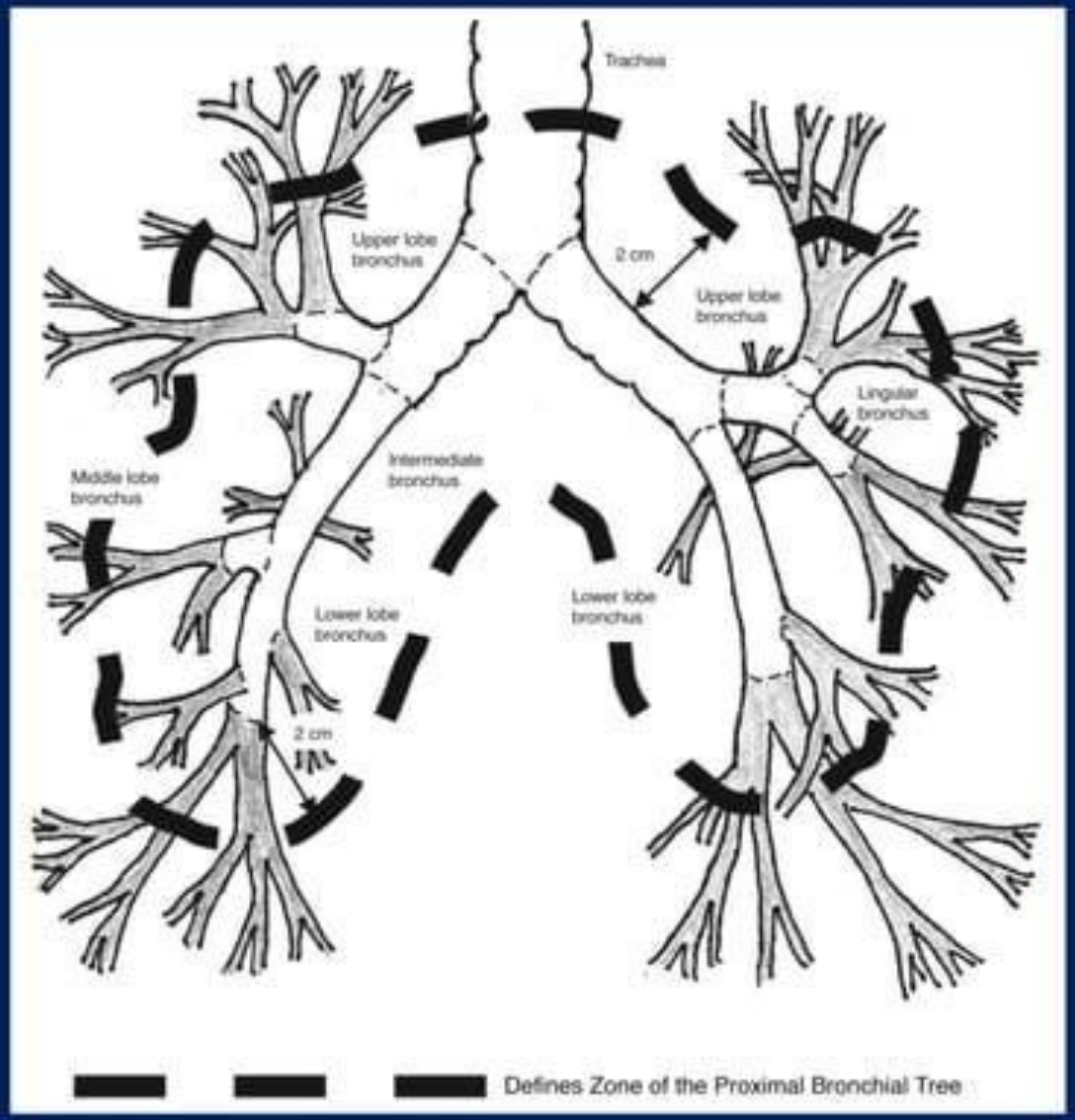
Tumour close hilar region



Tumour close to ventricle

Close to critical structures:
'Difficult to treat' tumours

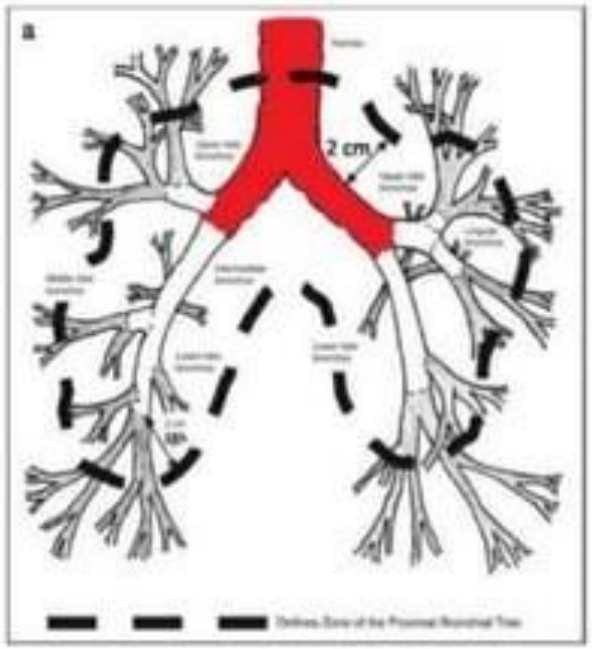
Central lung tumours as per RTOG0813



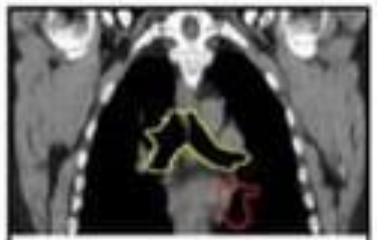
Tumour within 2 cm of trachea, principle bronchus & vascular structures

NO FLY ZONE

TYPE OF LESIONS



b Ultracentral tumor



c Central tumor

The black dashed line defines the location of tumors that are central relative to the proximal bronchial tree. The term central has been widened to include the region within 2 cm in all directions of any mediastinal critical structure, including the bronchial tree/trachea, esophagus, heart, brachial plexus, major vessels, spinal cord, phrenic nerve, and recurrent laryngeal nerve. The region shaded red shows the trachea and main bronchi, and lesions with a PTV which overlaps \this region are considered as ultracentral.

b Example of an ultracentral tumor (planning target volume in red, and main bronchi/trachea in yellow).

c Example of a central tumor

PRINCIPLES OF RADIATION THERAPY

Please note: Tables 2–5 provide doses and constraints used commonly or in past clinical trials as useful references rather than specific recommendations.

Table 2. Commonly Used Doses for SABR

Total Dose	# Fractions	Example Indications
25–34 Gy	1	Peripheral, small
45–60 Gy	3	Peripheral tumors
48–50 Gy	4	Central or peripheral tumors <4–5 cm
50–55 Gy	5	Central or peripheral tumors
60–70 Gy	8–10	Central tumors

Table 3. Maximum Dose Constraints for SABR*

OAR/Regimen	1 Fraction	3 Fractions	4 Fractions	5 Fractions
Spinal cord	14 Gy	18 Gy (6 Gy/fx)	26 Gy (6.5 Gy/fx)	30 Gy (6 Gy/fx)
Esophagus	15.4 Gy	27 Gy (9 Gy/fx)	30 Gy (7.5 Gy/fx)	105% of PTV prescription^
Brachial plexus	17.5 Gy	24 Gy (8 Gy/fx)	27.2 Gy (6.8 Gy/fx)	32 Gy (6.4 Gy/fx)
Heart/ pericardium	22 Gy	30 Gy (10 Gy/fx)	34 Gy (8.5 Gy/fx)	105% of PTV prescription^
Great vessels	37 Gy	NS	49 Gy (12.25 Gy/fx)	105% of PTV prescription^
Trachea & proximal bronchi	20.2 Gy	30 Gy (10 Gy/fx)	34.8 Gy (8.7 Gy/fx)	105% of PTV prescription^
Rib	30 Gy	30 Gy (10 Gy/fx)	40 Gy (10 Gy/fx)	NS
Skin	26 Gy	24 Gy (8 Gy/fx)	36 Gy (9 Gy/fx)	32 Gy (6.4 Gy/fx)
Stomach	12.4 Gy	NS	27.2 Gy (6.8 Gy/fx)	NS

Toxicities

- Chest wall pain
- Rib fracture
- Pneumonitis

Severe Toxicities

Bronchial / Tracheal stenosis

Bronchial / Tracheal necrosis

Esophageal perforation

Massive hemoptysis

Pulmonary necrosis

Management of Stage Ill NSCLC

-Locoregionally advanced stages

IIIA surgery feasible
IIIB surgery not feasible

-Usually combined therapy approach
-Optimal regime uncertain
-Trend toward trimodality therapy
-Initial nonoperative treatment generally recommended
-No single regime for all patients (clinical heterogeneity)
-Management individually to be discussed (tumor board)

Factors Favoring Use of Surgery in N2 Patients

- Single involved LN station > multiple involved stations
- Microscopic N2 > clinical N2 (especially if bulky LN >3cm)
- Successful downstaging of the mediastinum s/p neoadjuvant therapy
- Avoiding pneumonectomy (especially right pneumonectomy)
- T3/4 due to size alone > invasion/extension
- Good PS, younger age, no weight loss, female gender
- Surgery should **NOT** be pursued for **cN3** Patients

Randomized Data Evaluating Surgery for IIIA NSCLC

- **Intergroup 0139/RTOG 0939/SWOG 93-36 (Albain 2009)**
  - 396 pts, stage IIIA (cT1-3pN2)
  - Randomized to NeoAdj Chemo-RT → Surgery vs. Definitive Chemo-RT

	MS	5Y-OS	M-PFS	5Y-DFS	Tx-related death	G3-4 esophagitis
NeoAdj→Surgery	23.6mo	27%	12.8mo	22%	8%	10%
Definitive chemo-RT	22.2mo	20%	10.5mo	11%	2%	23%
Significance	NS	NS	SS	SS		

  - Subset analysis:
    - **Lobectomy** vs. matched chemo-RT (MS 2.8 years vs. 1.8 years, **SS**)
    - **Pneumonectomy** vs. matched chemo-RT (MS 1.6 years vs. 2.4 years, NS)
      - 26% mortality rate in pneumonectomy group
  - Conclusion: Both approaches remain valid options

Randomized Data Evaluating Surgery for IIIA NSCLC

- **EORTC 08941 (van Meerbeeck, 2007)**
  - 579 pts, "unresectable" N2 NSCLC received 3c induction Pt-based chemo
  - Nonprogressors after chemotherapy randomized to surgery vs. RT
    - RT arm used older techniques of 3DCRT and included elective nodes
    - Surgery arm included 47% pneumonectomies; only 50% had R0 resection
  - Results:
    - Surgery → ↑ LC but no difference in 5Y-OS (~15%) or MS (16.5mo)
    - Surgery → ↑ Tx-related mortality (9% vs. <1%)
  - Conclusions:
    - Surgery did not improve OS or PFS.
    - Given low morbidity and mortality, RT should be preferred modality

Post-Operative Therapy

- Adjuvant Chemotherapy:
  - pN+
  - pT3-4
  - +/- pT2a/b N0 if high risk features (>4cm tumor, high grade, LVSI, visceral pleural involvement, or pNx
- Adjuvant Radiation:
  - Positive margin not amenable to re-resection
  - pN2
  - +/- pN1 in patient not getting adjuvant chemotherapy

Radiotherapy for Stage Ill NSCLC

Definitive radiotherapy alone

-for patients who are not fit for combined treatment
-isolated thoracic recurrence after surgery
-palliative for patients with poor performance status or stage IV

Early randomized trial: RT vs. Placebo (Roswit 1968)
modest but significant survival benefit (18 vs. 14% at 1 year)

RT alone:	MS	lOmts.
	5y-OS	5%

Factors associated with improved prognosis:
(Basaki 2006, RTOG 93-11 2008)
-small primary tumor
-small total tumor volume

Radiotherapy for Stage Ill NSCLC

Dose and local control

RTOG phase III trial: (Perez 1986)

	40Gy	**SOGy**	**60Gy**	(2Gy/fx)
Local Control	52%	62°/o	73%	
Survival		similar		

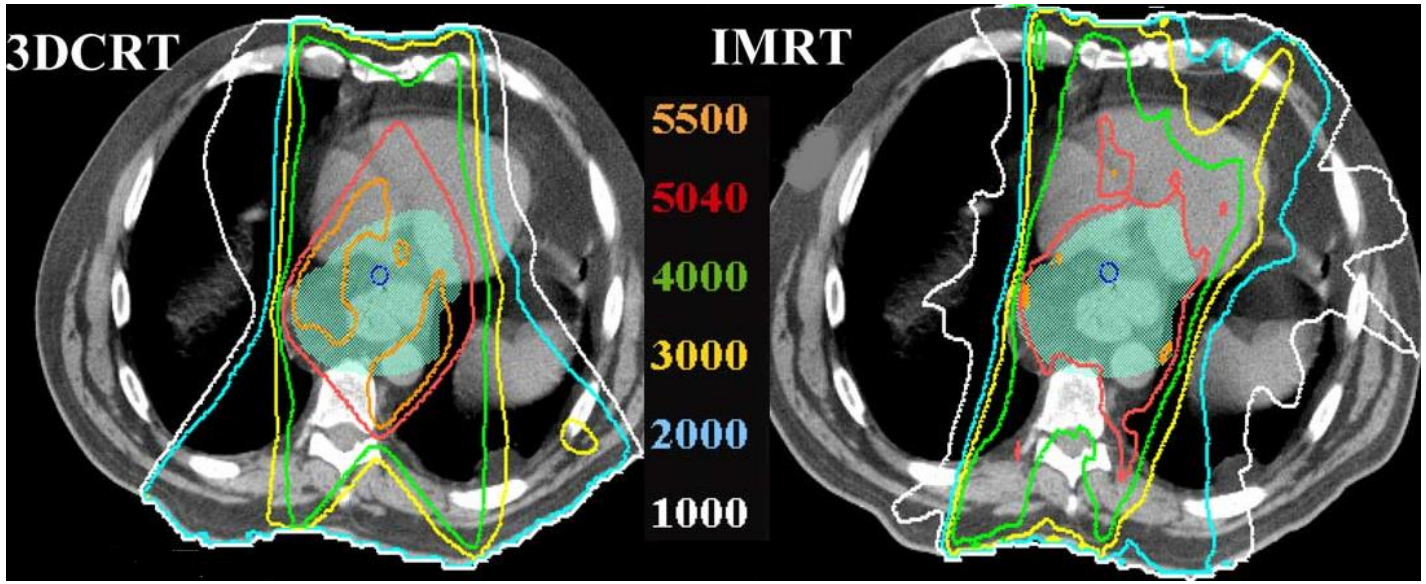
-60Gy / 30 fractions: standard today

-phase II data show better local control with higher doses
-limiting factor: normal tissue tolerance

Improved therapeutic index -altered fractionation schedules
-IMRT, IGRT, Tomotherapy, Protons..

Conventional Fractionation Using 3-D CRT/IMRT

- For locally advanced NSCLC
  - Larger target volumes encompassing primary tumor and involved nodes
- Target often in close proximity to normal structures. Decrease toxicity by:
  - Using lower dose/fraction → more repair of normal tissue DNA damage
    - Typically 1.8-2.0 Gy/fraction in 30-35 fractions, to a total dose of 60-70Gy or 1.5 Gy twice daily to 45 Gy for limited stage SCLC
  - Using IMRT (or proton therapy) to shape dose away from normal organs
    - More “conformal” than 3-D CRT



Hypofractionation

- 60 – 66 Gy in 15 to 20 #
- 60 – 75 Gy in 15 to 25 #
- 55 Gy in 20 #

Why Hypofractionation

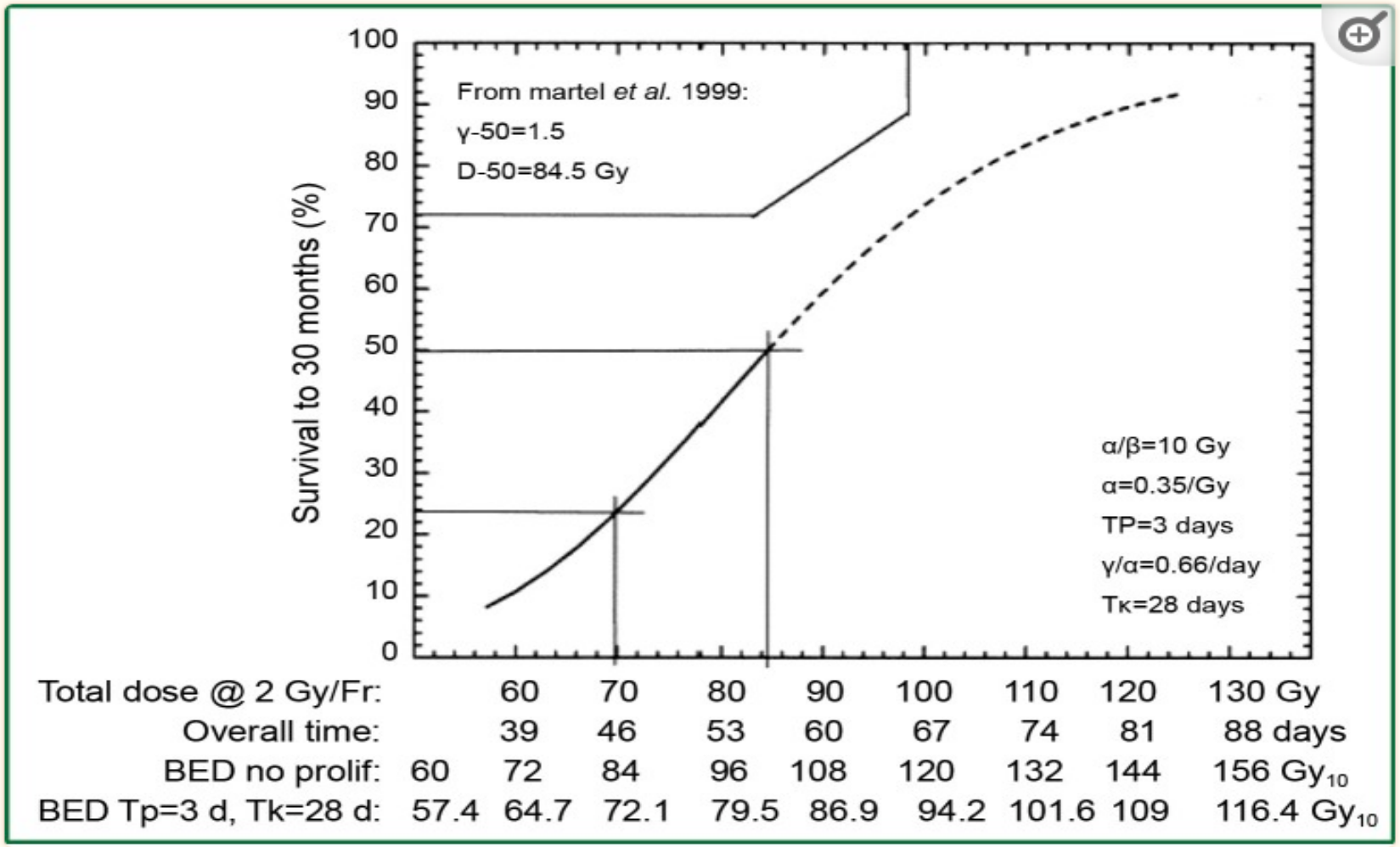


Figure 1

Tumor control probability and biological effective dose. The dose response relationship is sigmoidal in one of the early dose escalation studies of non-small cell lung cancer (NSCLC) performed in University of Michigan.

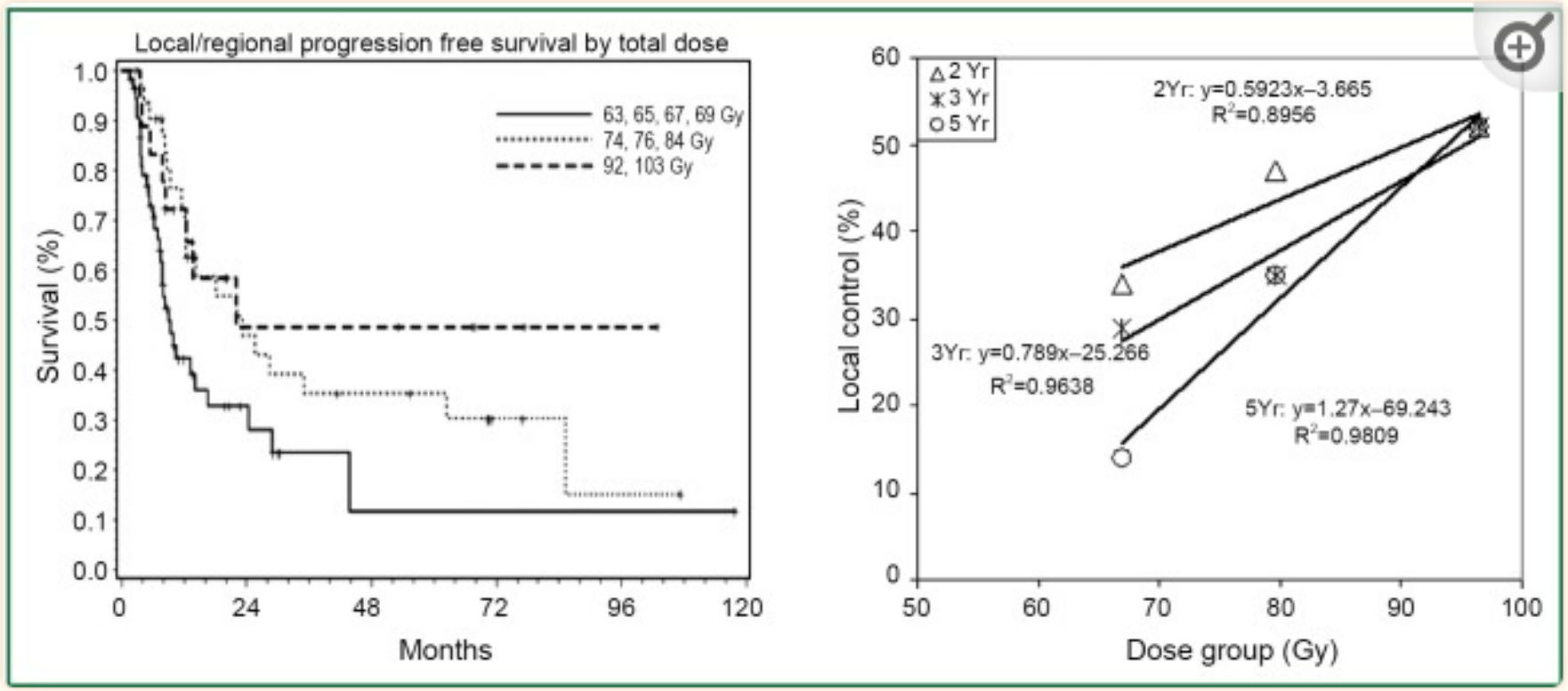
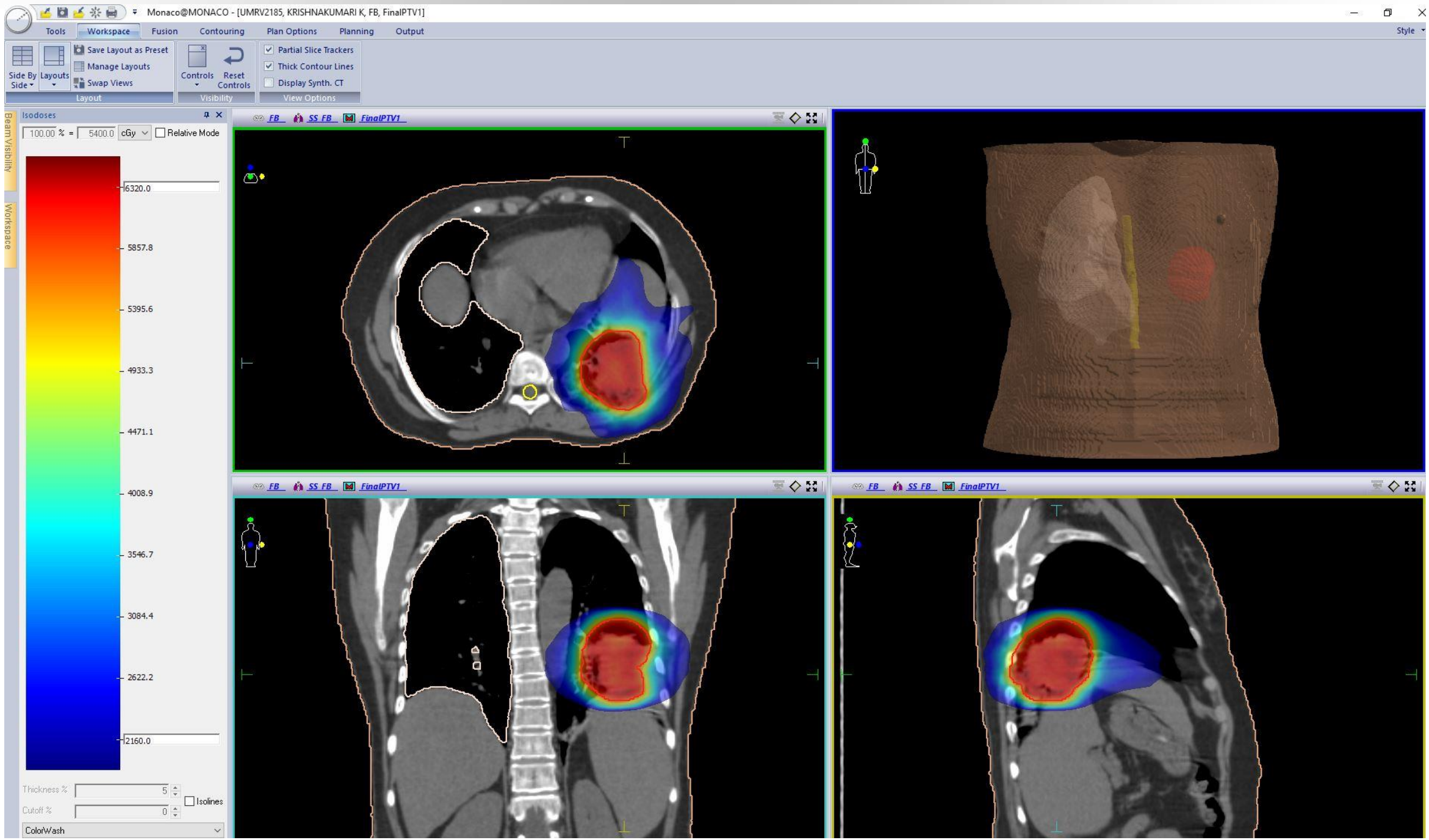


Figure 2

Local tumor control increases with higher dose radiation. Radiation dose is associated with long-term tumor control. Dose response relationship is steeper for longer follow-up.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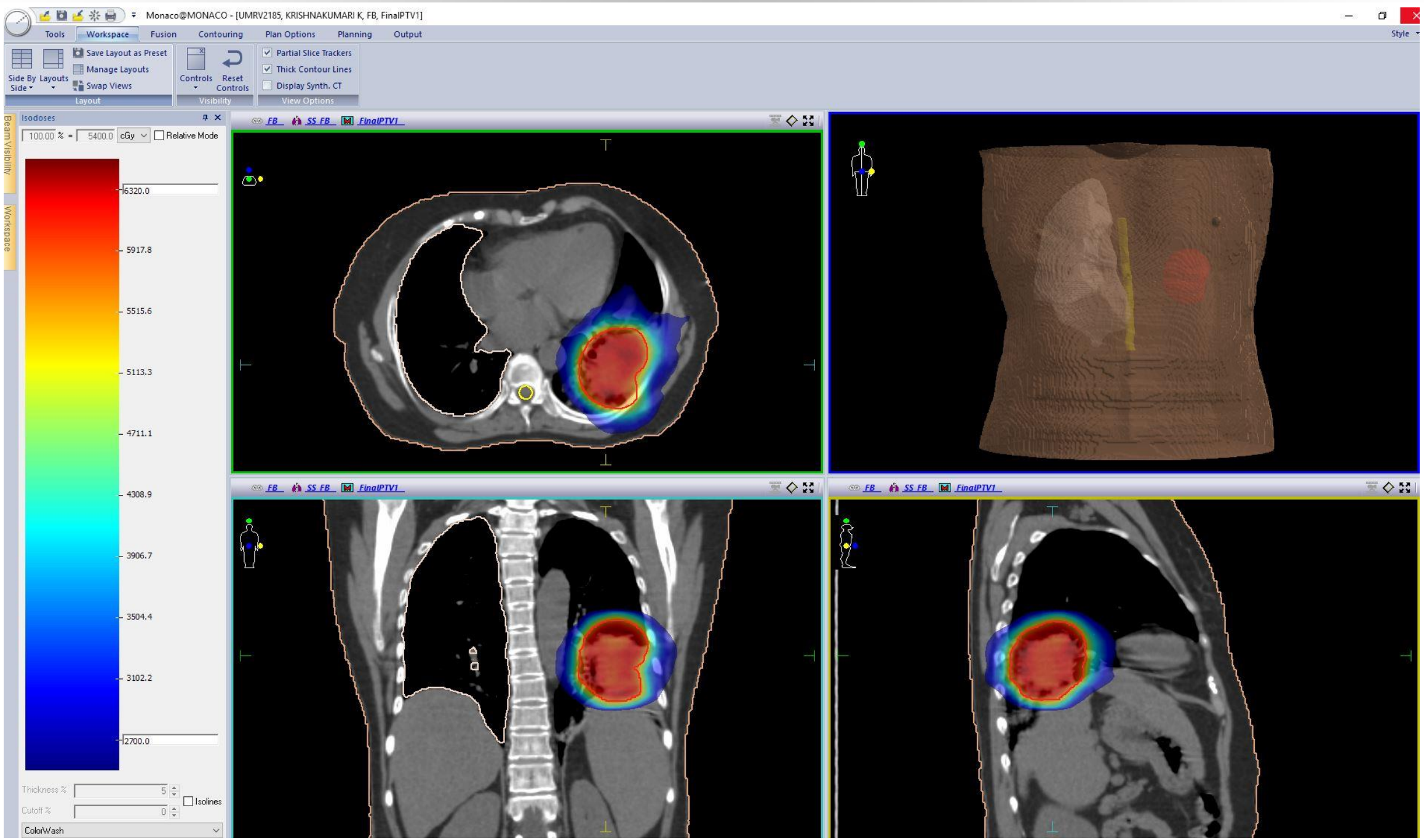
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Relative Mode
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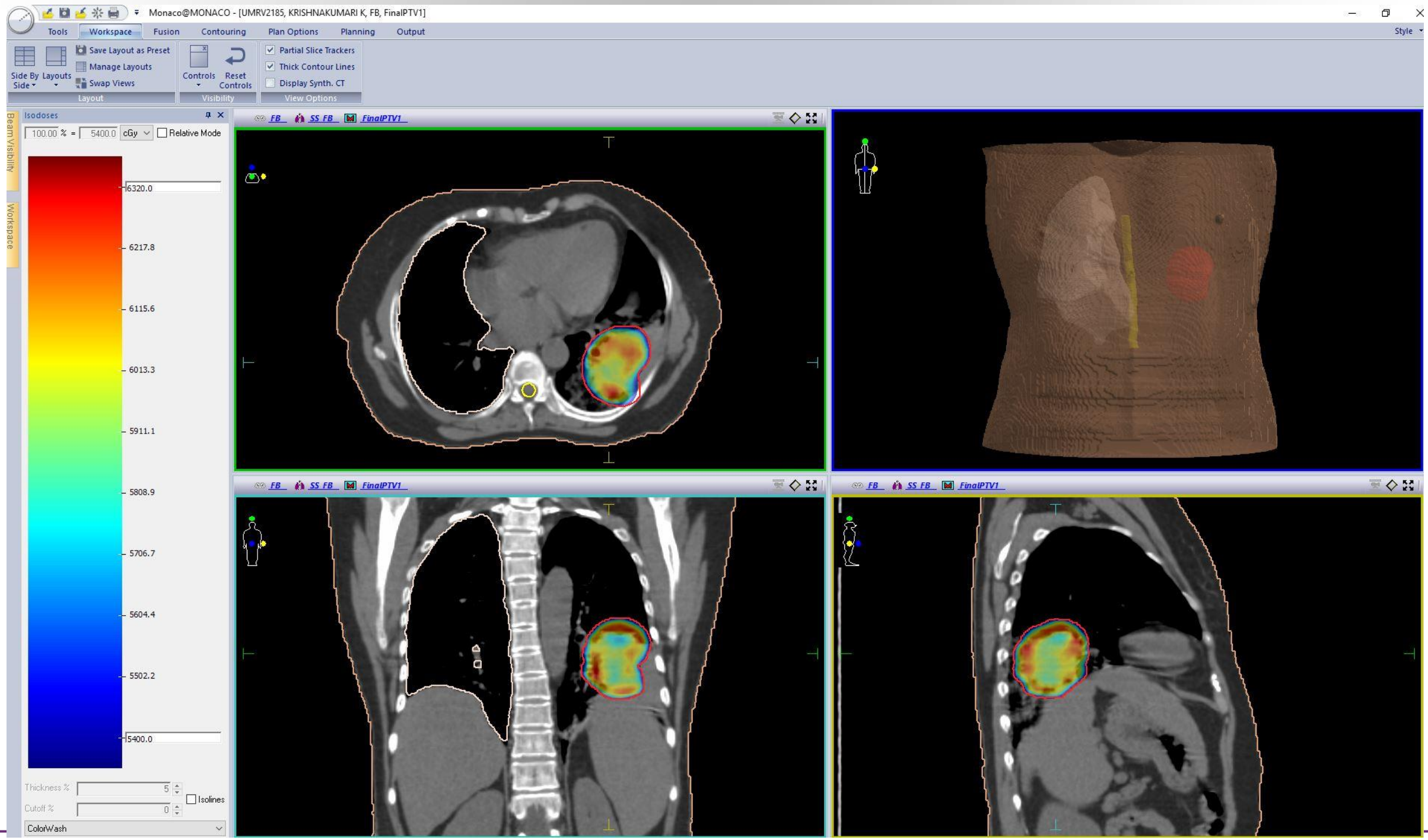
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How to Add Chemo to Definitive RT

- Both sequential and concurrent chemo → survival benefit
  - Concurrent chemo → improved local control → improved survival
    - At expense of ↑ in-field toxicity (especially esophagitis)

Trial	Patients, *n*	Med. Survival, *mo*		% Survival, *y*		% Esophagitis (Gr. 3-4)	
		S	C	S	C	S	C
Furuse[15]	314	13.3	16.5	8	16(5)	4	23
RTOG-9410[16]	400	14.6	17.1	12	21(4)	5	26
GLOT[17]	212	13.9	15.6	24	35(2)	3	17
Czech[19]	102	13.2	20.6	15	42(2)	4	28
BROCAT[20]	303	14.0	19.0	—	—	0	26
LAMP[21]	178	13.8	17.4	31	33(2)	3	26

What Type of Chemotherapy is Used?

- Neoadjuvant/Adjuvant/Sequential:
  - Cisplatin + (vinorelbine, etoposide, gemcitabine, docetaxel or pemetrexed*)
  - Carboplatin + (paclitaxel, gemcitabine or pemetrexed*)

- Concurrent with RT:
  - Cisplatin + (etoposide, vinblastine or pemetrexed*)
  - Carboplatin + paclitaxel (+/- 2 additional full-dose cycles)

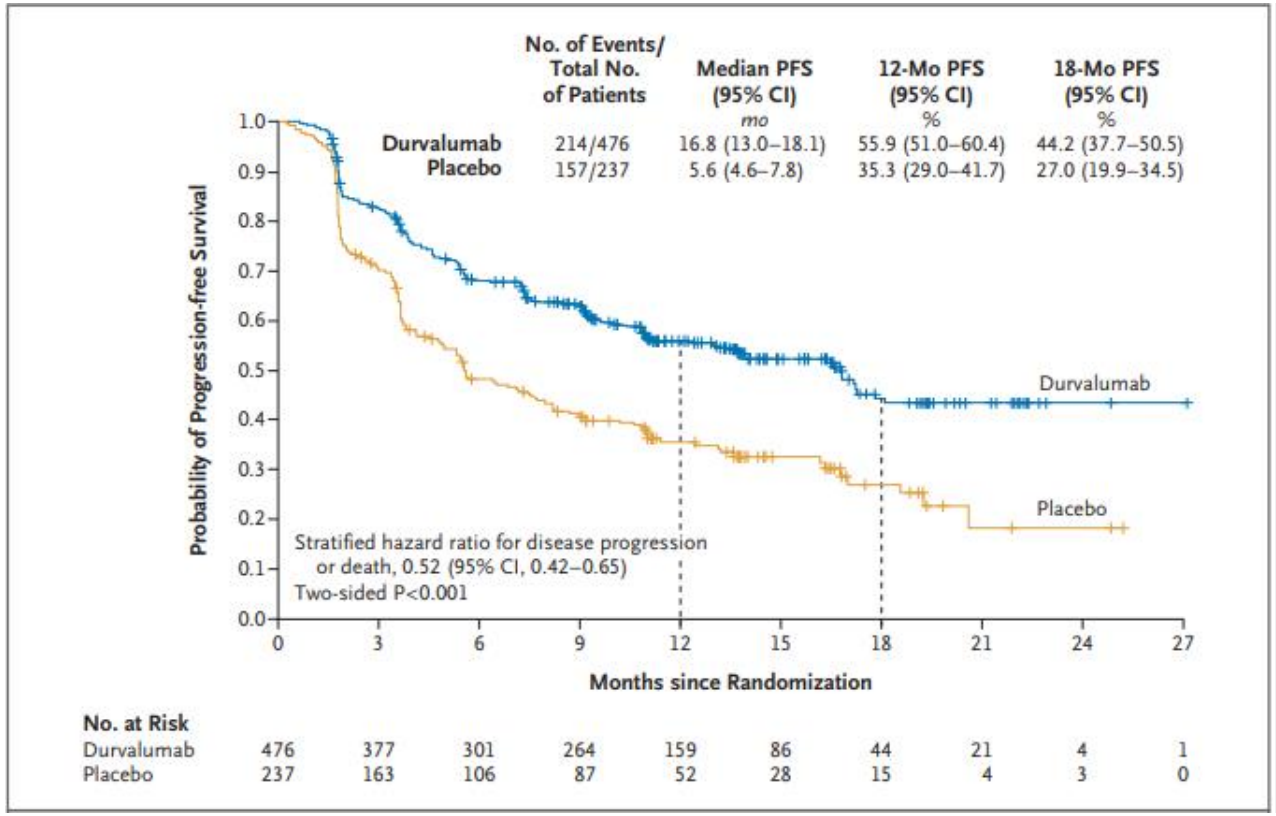
- Consolidation after chemo-RT:
  - Durvalumab q2weeks for up to 12 months

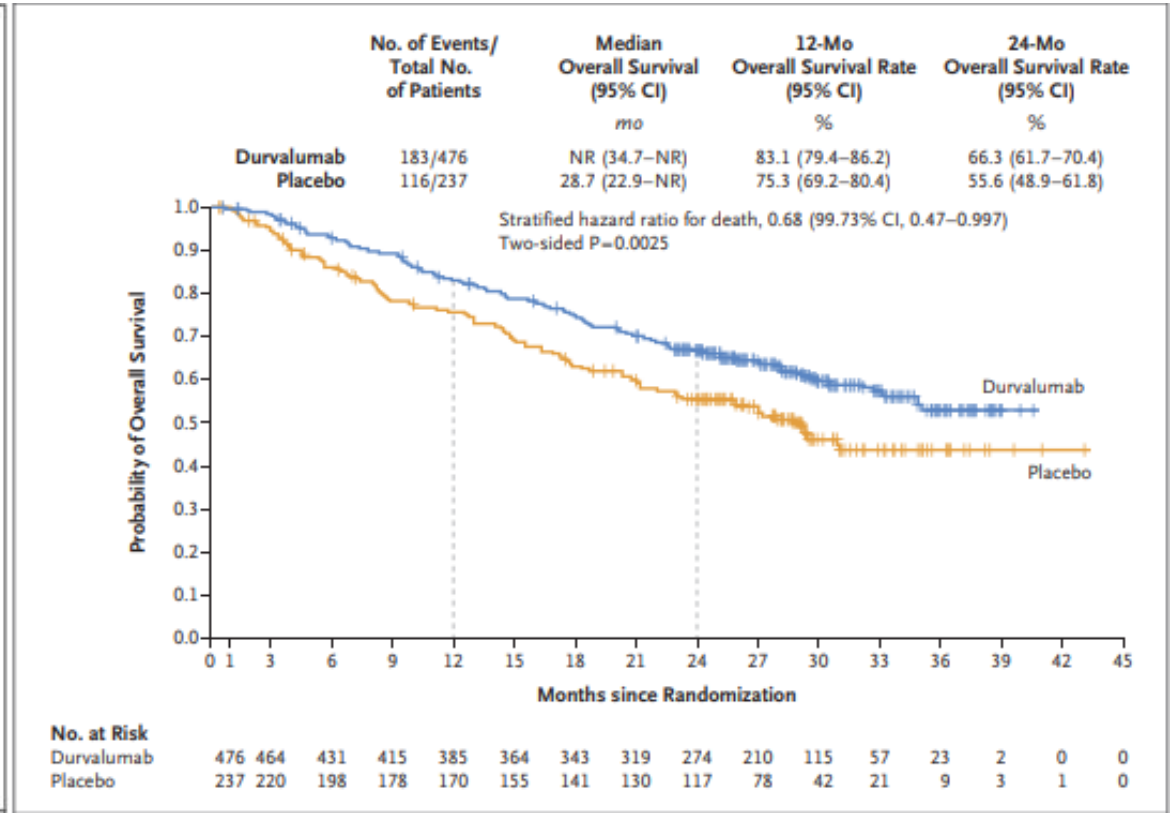
* for non-squamous histology only

Immunotherapy

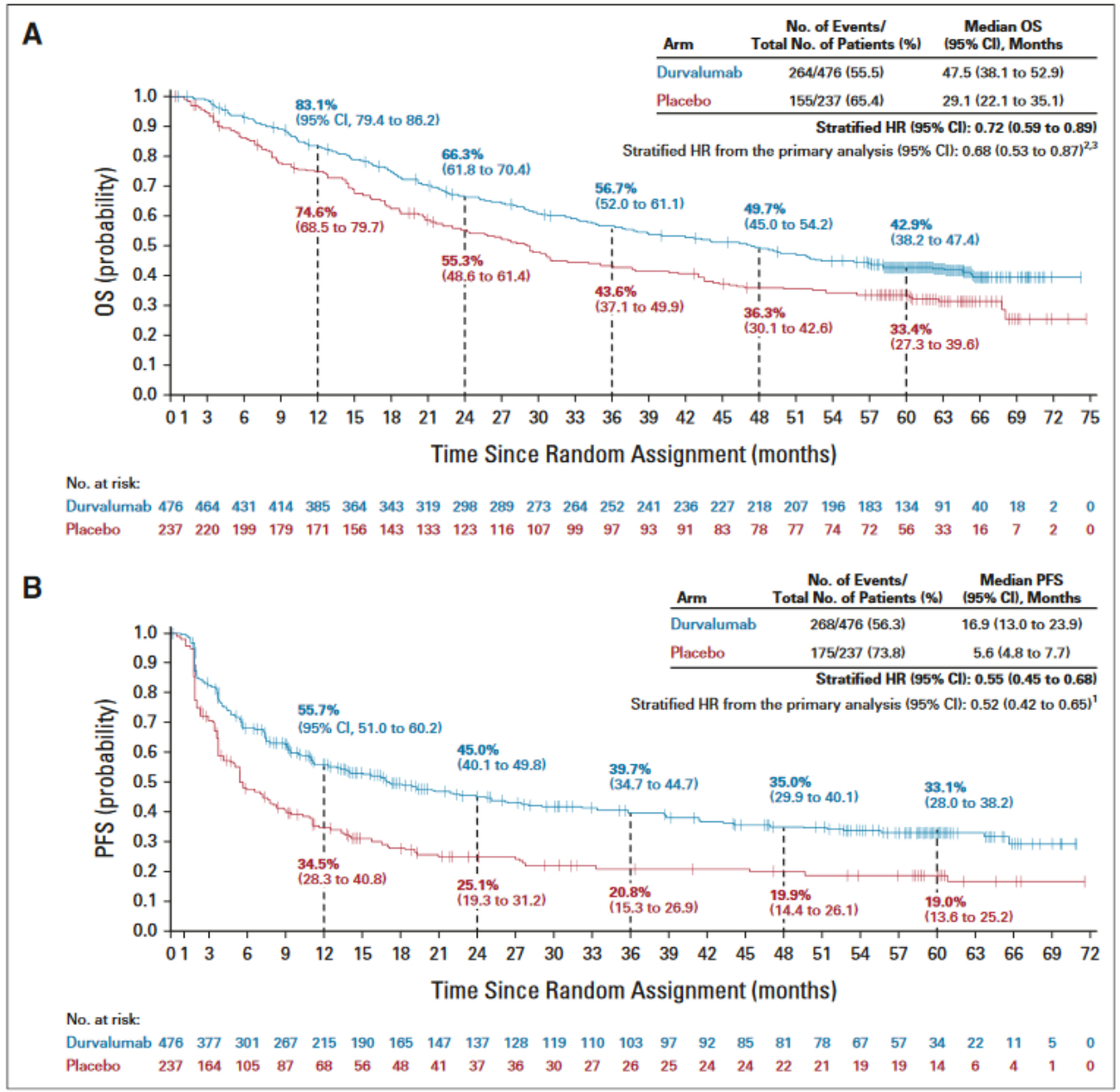
Immunotherapy May Change Our Approach to Locoregional Management Too

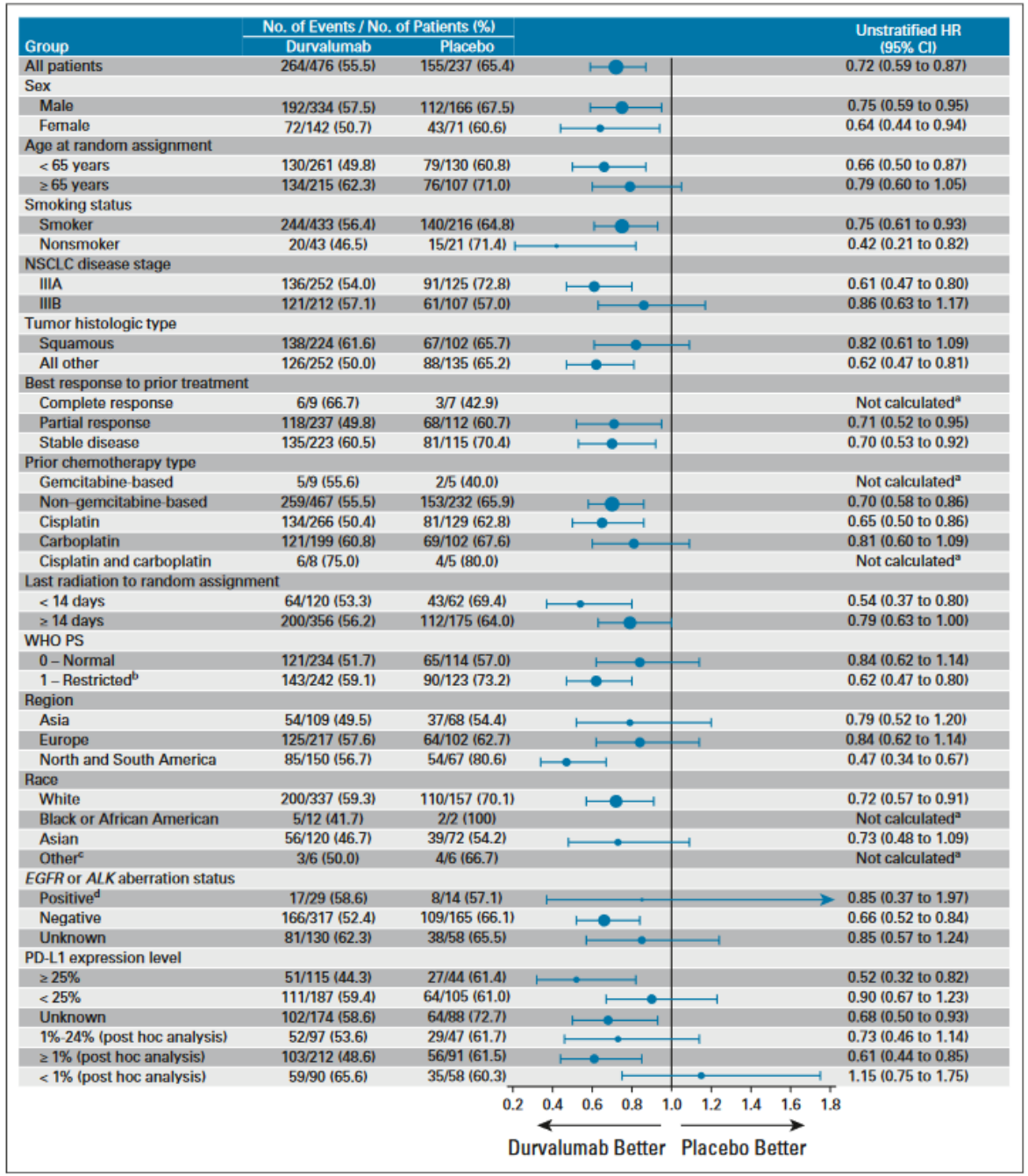
-





Five-Year Survival With Durvalumab After CRT in Stage III NSCLC




Group
No. of Events / No. of Patients (%)
Durvalumab
Placebo
Unstratified HR (95% CI)
All patients 264/476 (55.5) 155/237 (65.4) 0.72 (0.59 to 0.87)
Sex
Male 192/334 (57.5) 112/166 (67.5) 0.75 (0.59 to 0.95)
Female 72/142 (50.7) 43/71 (60.6) 0.64 (0.44 to 0.94)
Age at random assignment
< 65 years 130/261 (49.8) 79/130 (60.8) 0.66 (0.50 to 0.87)
≥ 65 years 134/215 (62.3) 76/107 (71.0) 0.79 (0.60 to 1.05)
Smoking status
Smoker 244/433 (56.4) 140/216 (64.8) 0.75 (0.61 to 0.93)
Nonsmoker 20/43 (46.5) 15/21 (71.4) 0.42 (0.21 to 0.82)
NSCLC disease stage
IIIA 136/252 (54.0) 91/125 (72.8) 0.61 (0.47 to 0.80)
IIIB 121/212 (57.1) 61/107 (57.0) 0.86 (0.63 to 1.17)
Tumor histologic type
Squamous 138/224 (61.6) 67/102 (65.7) 0.82 (0.61 to 1.09)
All other 126/252 (50.0) 88/135 (65.2) 0.62 (0.47 to 0.81)
Best response to prior treatment
Complete response 6/9 (66.7) 3/7 (42.9) Not calculated[a]
Partial response 118/237 (49.8) 68/112 (60.7) 0.71 (0.52 to 0.95)
Stable disease 135/223 (60.5) 81/115 (70.4) 0.70 (0.53 to 0.92)
Prior chemotherapy type
Gemcitabine-based 5/9 (55.6) 2/5 (40.0) Not calculated[a]
Non–gemcitabine-based 259/467 (55.5) 153/232 (65.9) 0.70 (0.58 to 0.86)
Cisplatin 134/266 (50.4) 81/129 (62.8) 0.65 (0.50 to 0.86)
Carboplatin 121/199 (60.8) 69/102 (67.6) 0.81 (0.60 to 1.09)
Cisplatin and carboplatin 6/8 (75.0) 4/5 (80.0) Not calculated[a]
Last radiation to random assignment
< 14 days 64/120 (53.3) 43/62 (69.4) 0.54 (0.37 to 0.80)
≥ 14 days 200/356 (56.2) 112/175 (64.0) 0.79 (0.63 to 1.00)
WHO PS
0 – Normal 121/234 (51.7) 65/114 (57.0) 0.84 (0.62 to 1.14)
1 – Restricted[b] 143/242 (59.1) 90/123 (73.2) 0.62 (0.47 to 0.80)
Region
Asia 54/109 (49.5) 37/68 (54.4) 0.79 (0.52 to 1.20)
Europe 125/217 (57.6) 64/102 (62.7) 0.84 (0.62 to 1.14)
North and South America 85/150 (56.7) 54/67 (80.6) 0.47 (0.34 to 0.67)
Race
White 200/337 (59.3) 110/157 (70.1) 0.72 (0.57 to 0.91)
Black or African American 5/12 (41.7) 2/2 (100) Not calculated[a]
Asian 56/120 (46.7) 39/72 (54.2) 0.73 (0.48 to 1.09)
Other[c] 3/6 (50.0) 4/6 (66.7) Not calculated[a]
EGFR or ALK aberration status
Positive[d] 17/29 (58.6) 8/14 (57.1) 0.85 (0.37 to 1.97)
Negative 166/317 (52.4) 109/165 (66.1) 0.66 (0.52 to 0.84)
Unknown 81/130 (62.3) 38/58 (65.5) 0.85 (0.57 to 1.24)
PD-L1 expression level
≥ 25% 51/115 (44.3) 27/44 (61.4) 0.52 (0.32 to 0.82)
< 25% 111/187 (59.4) 64/105 (61.0) 0.90 (0.67 to 1.23)
Unknown 102/174 (58.6) 64/88 (72.7) 0.68 (0.50 to 0.93)
1%-24% (post hoc analysis) 52/97 (53.6) 29/47 (61.7) 0.73 (0.46 to 1.14)
≥ 1% (post hoc analysis) 103/212 (48.6) 56/91 (61.5) 0.61 (0.44 to 0.85)
< 1% (post hoc analysis) 59/90 (65.6) 35/58 (60.3) 1.15 (0.75 to 1.75)
0.2 0.4 0.6 0.8 1.0 1.2 1.4 1.6 1.8
Durvalumab Better
Placebo Better

Understanding Radiotherapy Techniques for Lung Cancer

Fusion Images

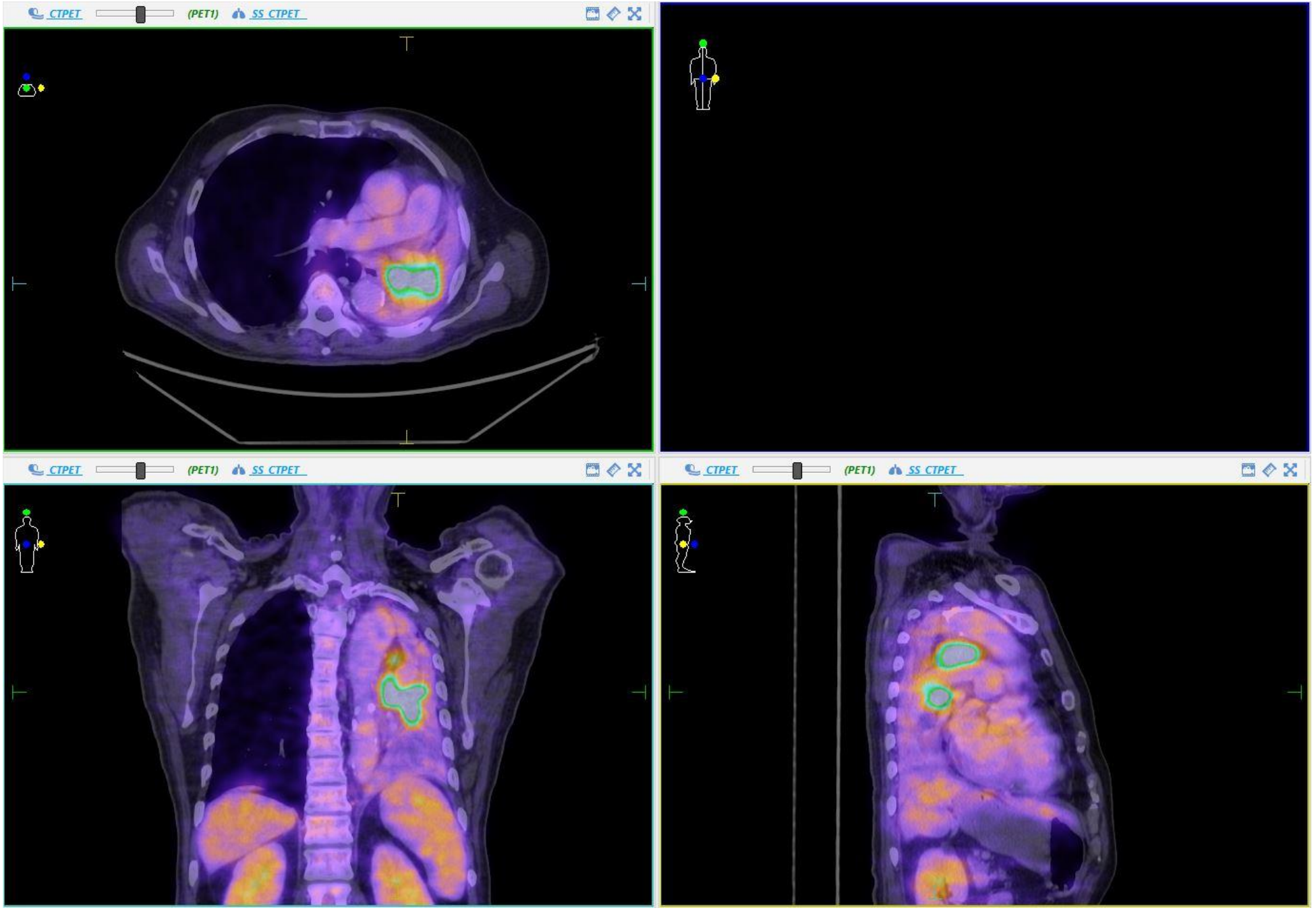
CT scan

- Planning CT scans should be acquired in treatment position, and incorporate techniques for evaluating motion compensation
- A planning CT scan should include the entire lung volume, and typically extends from the level of the cricoid cartilage to the second lumbar vertebra
- Slice thickness of 2–3 mm is recommended
- IV contrast should be used
- 4D-CT is recommended

Fusion Images

PET scanning

The equipment used for patient immobilisation during PET scans should be identical to that used for CT scanning and treatment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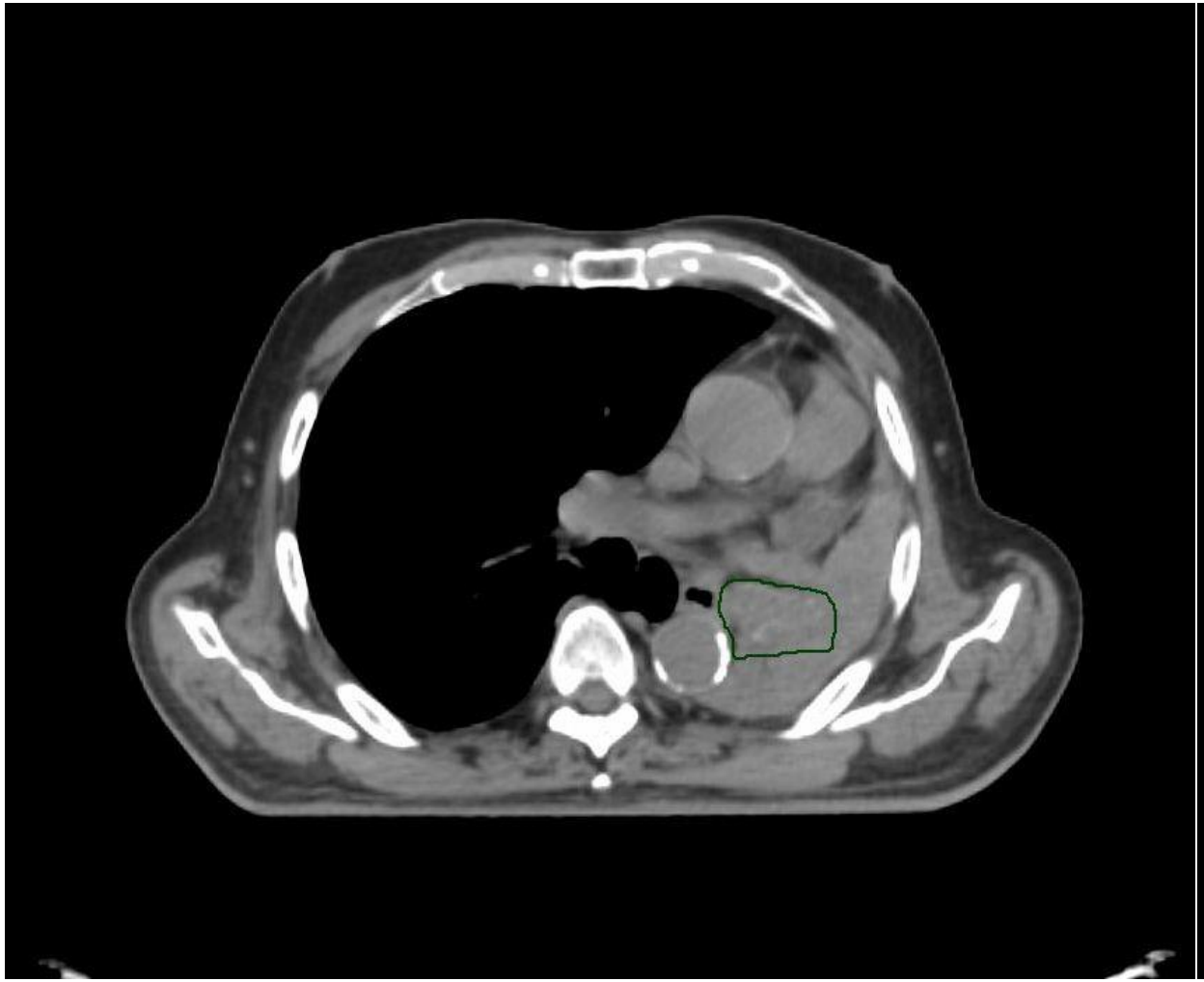

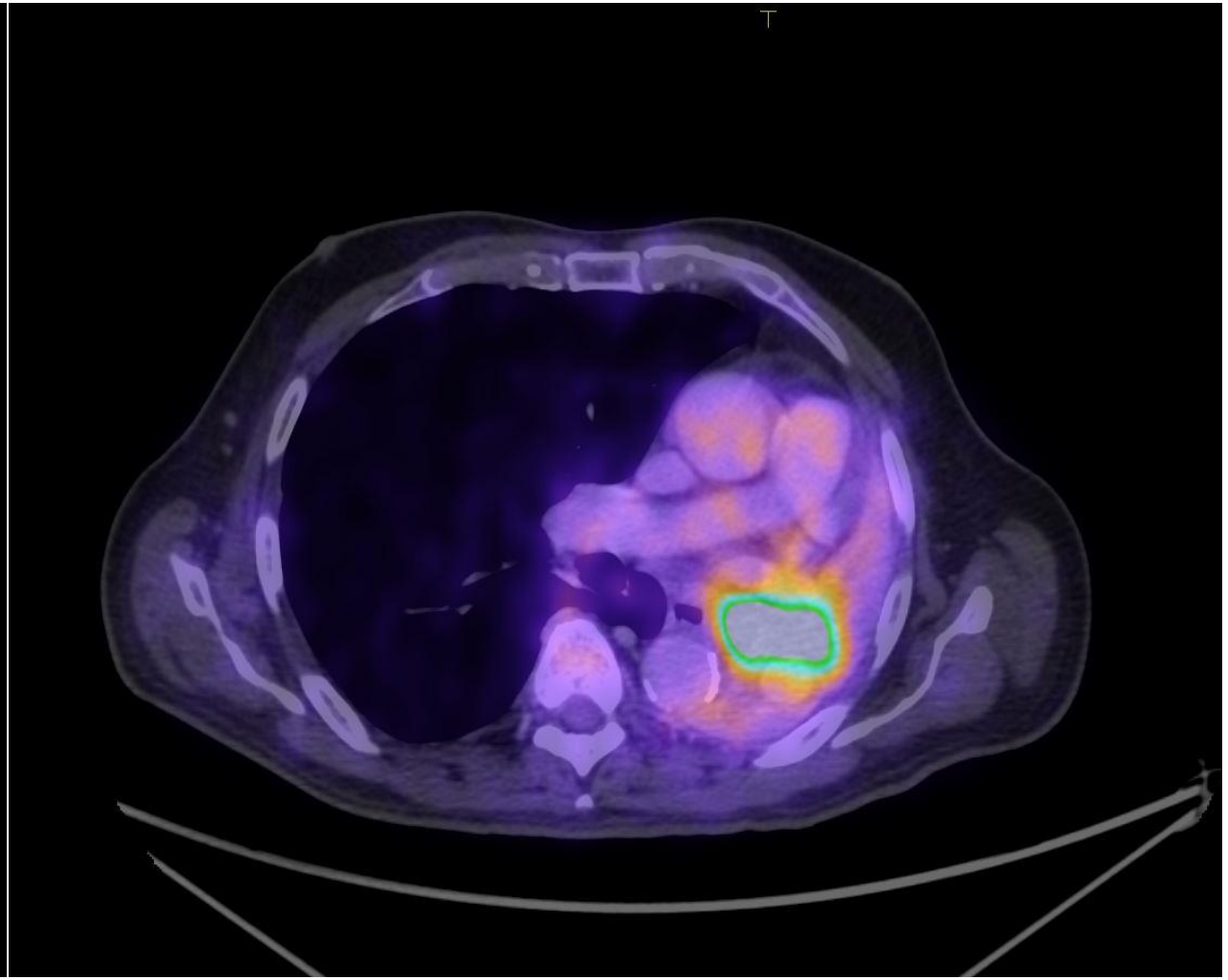

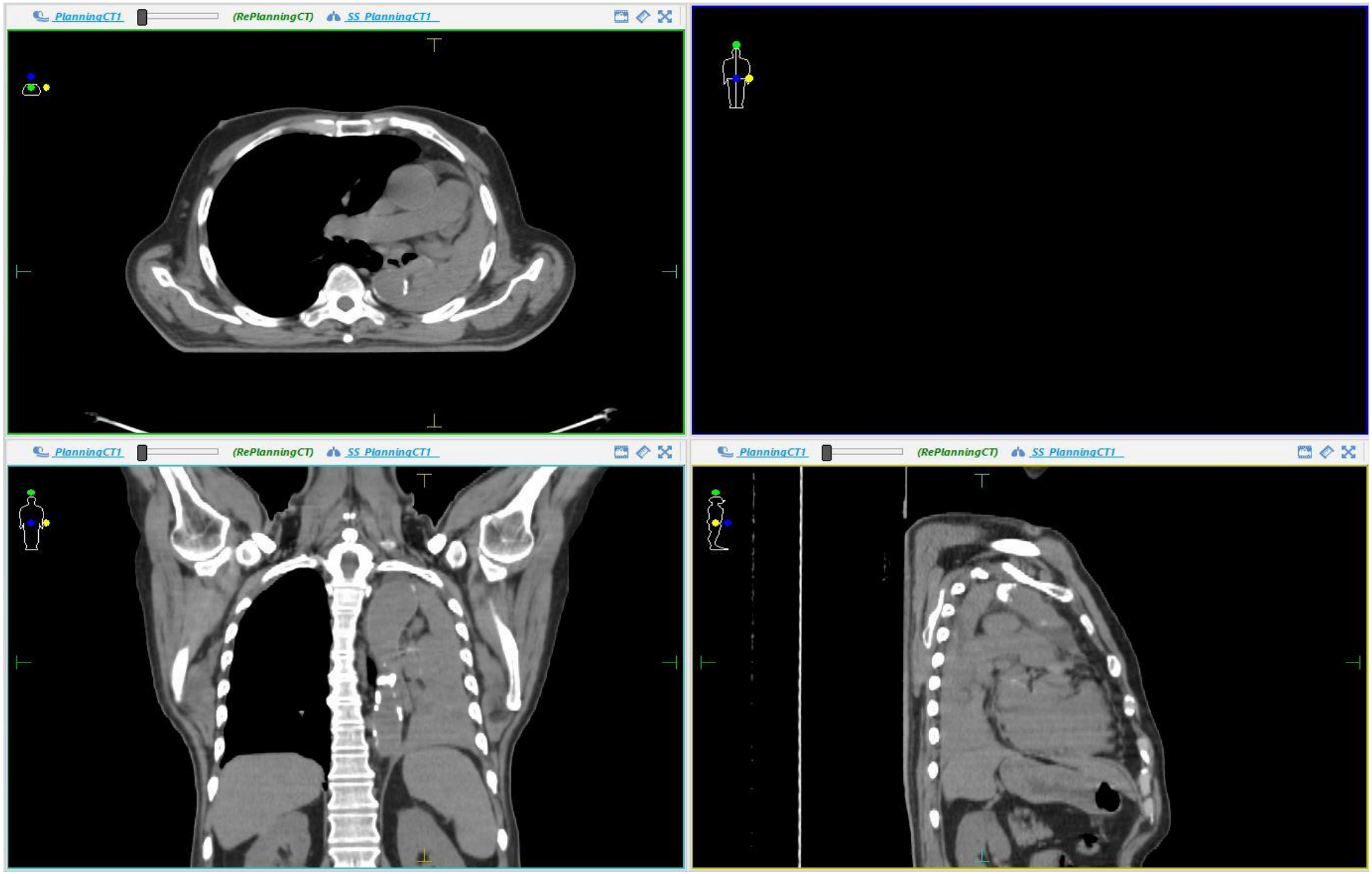
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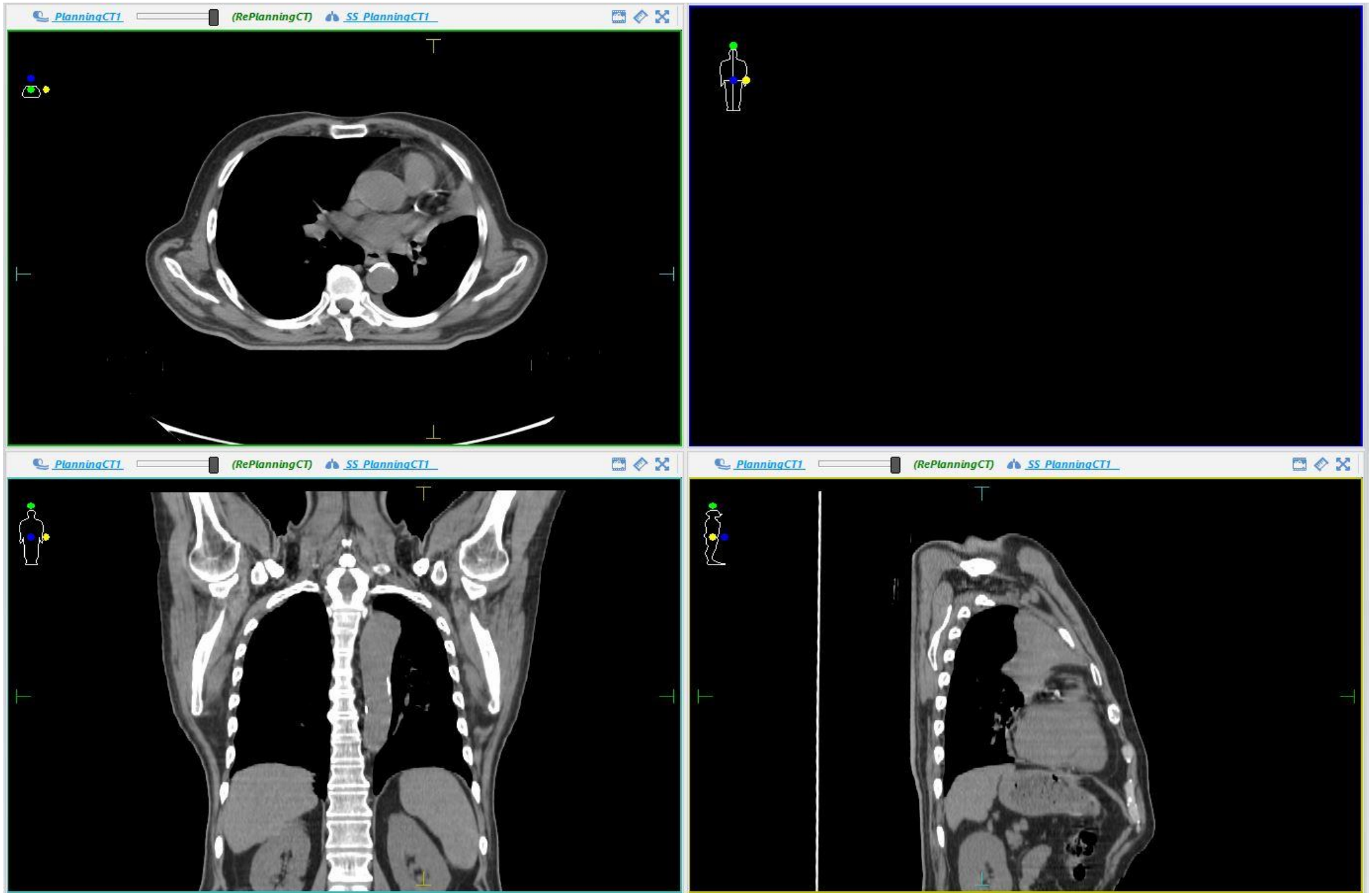
Tumour and nodal changes

Inter-fractional tumour shifts

- Inter-fractional shifts between primary tumour and vertebra positions range from 5 to 7 mm on average (3D vector), but may be as high as 3 cm
- Image guidance and patient setup corrections are essential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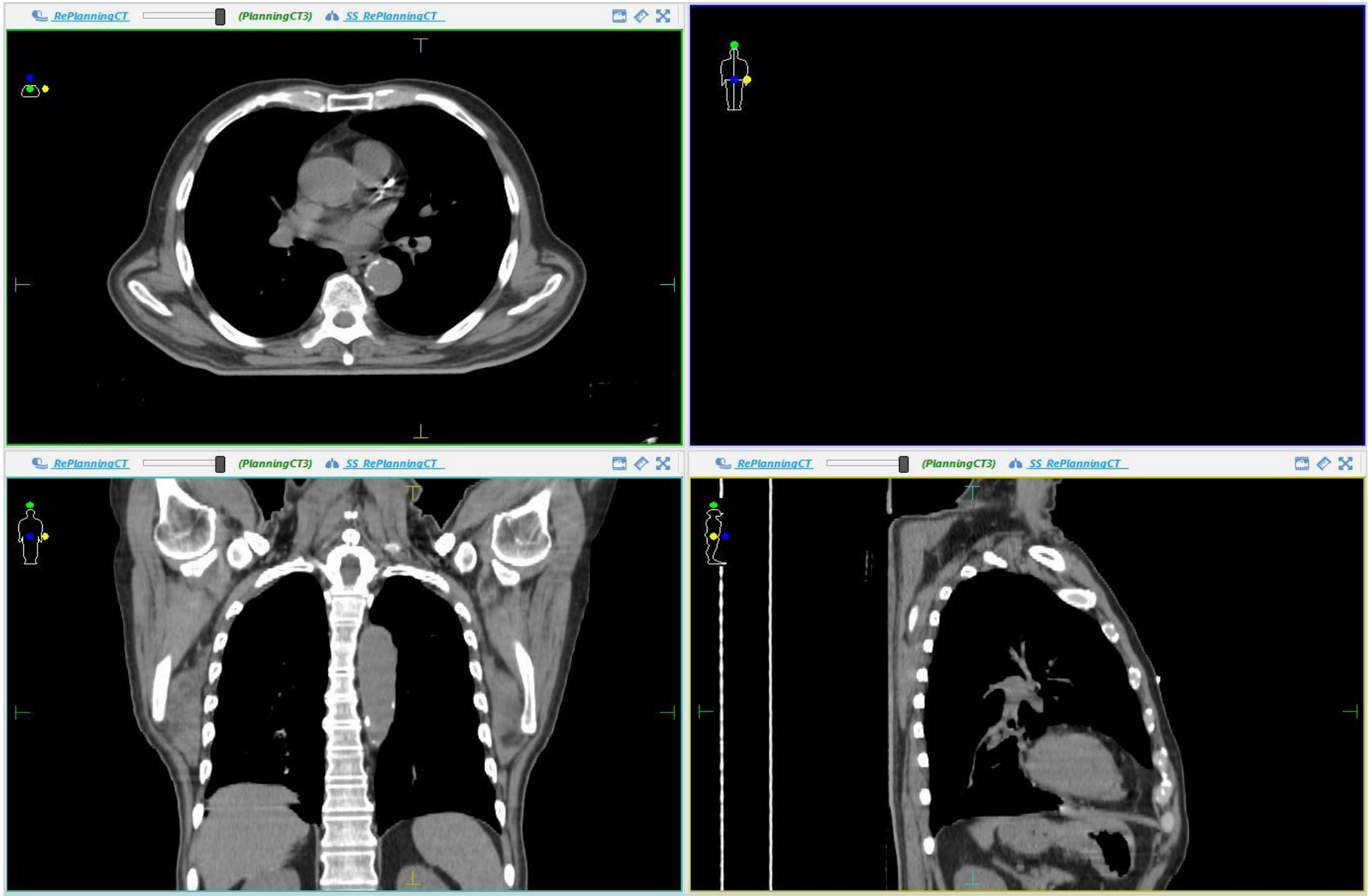
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While contouring

- Lung window – for extent of parenchymal lesion
- Soft- tissue window- adjacent structures
- Contour GTV on free breathing and MIP
- Combine GTVs for ITV
- Evaluate tumor motion and generate PTV

Target Volume Definitions

GTV

- CT with the settings: W= 1600 and L = 600 for parenchyma, and W= 400 and L = 20 for mediastinum should be used
- Elective nodal irradiation is not indicated in any patient

CTV

- In SBRT treatments, CTV margins are generally not used

ITV

- Target representing the range of GTV motion through the breathing cycle

PTV

- ITV + 3 to 10 mm margin; Respiratory motion is a patient-specific factor which should be determined before treatment, typically using a pre-treatment 4D-CT or 4D PET/CT scan

Margins

SBRT with conventional Linac

- ITV : delineated based upon tumor motion on 4D CT
- CTV – Not applicable
- PTV – 5mm uniform expansion
- Hypofractionation
- ITV
- CTV 5 to 8 mm uniform expansion (Elective -nodes not included)
- PTV 3 to 5 mm

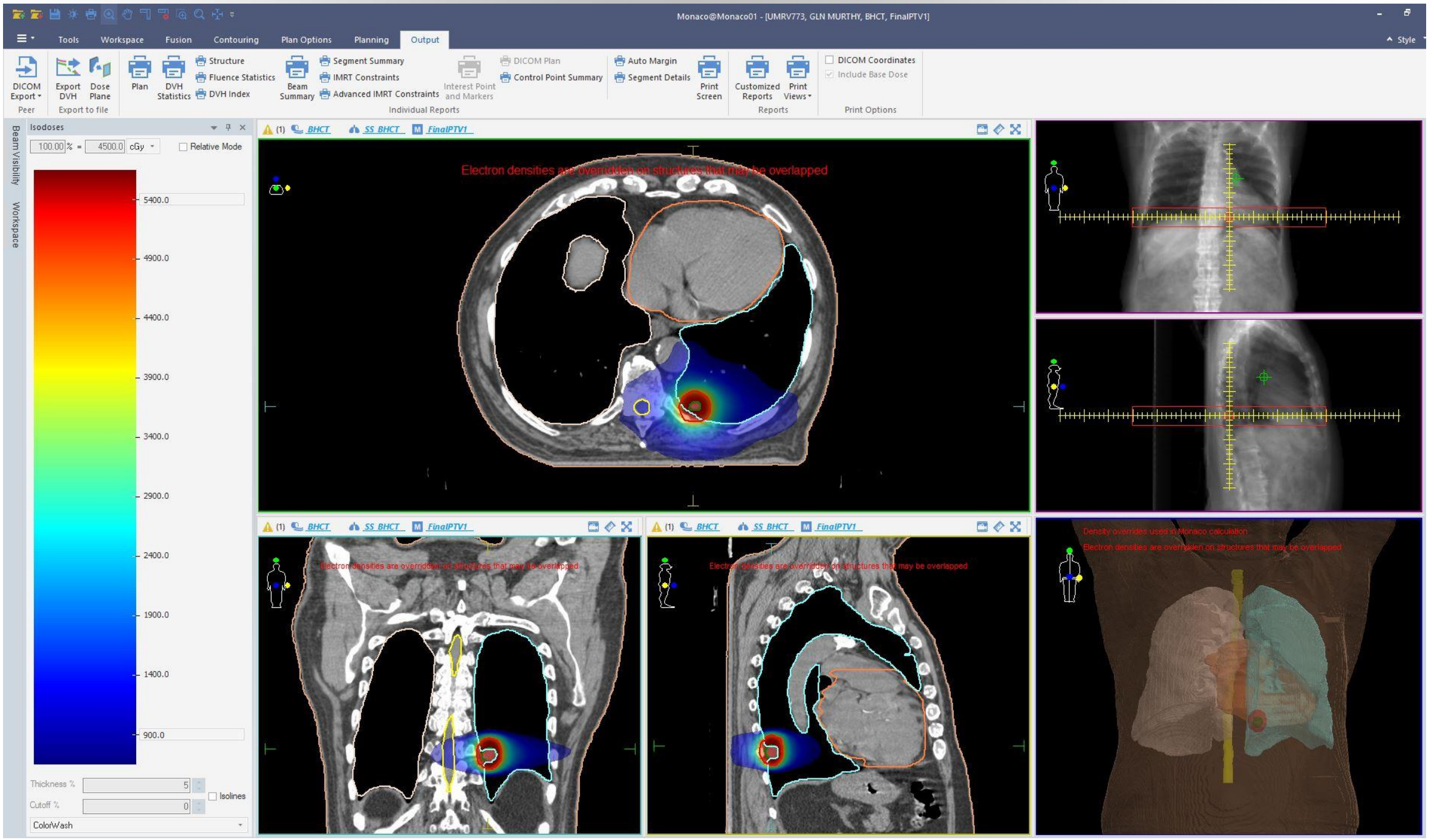
Target volumes definition

PRV

For serial organs, including the spinal cord, the main bronchi, the brachial plexus, the oesophagus and large blood vessels, the use of a PRV might be helpful, since it reduces the probability of over dosage

Metastases

- Oligometastases
- Up to 3 mets
- Less than 5 cm
- Minimum of 6 months DFS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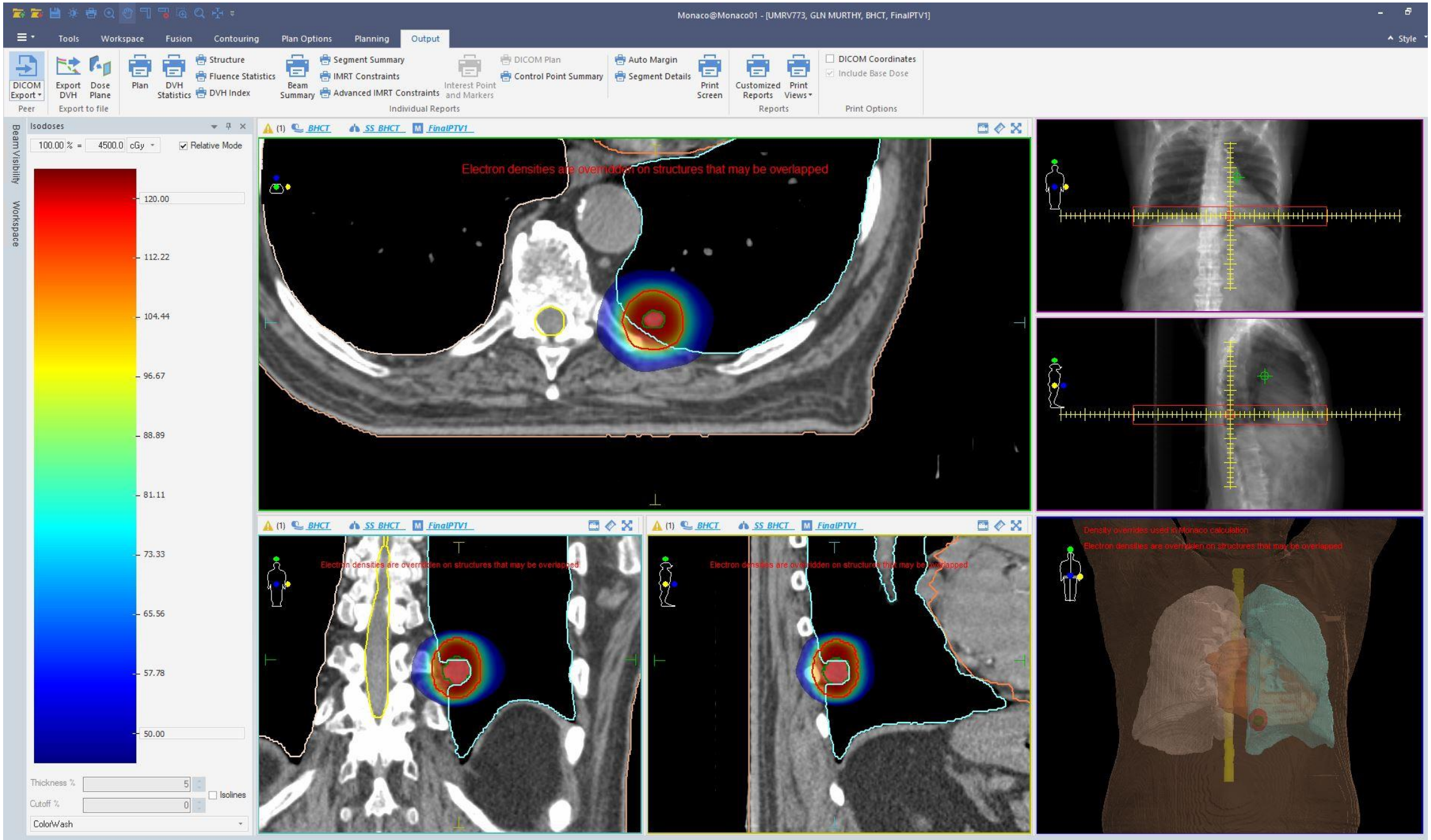
Export to file
Plan
DVH Statistics
Structure
Fluence Statistics
DVH Index
Beam Summary
Segment Summary
IMRT Constraints
Advanced IMRT Constraints
Interest Point and Markers
DICOM Plan
Control Point Summary
Individual Reports
Auto Margin
Segment Details
Print Screen
Customized Reports
Print Views
Reports
DICOM Coordinates
Include Base Dose
Print Options
Beam Visibility
Workspace
Isodoses
100.00 % = 4500.0 cGy
Relative Mode
5400.0
4900.0
4400.0
3900.0
3400.0
2900.0
2400.0
1900.0
1400.0
900.0
Thickness %
5
Isolines
Cutoff %
0
ColorWash
(1) BHCT SS BHCT FinalPTV1
Electron densities are overridden on structures that may be overlapped
Density overrides used in Monaco calculation
Electron densities are overridden on structures that may be overlapped


Monaco@Monaco01 - [UMRV773, GLN MURTHY, BHCT, FinalPTV1]
Tools
Workspace
Fusion
Contouring
Plan Options
Planning
Output
Style
DICOM Export
Export DVH
Dose Plane
Peer
Export to file
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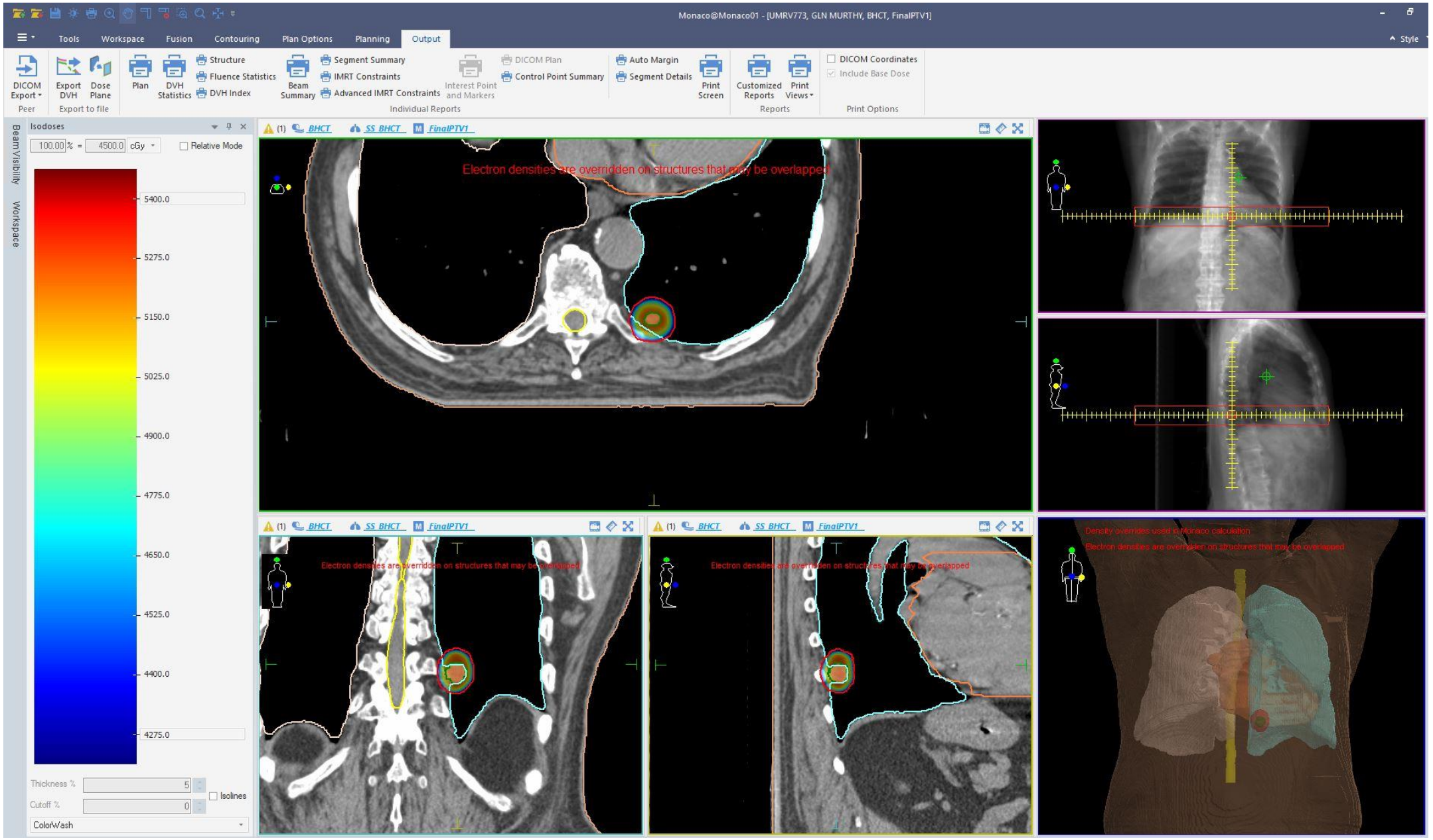
Customized Reports
Print Views
Reports
DICOM Coordinates
Include Base Dose
Print Options
Beam Visibility
Workspace
Isodoses
100.00 % = 4500.0 cGy
Relative Mode
120.00
112.22
104.44
96.67
88.89
81.11
73.33
65.56
57.78
50.00
Thickness %
Cutoff %
Isolines
ColorWash
(1) BHCT
SS BHCT
FinalPTV1
Electron densities are overridden on structures that may be overlapped
Density overrides used in Monaco calculation


Monaco@Monaco01 - [UMRV773, GLN MURTHY, BHCT, FinalPTV1]
Tools
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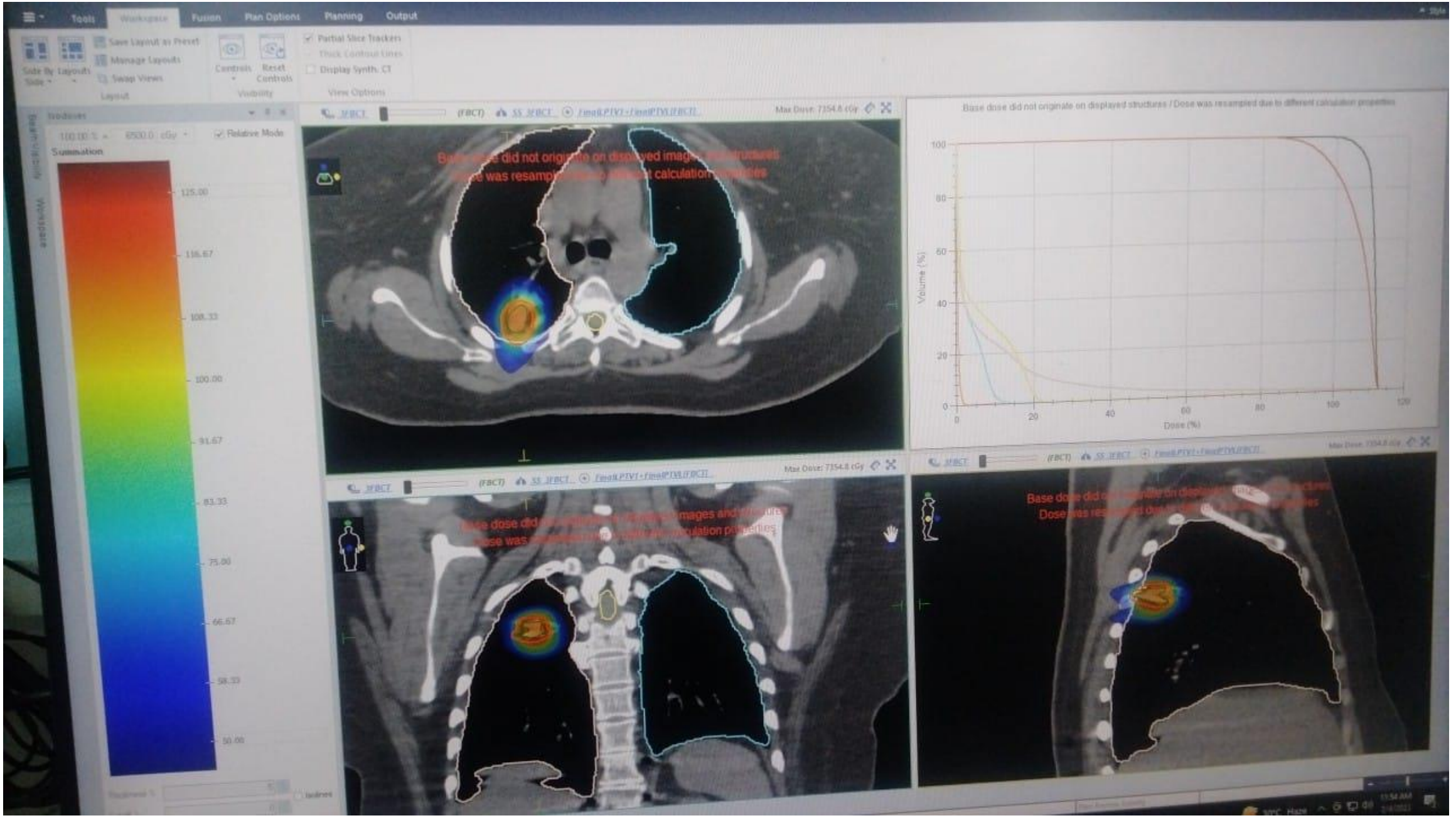
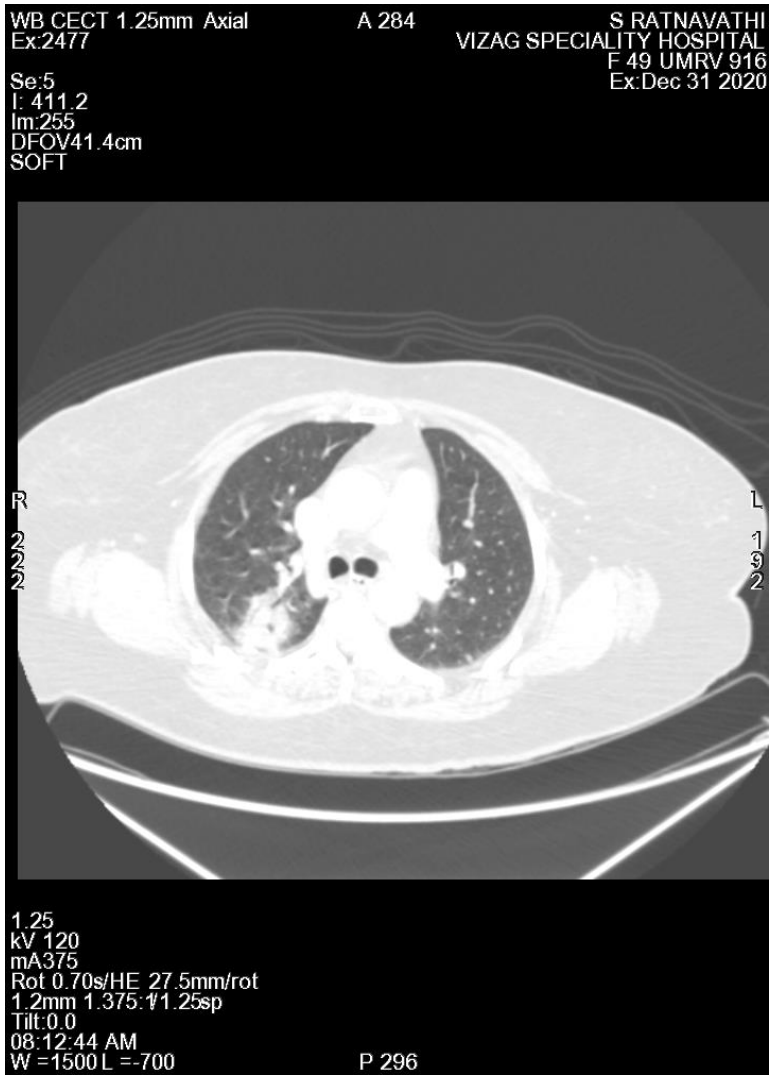
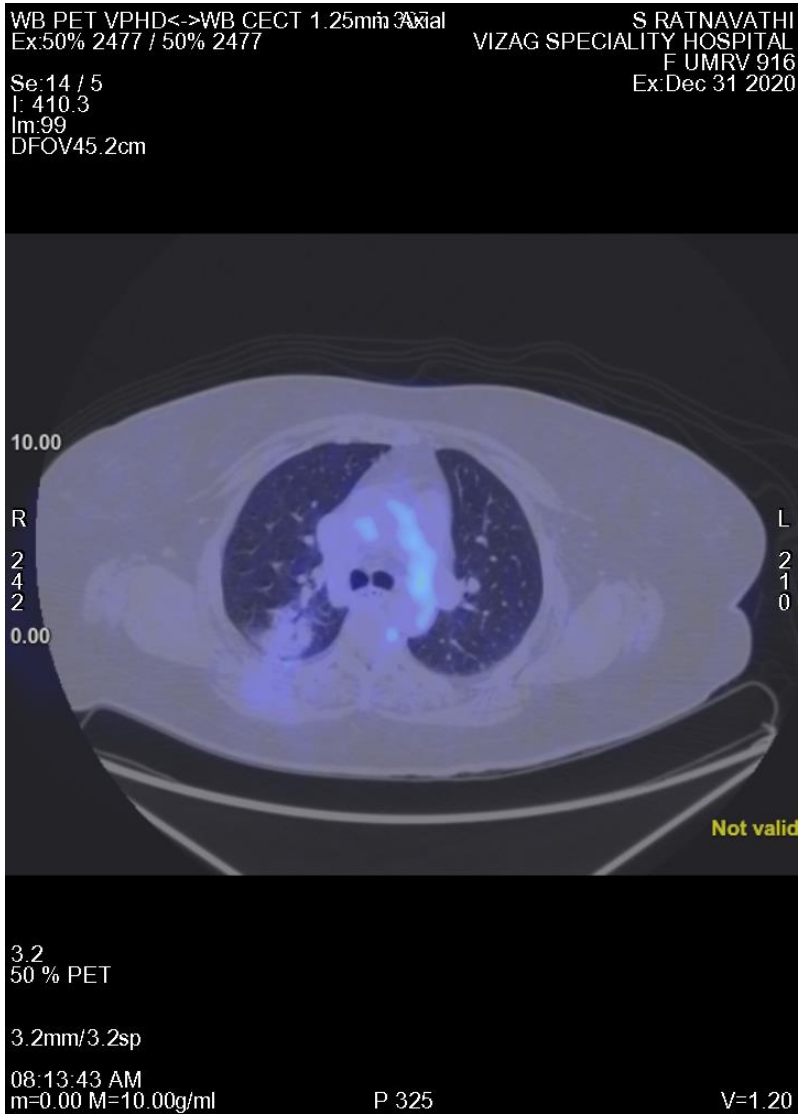
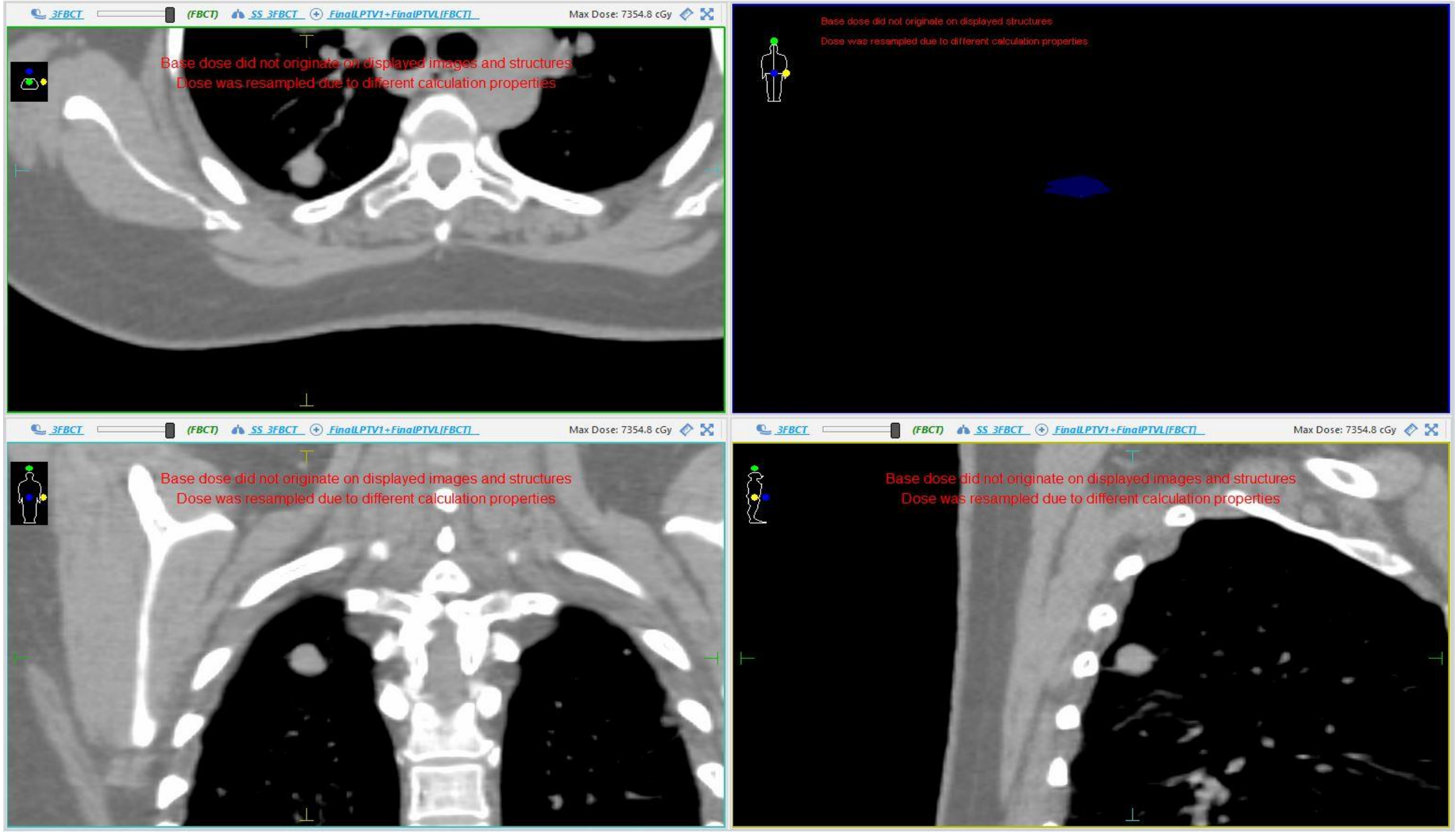
Customized Reports
Print Views
Reports
DICOM Coordinates
Include Base Dose
Print Options
Beam Visibility
Workspace
Isodoses
100.00 % = 4500.0 cGy
Relative Mode
5400.0
5275.0
5150.0
5025.0
4900.0
4775.0
4650.0
4525.0
4400.0
4275.0
Thickness %
5
Cutoff %
0
Isolines
ColorWash
(1) BHCT
SS BHCT
FinalPTV1
Electron densities are overridden on structures that may be overlapped
Density overrides used in Monaco calculation
Electron densities are overridden on structures that may be overlapped


Tools
Workspace
Fusion
Plan Options
Planning
Output
Save Layout as Preset
Manage Layouts
Swap Views
Layout
Controls
Reset Controls
Visibility
Partial Slice Trackers
Thick Contour Lines
Display Synth. CT
View Options
Windows
Summation
Relative Mode
125.00
116.67
108.33
100.00
91.67
83.33
75.00
66.67
58.33
50.00
Base dose did not originate on displayed structures / Dose was resampled due to different calculation properties
Volume (%)
Dose (%)
0
20
40
60
80
100
120

- 45 Gy / 5 # - Lung

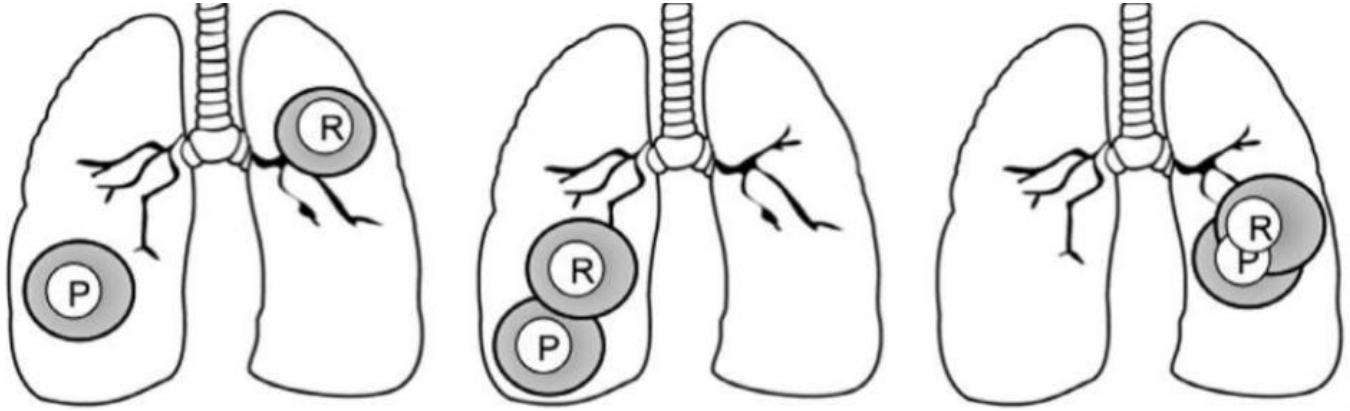

WB CECT 1.25mm Axial
A 284
S RATNAVATHI
VIZAG SPECIALITY HOSPITAL
F 49 UMRV 916
Ex:Dec 31 2020
Ex:2477
Se:5
I: 411.2
Im:255
DFOV41.4cm
SOFT
R
L
222
192
1.25
kV 120
mA375
Rot 0.70s/HE 27.5mm/rot
1.2mm 1.375:1 1.25sp
Tilt:0.0
08:12:44 AM
W =1500 L =-700
P 296


WB PET VPHD<->WB CECT 1.25mm Axial
S RATNAVATHI
VIZAG SPECIALITY HOSPITAL
F UMRV 916
Ex:Dec 31 2020
Ex:50% 2477 / 50% 2477
Se:14 / 5
I: 410.3
Im:99
DFOV45.2cm
10.00
R
L
242
210
0.00
Not valid
3.2
50 % PET
3.2mm/3.2sp
08:13:43 AM
m=0.00 M=10.00g/ml
P 325
V=1.20

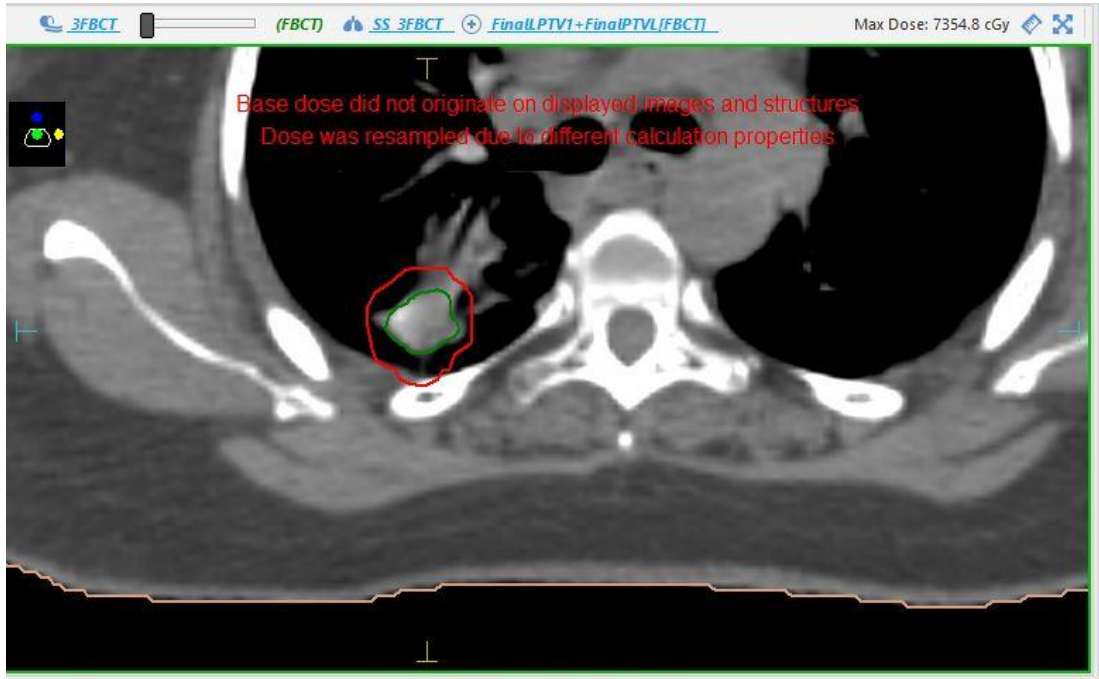

3FBCT
(FBCT)
SS 3FBCT
FinalLPTV1+FinalPTVL[FBCT]
Max Dose: 7354.8 cGy
Base dose did not originate on displayed images and structures
Dose was resampled due to different calculation properties
Base dose did not originate on displayed structures
Dose was resampled due to different calculation properties
3FBCT
(FBCT)
SS 3FBCT
FinalLPTV1+FinalPTVL[FBCT]
Max Dose: 7354.8 cGy
Base dose did not originate on displayed images and structures
Dose was resampled due to different calculation properties
3FBCT
(FBCT)
SS 3FBCT
FinalLPTV1+FinalPTVL[FBCT]
Max Dose: 7354.8 cGy
Base dose did not originate on displayed images and structures
Dose was resampled due to different calculation properties

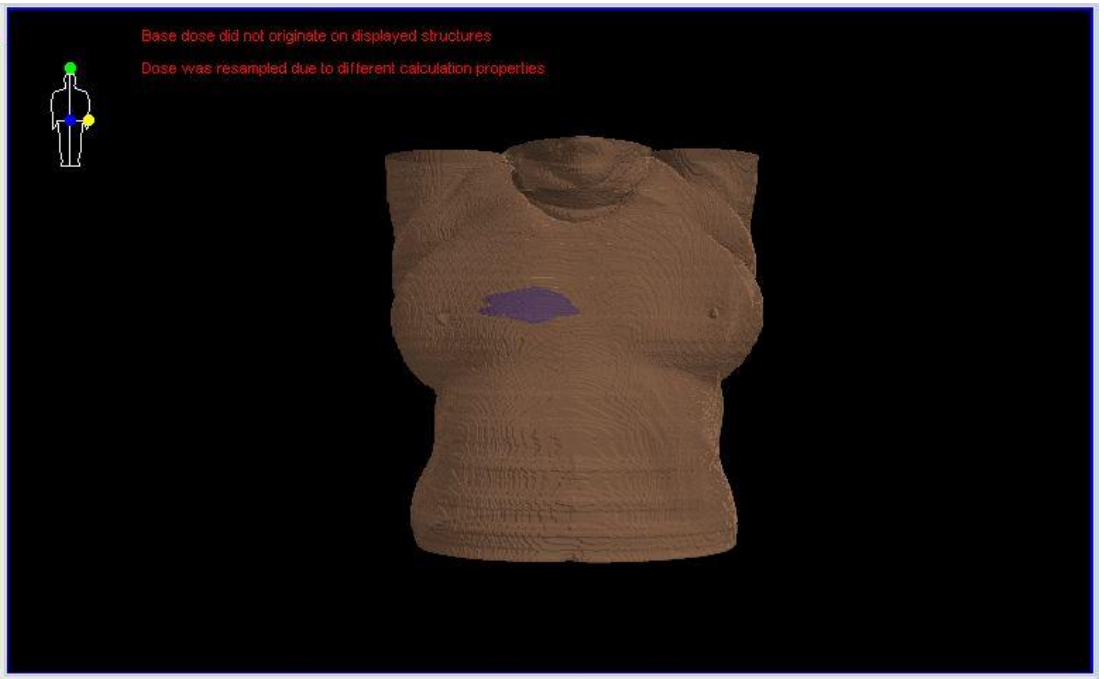
Reirradiation of the Thorax

- Feasibility of treating with curative intent depends on site of primary (P) and recurrent (R) tumors



- Advanced treatment techniques are particularly useful for sparing normal tissue (e.g., IMRT, SBRT, protons)
  - Reirradiating central structures (e.g., esophagus, airway) most challenging
  - Long-term toxicity is the major concern – impacted by dose/fraction


3FBCT
(FBCT)
SS 3FBCT
FinalLPTV1+FinalPTVL[FBCT]
Max Dose: 7354.8 cGy
Base dose did not originate on displayed images and structures
Dose was resampled due to different calculation properties

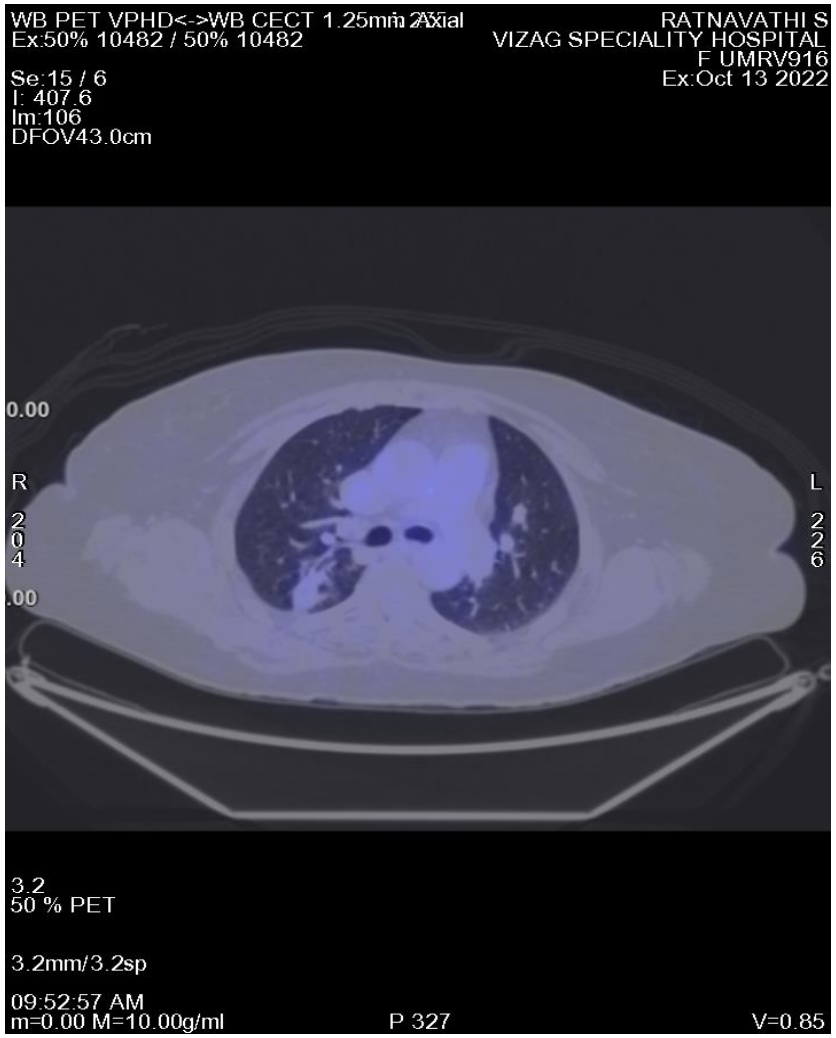

Base dose did not originate on displayed structures
Dose was resampled due to different calculation properties

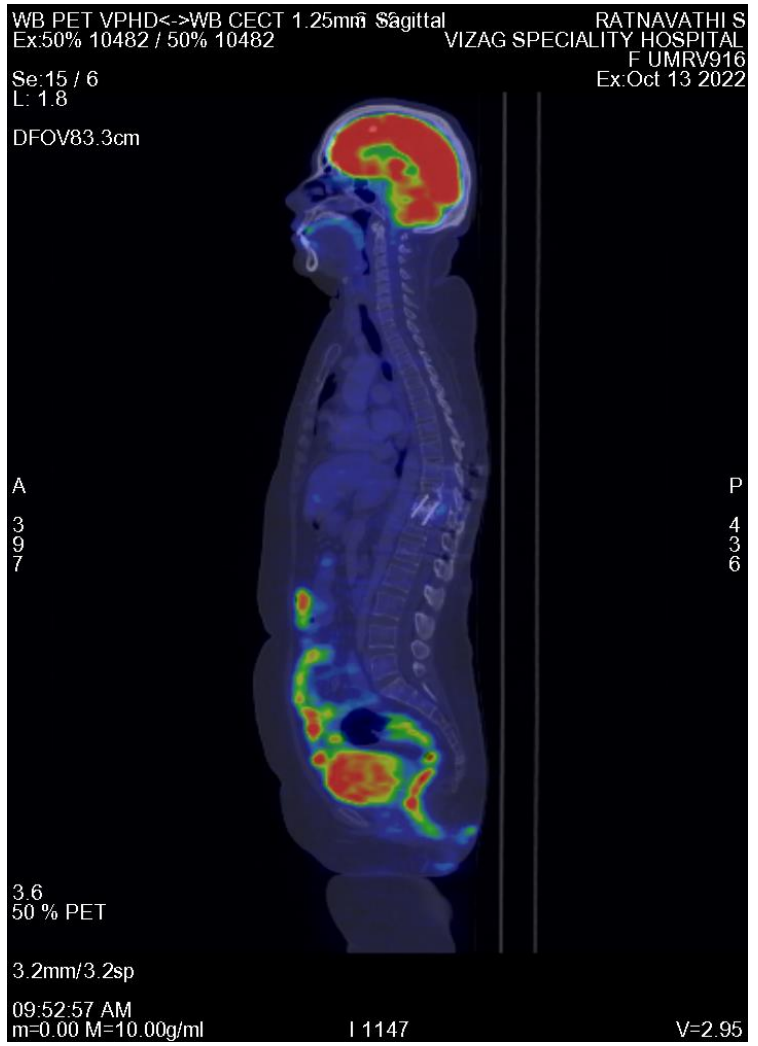

3FBCT
(FBCT)
SS 3FBCT
FinalLPTV1+FinalPTVL[FBCT]
Max Dose: 7354.8 cGy
Base dose did not originate on displayed images and structures
Dose was resampled due to different calculation properties

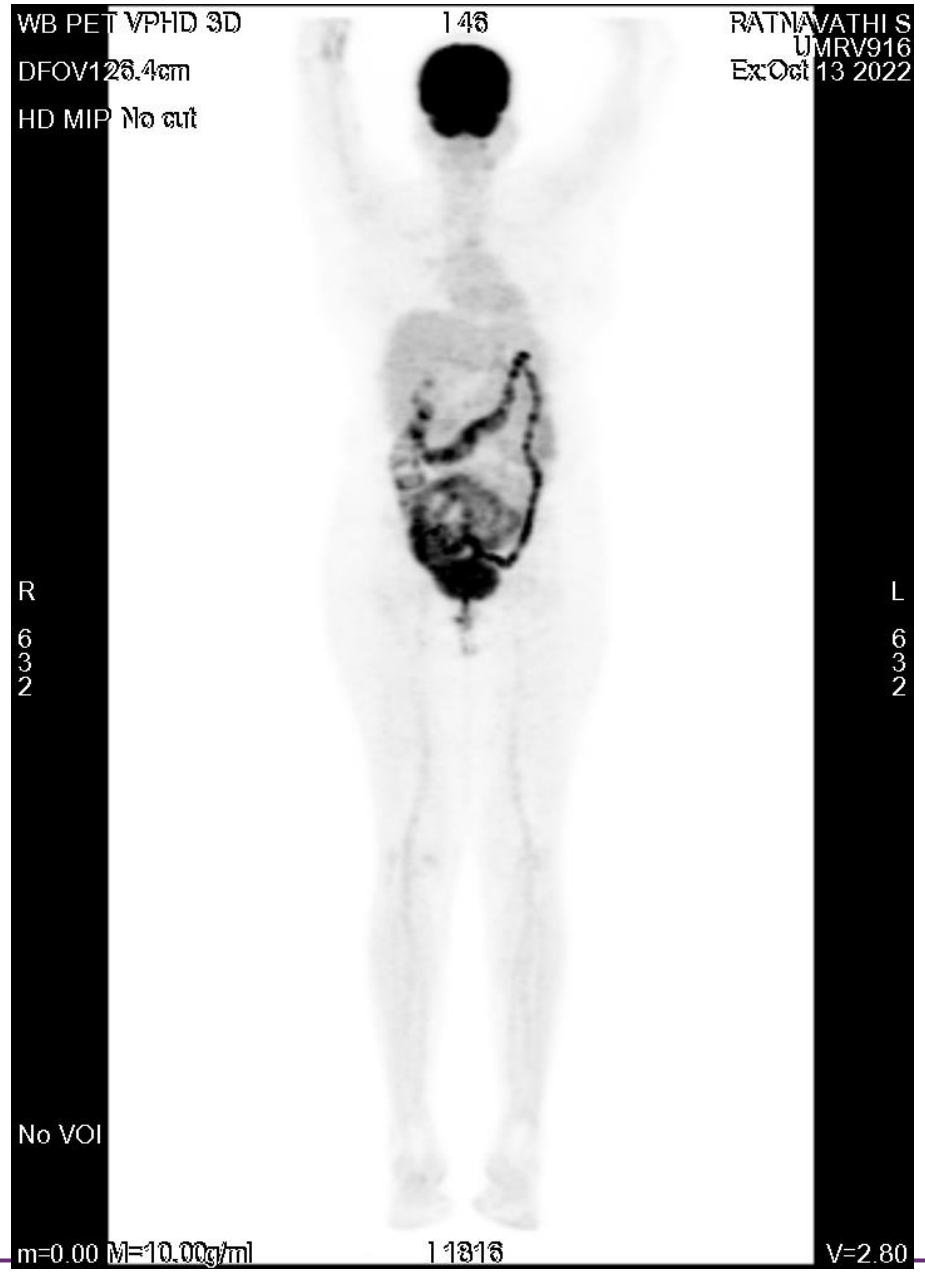

3FBCT
(FBCT)
SS 3FBCT
FinalLPTV1+FinalPTVL[FBCT]
Max Dose: 7354.8 cGy
Base dose did not originate on displayed images and structures
Dose was resampled due to different calculation properties

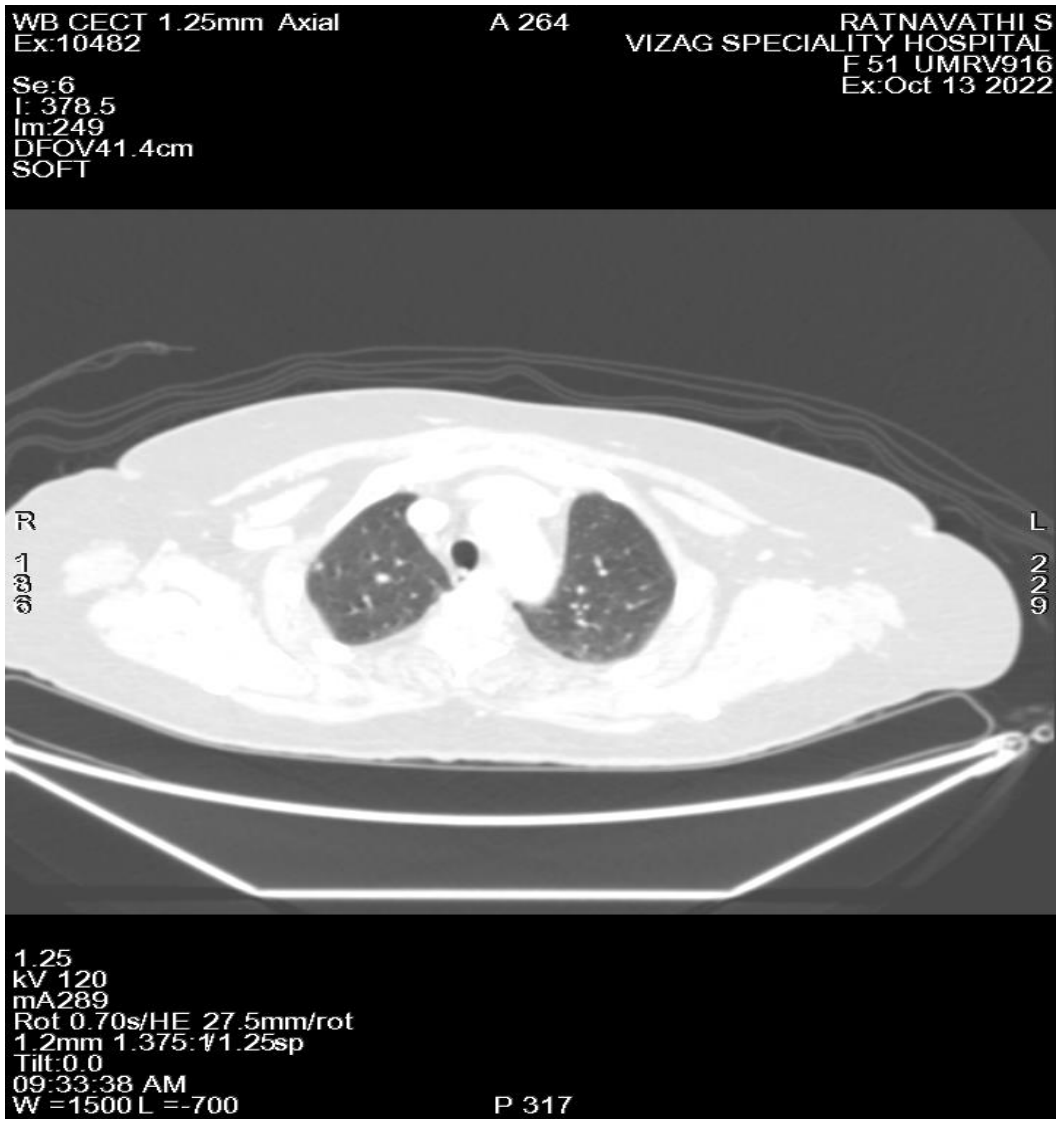
- **20 Gy in 4 #**

Oct 2022


WB PET VPHD<->WB CECT 1.25mm Axial
Ex:50% 10482 / 50% 10482
RATNAVATHI S
VIZAG SPECIALITY HOSPITAL
F UMRV916
Ex:Oct 13 2022
Se:15 / 6
I: 407.6
Im:106
DFOV43.0cm
0.00
R
L
2
0
4
.00
2
2
6
3.2
50 % PET
3.2mm/3.2sp
09:52:57 AM
m=0.00 M=10.00g/ml
P 327
V=0.85


WB PET VPHD<->WB CECT 1.25mm Sagittal
Ex:50% 10482 / 50% 10482
RATNAVATHI S
VIZAG SPECIALITY HOSPITAL
F UMRV916
Ex:Oct 13 2022
Se:15 / 6
L: 1.8
DFOV83.3cm
A
P
3
9
7
4
3
6
3.6
50 % PET
3.2mm/3.2sp
09:52:57 AM
m=0.00 M=10.00g/ml
I 1147
V=2.95


WB PET VPHD 3D
146
RATNAVATHI S
UMRV916
DFOV126.4cm
Ex:Oct 13 2022
HD MIP No cut
R
6
3
2
L
6
3
2
No VOI
m=0.00 M=10.00g/ml
11816
V=2.80


WB CECT 1.25mm Axial
A 264
Ex:10482
RATNAVATHI S
VIZAG SPECIALITY HOSPITAL
F 51 UMRV916
Ex:Oct 13 2022
Se:6
I: 378.5
Im:249
DFOV41.4cm
SOFT
R
L
1.25
kV 120
mA289
Rot 0.70s/HE 27.5mm/rot
1.2mm 1.375:1/1.25sp
Tilt:0.0
09:33:38 AM
W =1500 L =-700
P 317

While Execution

- SBRT
- Daily CBCT
- 4D CBCT for >1 cm motion tumors
- Hypo
- CBCT on day 1
- 4D CBCT for >1 cm motion
- Daily CBCT if PTV is close