4D Radiotherapy in early ca Lung

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Presentation focus on ----

- Limitation of Conventional RT
- Why Interest in early lung cancer Radiation
- Problem of moving tumor
- How to overcome it?
- Technique of 4D Radiation in ca Lung

Ca Lung

- Lung cancer frequent cause of cancer death
- 15-20% early stage (may increase with adoption of spiral CT for widespread screening)
- Surgery treatment of choice for stage I & II NSCLC
- Many pts not suitable for surgery due to poor lung functions or other co-morbidities

Management

- Management is based on disease stage

Stage groupings of TNM subsets			
Stage IA	T1	N0	M0
Stage IB	T2	N0	M0
Stage IIA	T1	N1	M0
Stage IIB	T2	N1	M0
	T3	N0	M0
Stage IIIA	T3	N1	M0
	T1-3	N2	M0
Stage IIIB	Any T	N3	M0
	T4	Any N	M0
Stage IV	Any T	Any N	M1

Adapted from: AJCC Cancer Staging Manual, 6th edition, New York, 2002.

- Stage I-II: early stage
- Stage IIIA: locally advanced (surgery feasible)
- Stage IIIB: locally advanced (surgery not feasible)
- Stage IV: metastatic disease

Management of Stage I + II NSCLC

-*Surgery alone is the standard treatment choice !*

-Lobectomy: optimal procedure

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

-No randomized trials, but excellent results

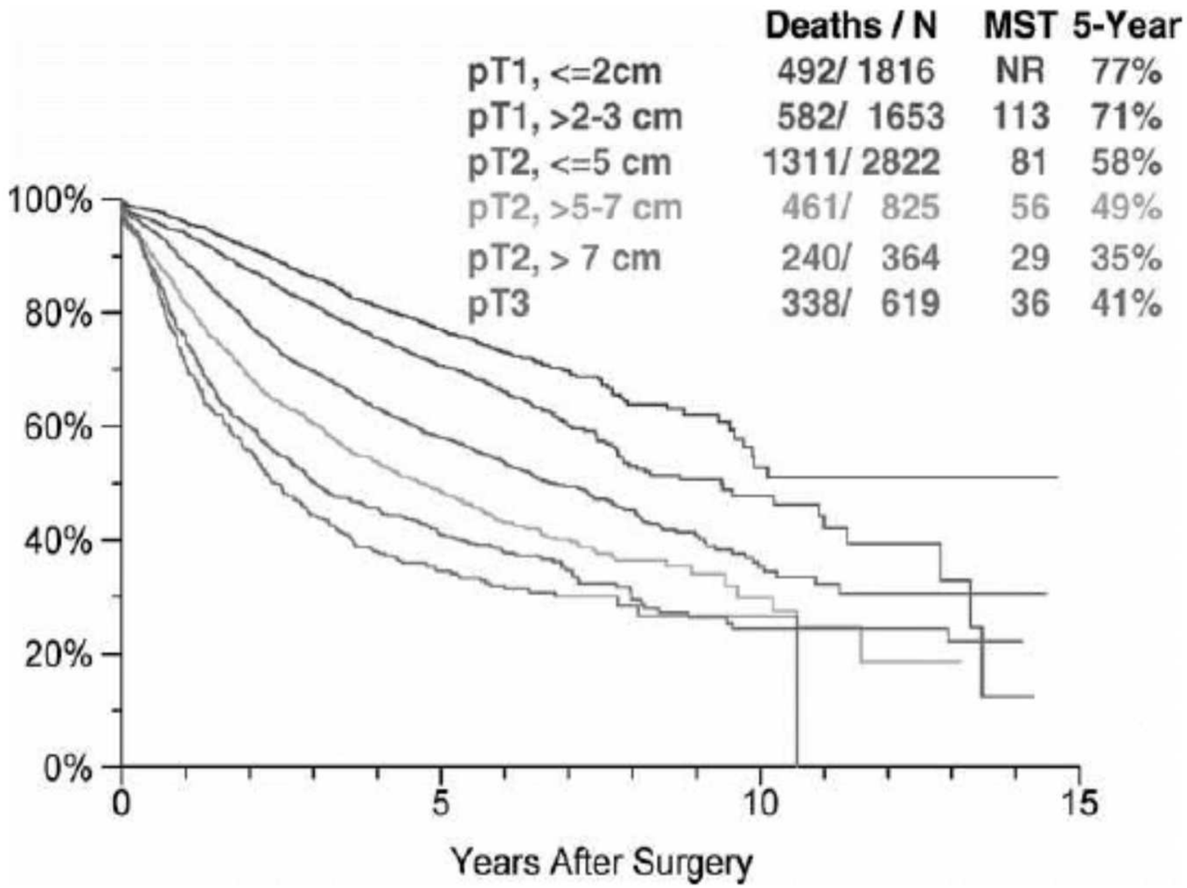
-Adjuvant Cisplatin-based CCT for stage II

for stage IB data is conflicting

-No adjuvant radiotherapy after radical surgery (i.e. R0)

Survival in resected stage I NSCLC

Rami-Porta R,2007



Overall survival for pT1-, pT2-, or pT3 pN0 R0 tumors (UICC classification)

RT in stage I+II NSCLC

- In recent past, there has been a resurgence in the role of radiation in early stage NSCLC because of the availability of newer technology of delivering precise radiation to the area of interest.

RT in stage I+II NSCLC

- **NOT FIT FOR RADICAL SURGERY**
  - OLD PTS
  - BAD LUNG eg EMPHYSEMA
  - MEDICALLY NOT FIT FOR SURGERY BECAUSE OF COMORBIDITY.

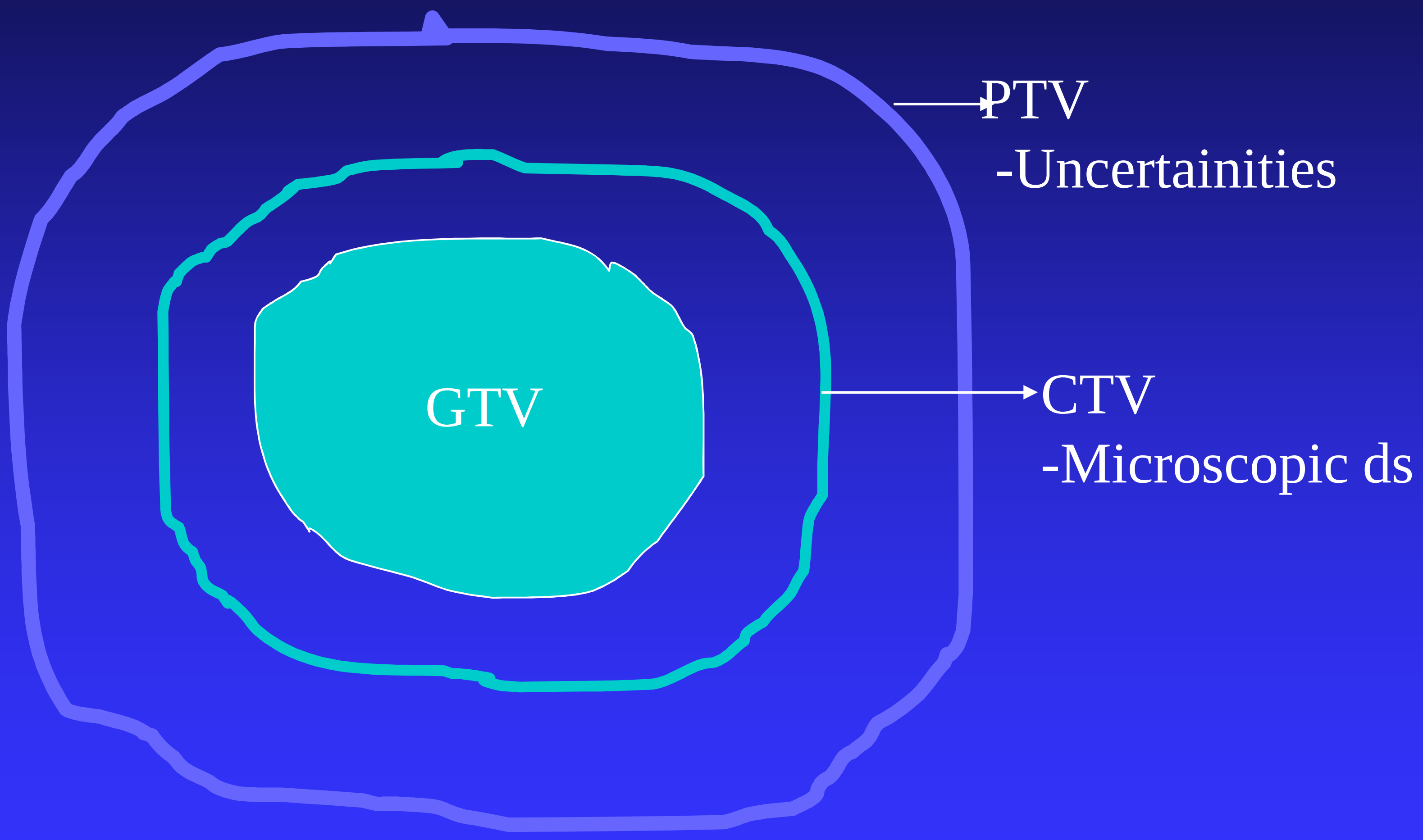
Conventional RT

- Results of conventional RT
  - Primary RT has inferior results compared to surgery
  - Dose escalation at cost of higher toxicity with still high rate of local failure

WHY???

- To find out the answer of BIG WHY? We need to understand the basic principal of radiotherapy planning

RT Planning



CTV (Microscopic Disease)

- ***To give adequate margins around GTV, we should have good understanding of pattern of local spread of ca lung.***

RT-Planning

1. Margin around primary tumour (microscopic spread)

Histopathologic quantification of subclinical cancer around the grossly visible primary (Giraud 2000):

Microscopic extension	**Adeno**	**Squamos**
mean value	2.69mm	1.48mm
5mm margin covers:	80%	91%
margin to cover 95%	**8mm**	**6mm**

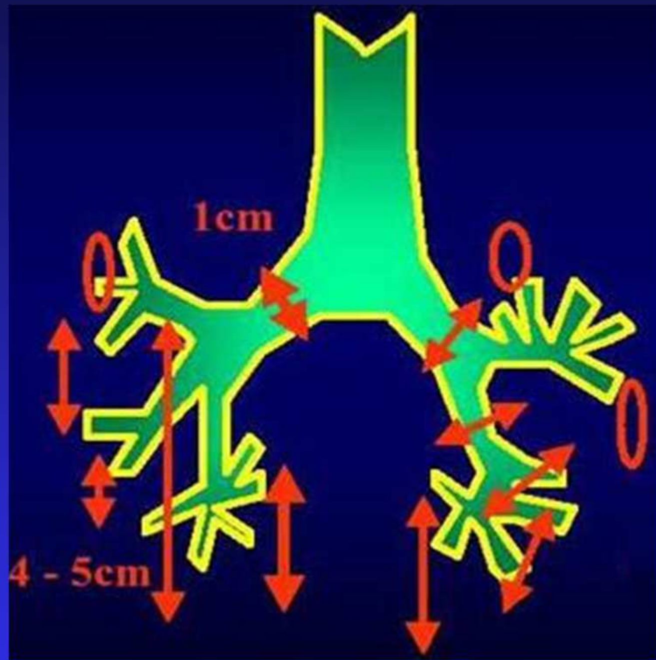
PTV (Uncertainty)

- One of the important reason of uncertainty in ca lung is motion of the tumor during respirations

Tumor Movement

Size of movement dependent on:
- tumour location in the lung
- fixation to adjacent structures
- lung capacity and oxygenation
- patient fixation and anxiety

Average movement in normal breathing:
- Upper lobe 0 - **0.5**cm
- Lower lobe 1.5 - **4.0**cm
- Middle lobe 0.5 - **2.5**cm
- Hilum 1.0 - **1.5**cm



Steppenwoolde 2004

PROBLEM WITH PTV

- PTV margins irradiate only normal tissue and led to--------
  - More complications (Pneumonitis)
  - Difficult to escalate the doses(Under dosing)

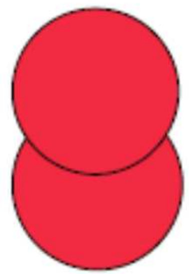
Conventional RT

Inferior results with more toxicities

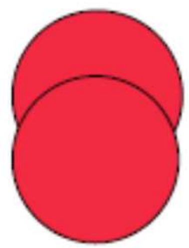
More the PTV more normal tissue RT

The problem of moving tumours

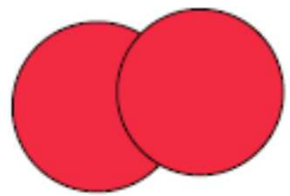
The problem of moving tumours



The problem of moving tumours



The problem of moving tumours



Movement

- How does the tumour shape and location change from day to day ?

Movement

- How does the tumour shape and location change from day to day ?

Inter-fractional

Movement

- How does the tumour shape and location change from day to day ?
- How does the tumour change during beam delivery ?

Inter-
fractional

Movement

- How does the tumour shape and location change from day to day ? — Inter-fractional
- How does the tumour change during beam delivery ? — Intra-fractional

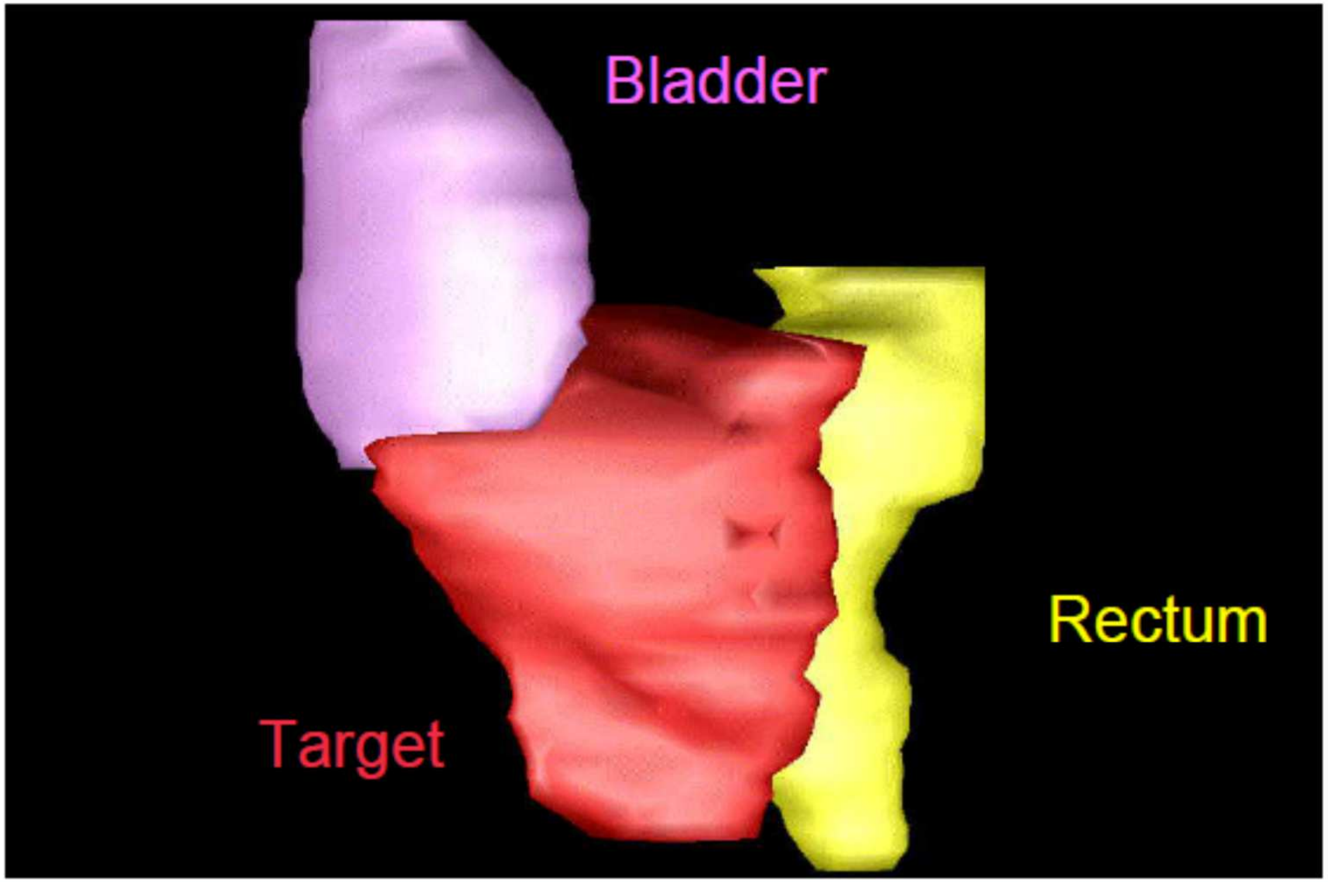
INTERFRACTION MOVEMENT

- POSITION MAY CHANGE EVERY DAY.
- REASONS ARE TWO:-
  - *DUE TO DISTENSABLE NORMAL ORGAN NEAR TARGET LIKE PROSTATE, CERVIX.*
  - *DUE TO SHRINKAGE OF TUMOR DURING TREATMENT.*

MOVEMENT DUE TO DISTENSIBLE NORMAL ORGAN NEAR THE TUMOR.

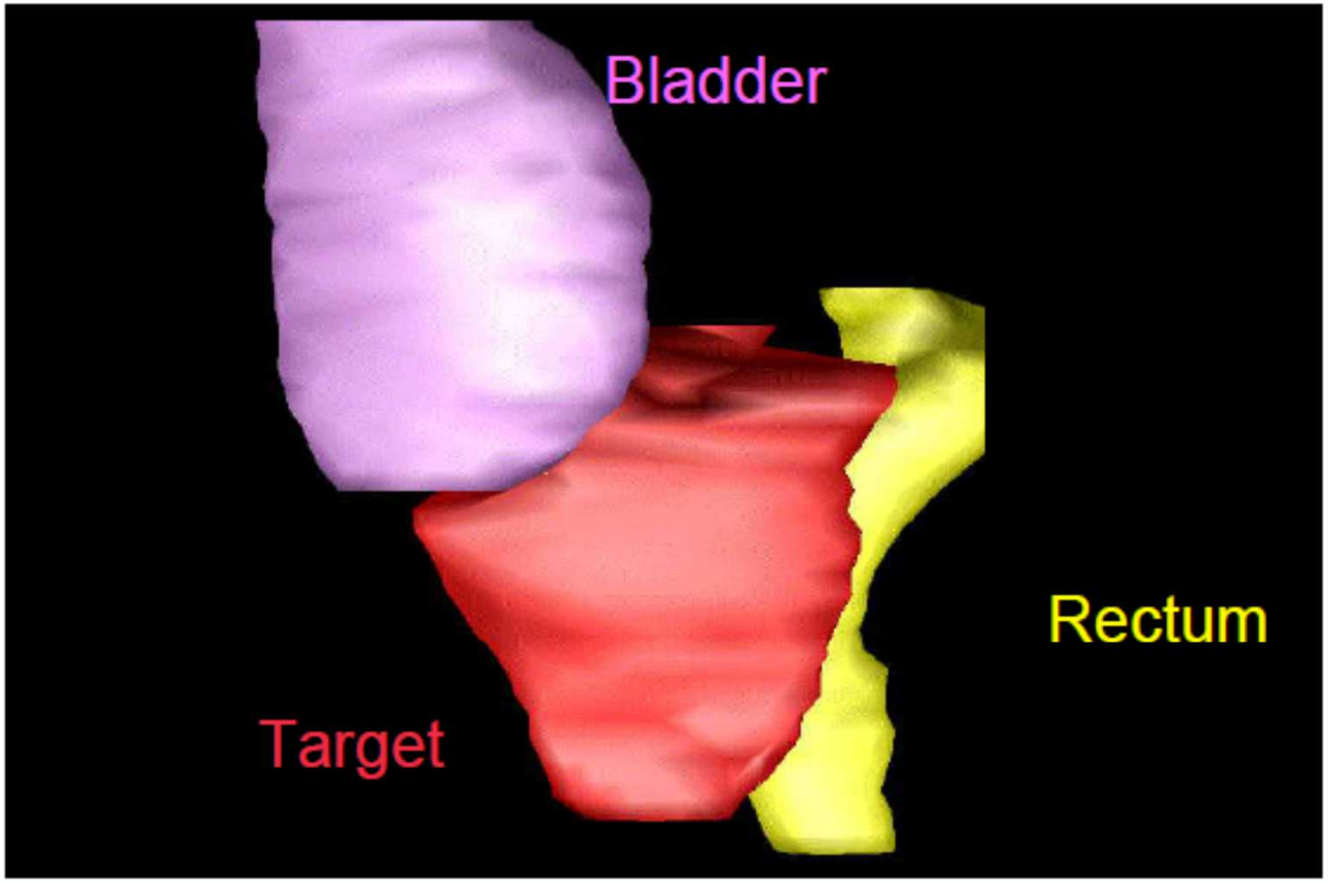
Movement

Example: Prostate – 1. Control - CT



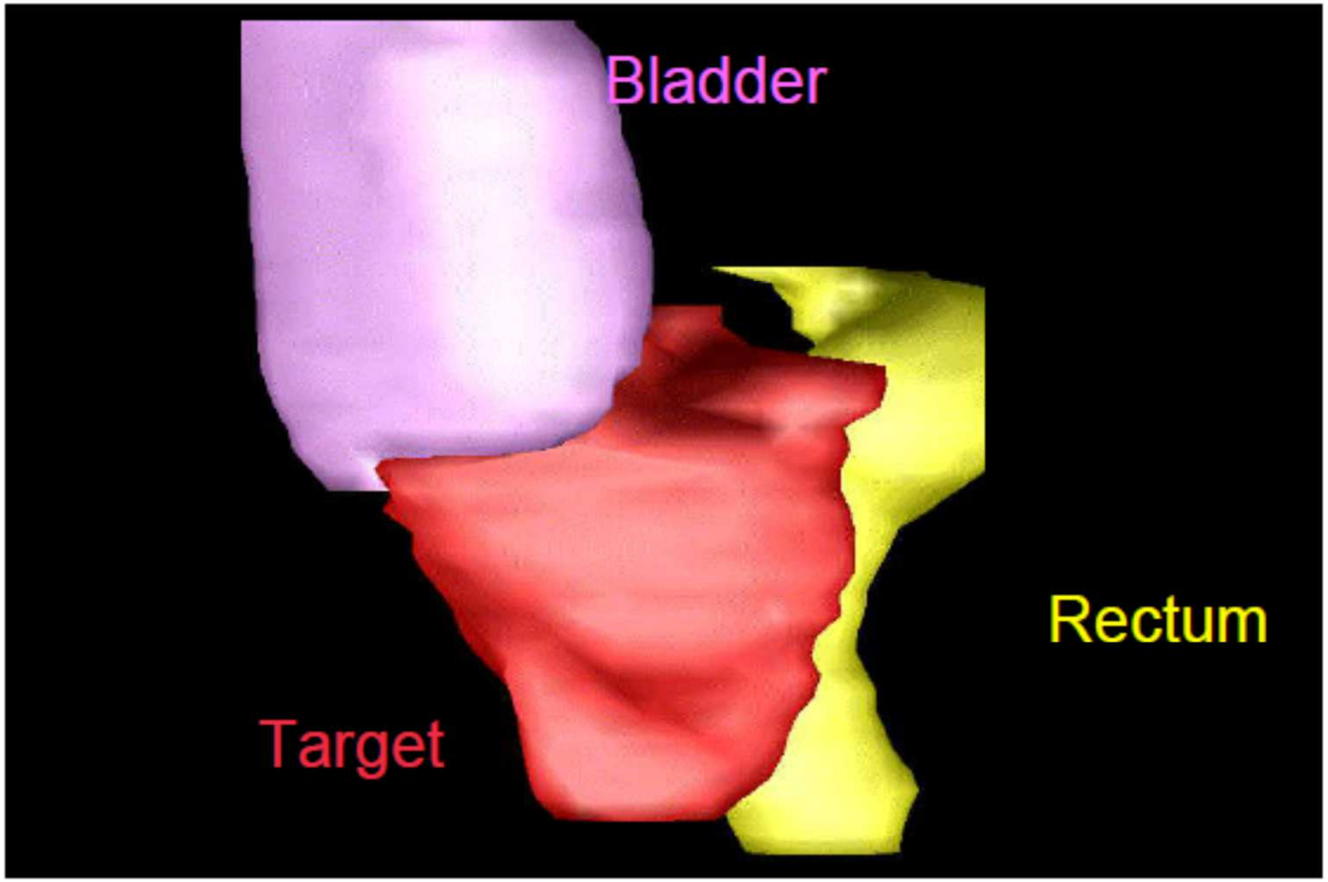
Movement

Example: Prostate – 2. Control - CT



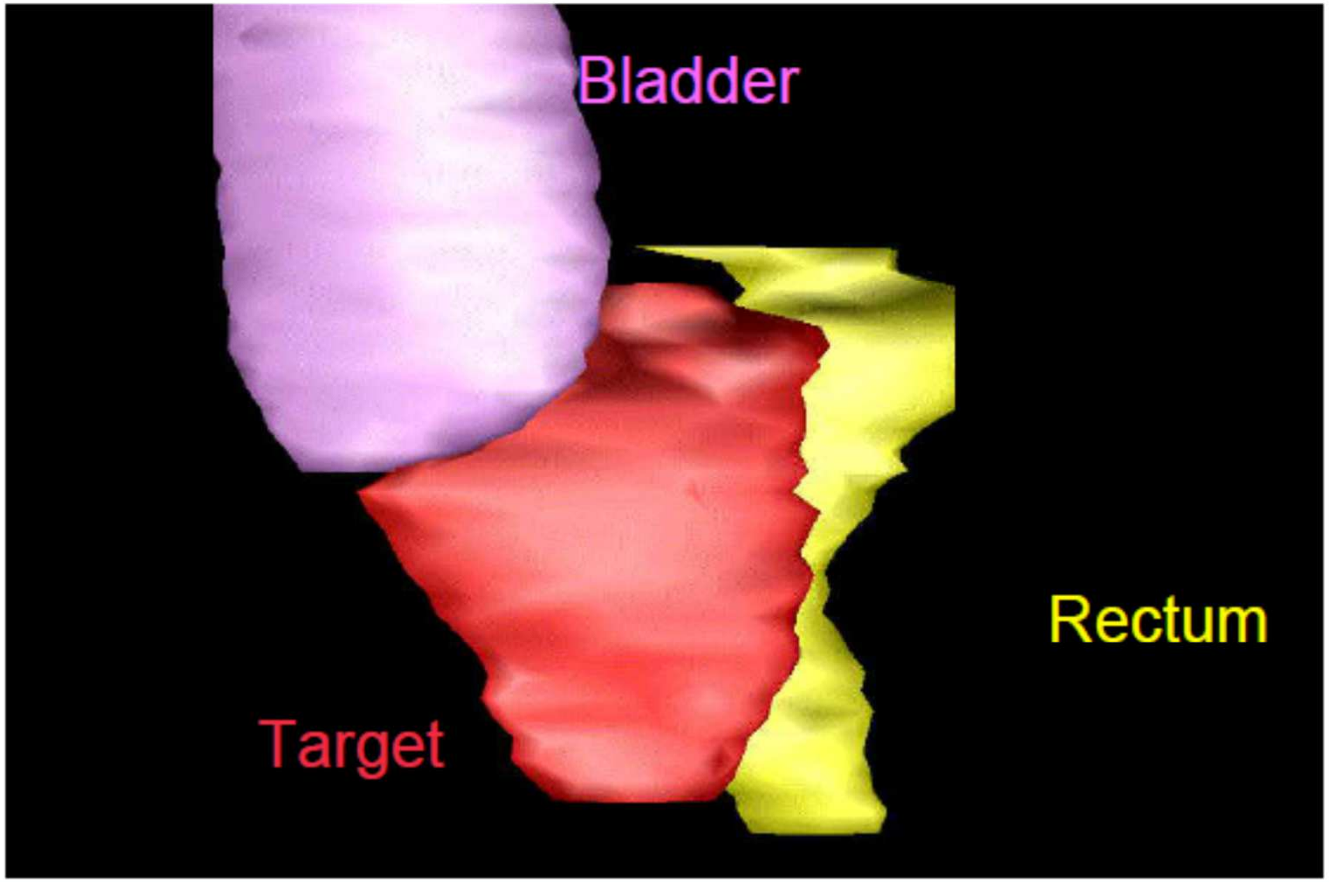
Movement

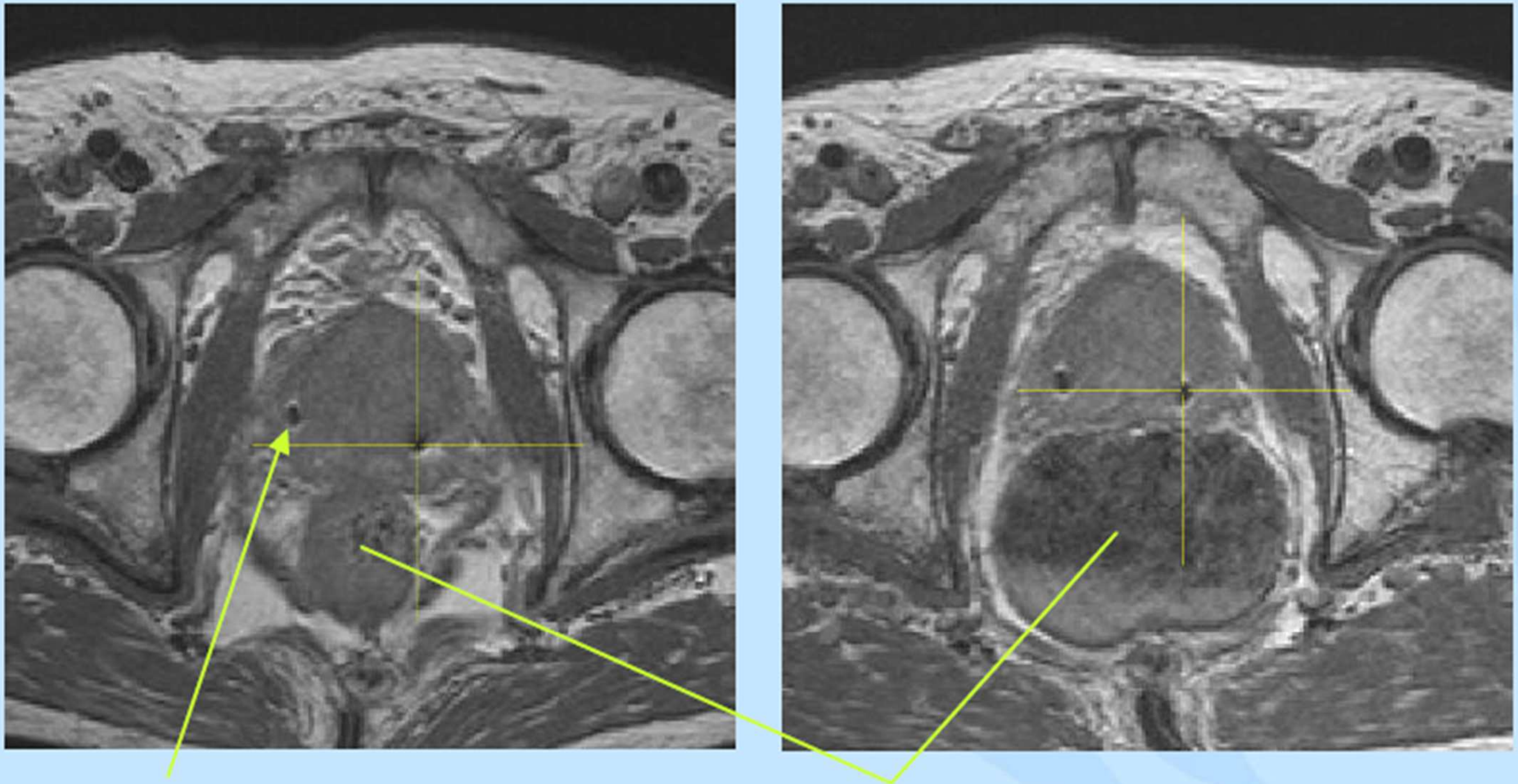
Example: Prostate – 3. Control - CT



Movement

Example: Prostate – 4. Control - CT





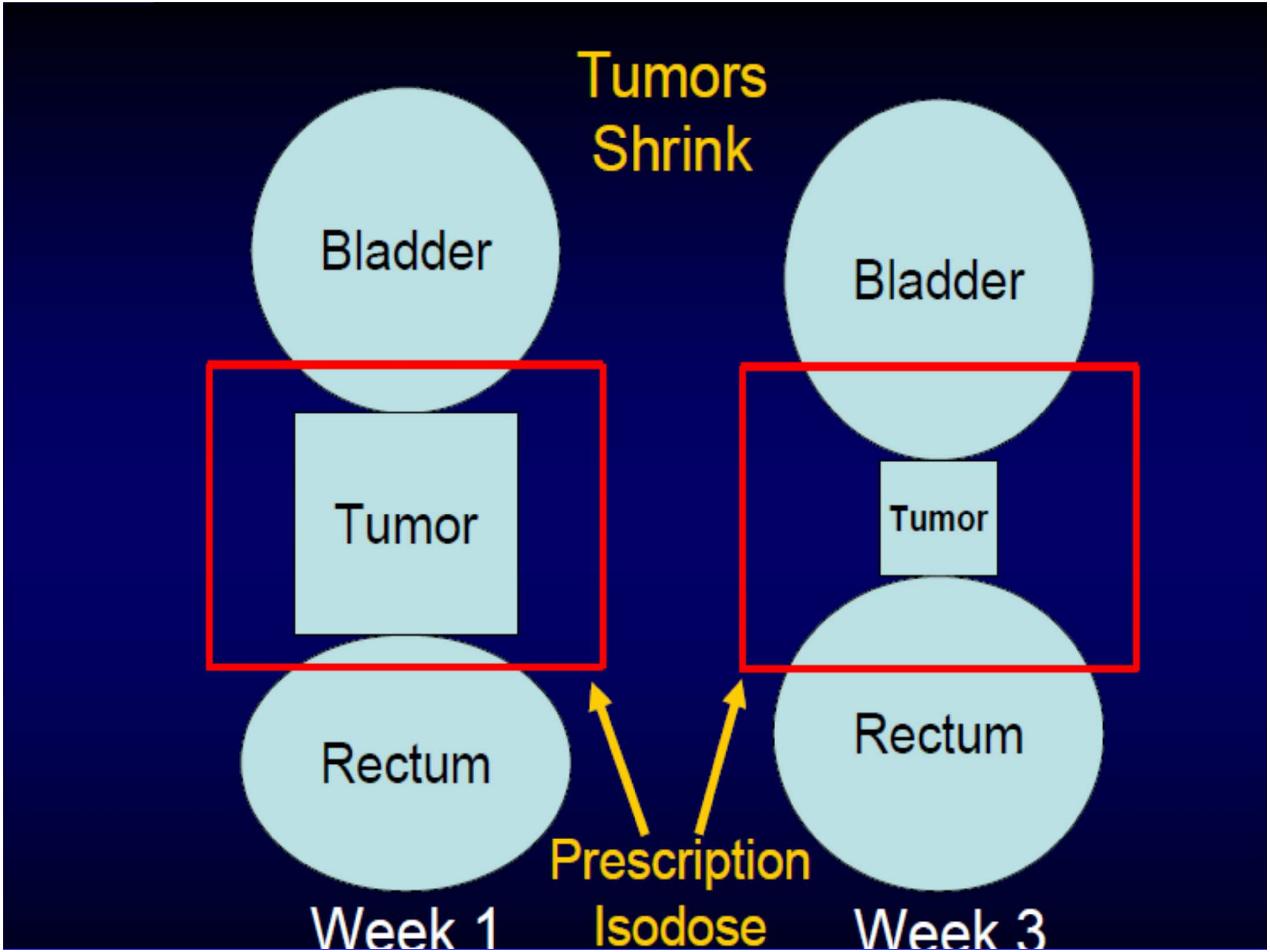
MRI compatible fiducial marker

Different rectum filling

T1 SE

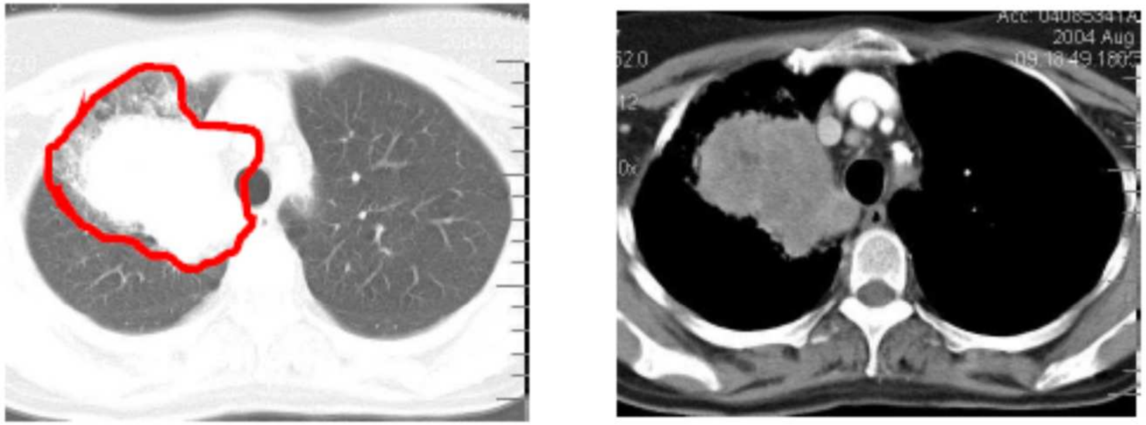
INTERFRACTION MOVEMENT

- DUE TO SHRINKAGE OF TUMOR DURING TREATMENT

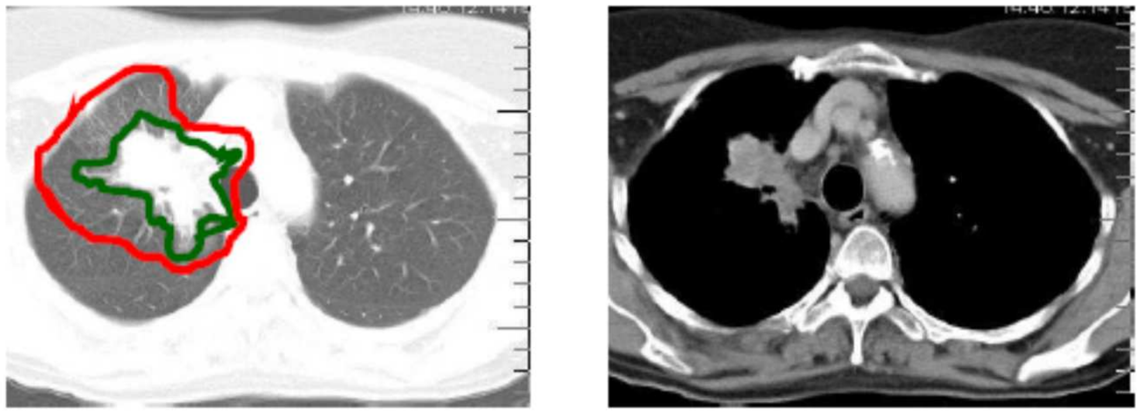

Tumors
Shrink
Bladder
Tumor
Rectum
Bladder
Tumor
Rectum
Prescription
Isodose
Week 1
Week 3

"Adaptive" radiotherapy: Risks of shrinking fields & PET-based dose painting

Pre-treatment



After 46 Gy

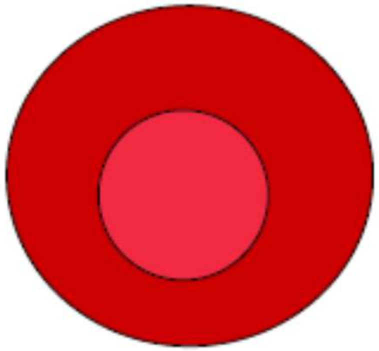


INTRAFRACTION MOVEMENT

- DUE TO RESPIRATION.
  - Mainly affect the ca lung and tumor of upper abdominal organ

Solution

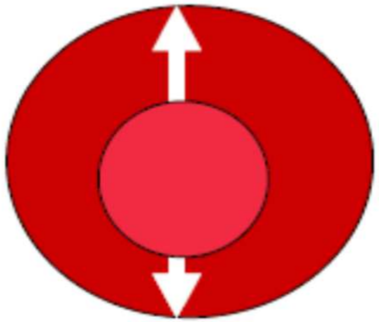
The problem of moving tumours



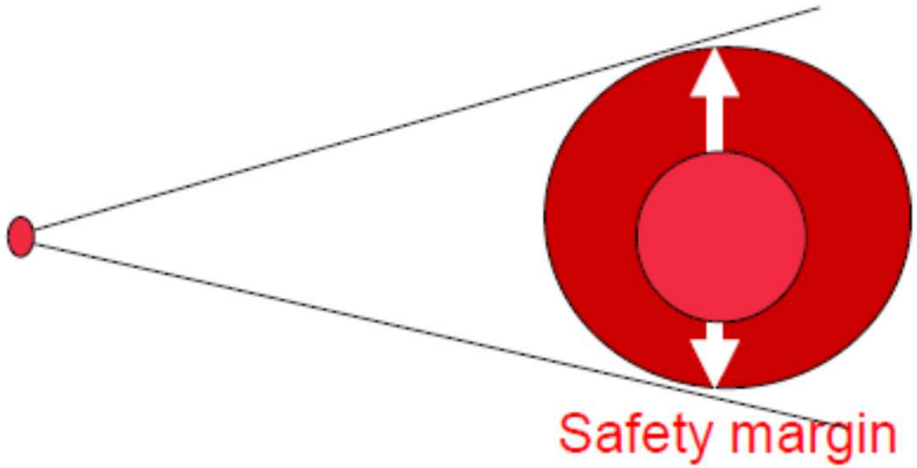
Safety margin

Solution

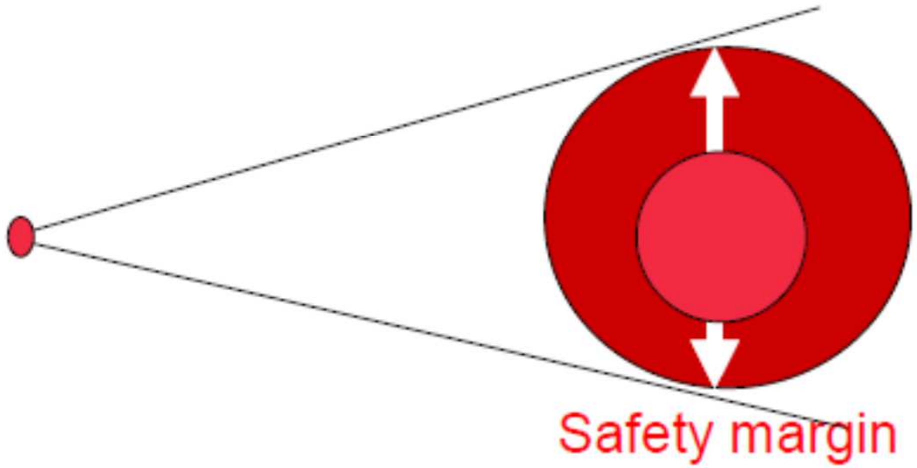
The problem of moving tumours



The problem of moving tumours



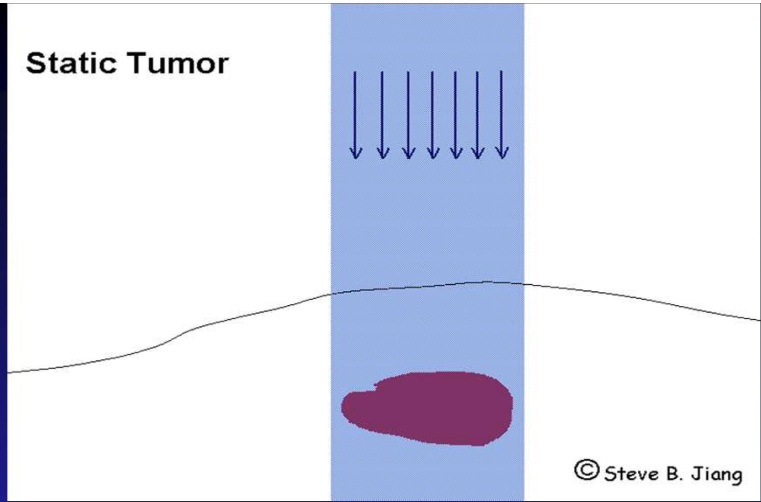
The problem of moving tumours

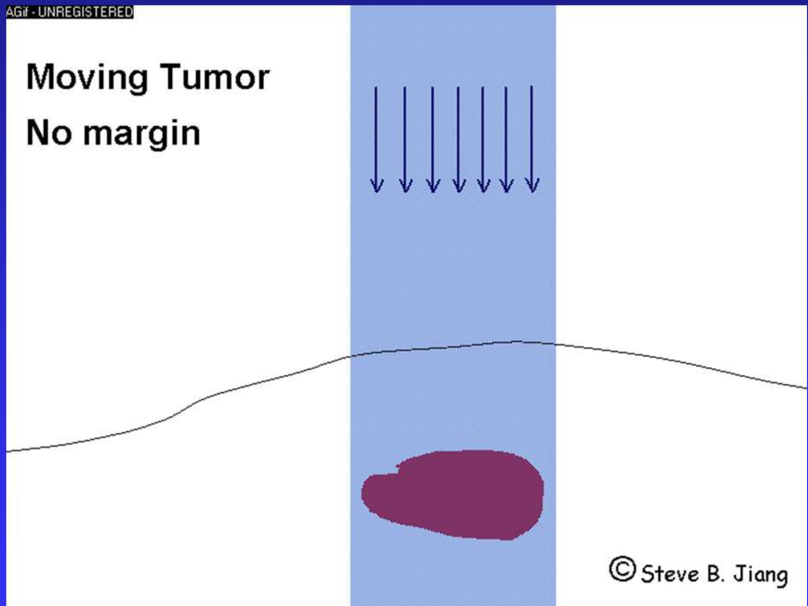


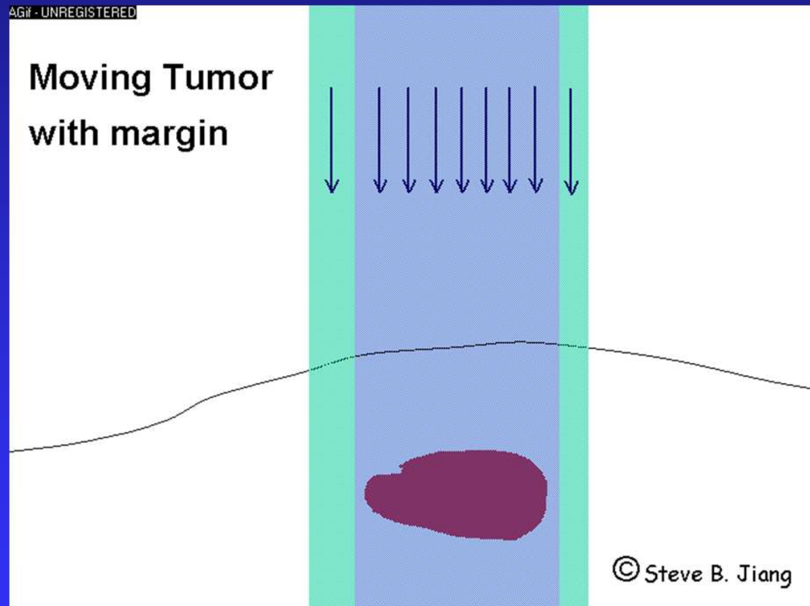
e.g.
1 cm tumour
with
3 cm movement

⬇

Irradiated volume increases by a factor of ~ 50 !!


Static Tumor
© Steve B. Jiang


AGif - UNREGISTERED
Moving Tumor
No margin
© Steve B. Jiang


AGif - UNREGISTERED
Moving Tumor
with margin
© Steve B. Jiang

BETTER SOLUTION

- If we minimizes these uncertainties, we can reduce the PTV margins and can put more tighter margins around CTV which allow us to-------------
  - Less normal tissue irradiation
  - Less complications
  - Escalate the dose to tumor

- How can we minimize the uncertainties of tumor movement during respiration.

ANSWER

- TREAT MOVING TARGET BY TRACKING

  GATED RADIOTHERAPY

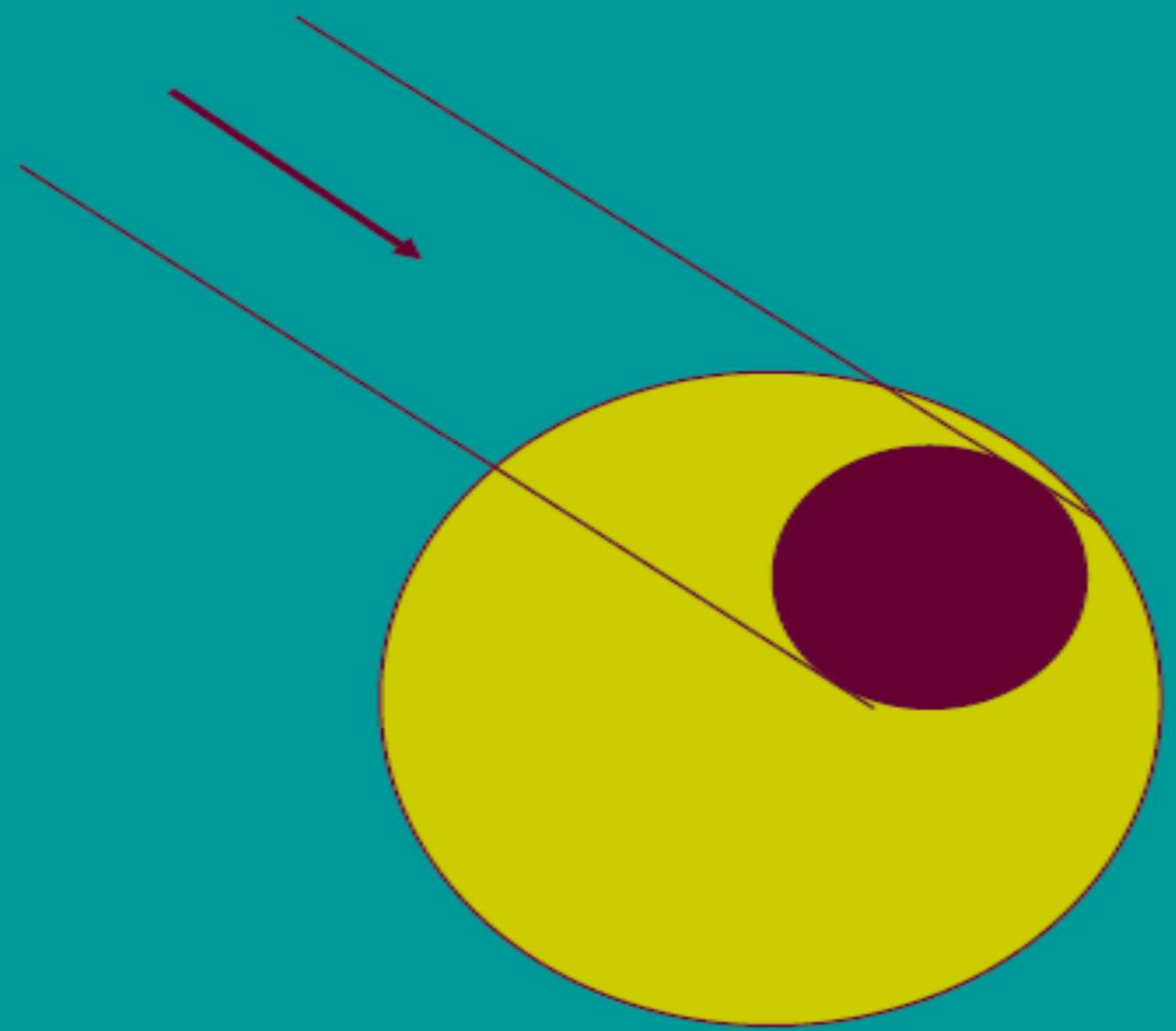
Gated Radiotherapy

- We evaluate the movement of the tumor in every patient and then treat accordingly

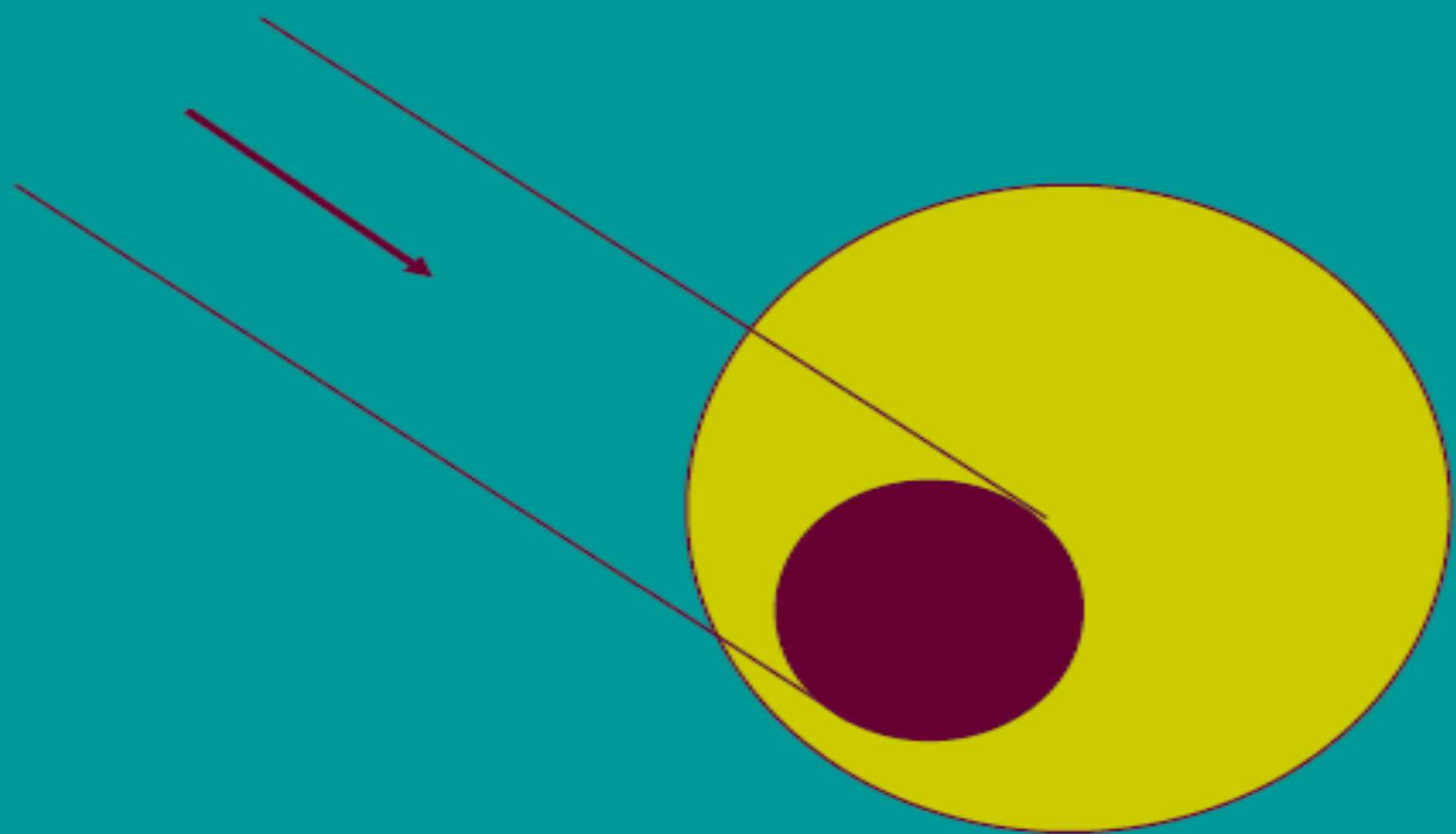
GATED RT

- TWO METHODS
  - BY CHASING AND TREATING THE MOVING TUMOR CONTINUOUSLY BY ROBOTIC ARM e.g.. **CYBER KNIFE**
  - BY TREATING MOVING TARGET AT A FIXED POSITION OF MOVEMENT.

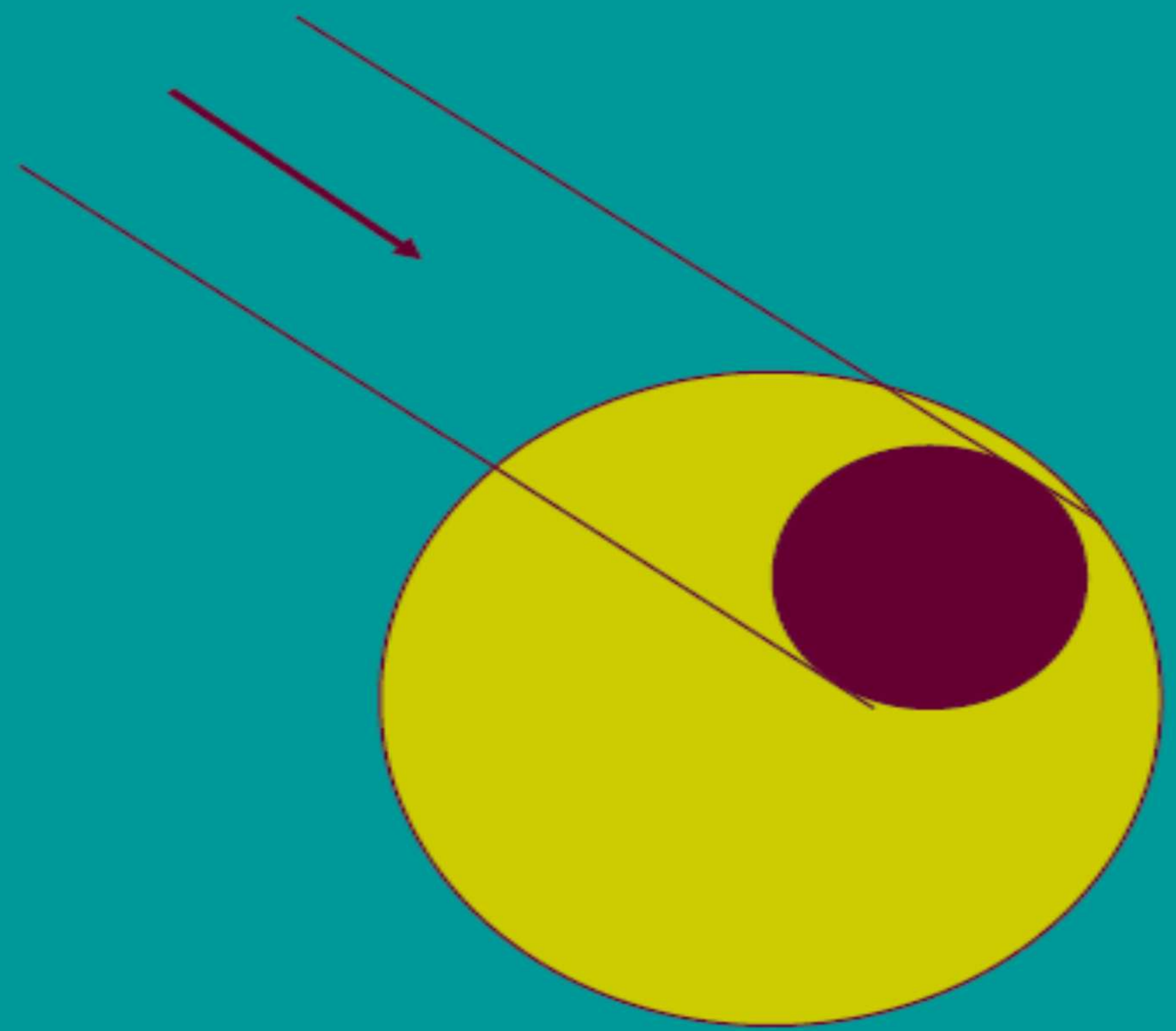
Robotic Arm



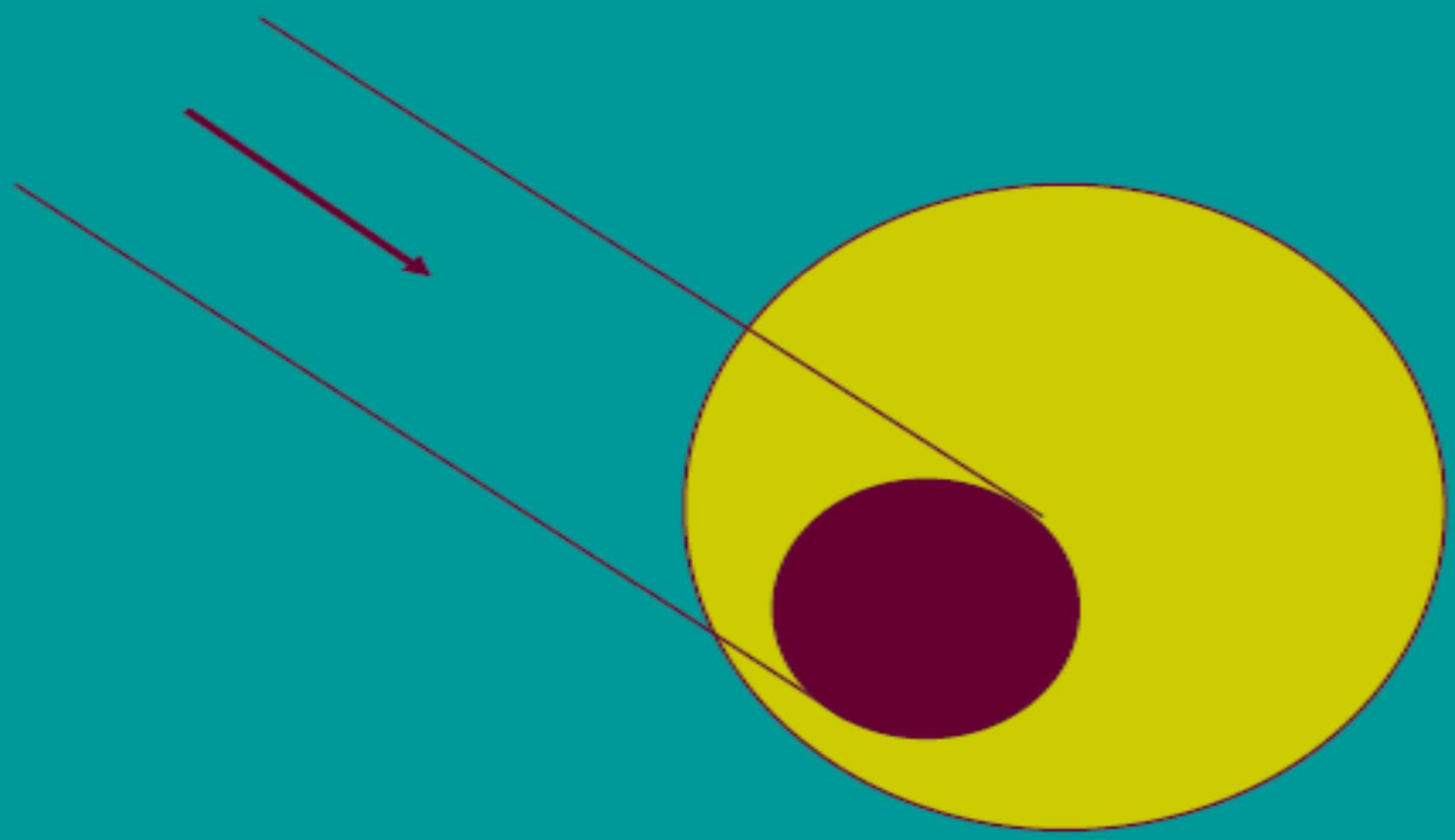
Robotic Arm



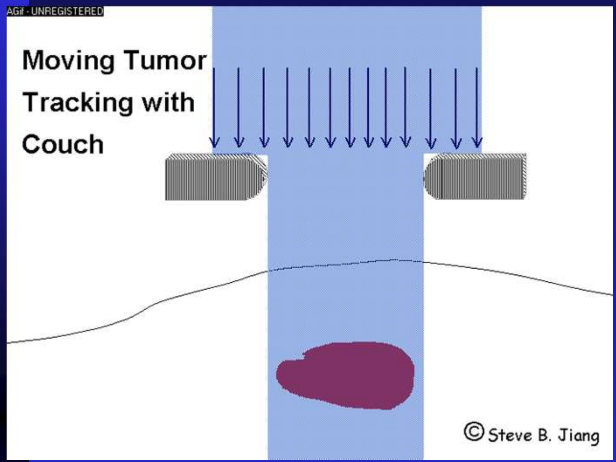
Robotic Arm

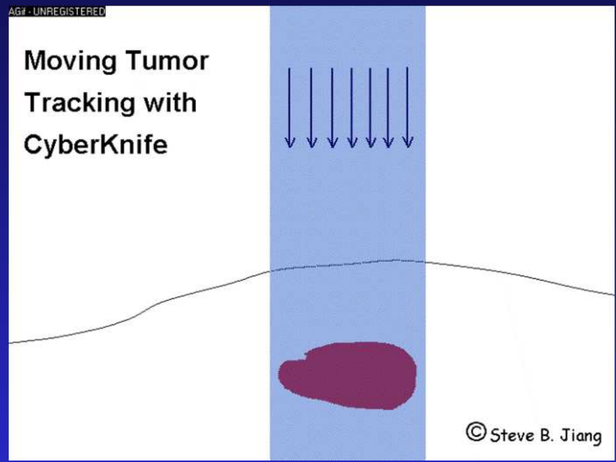


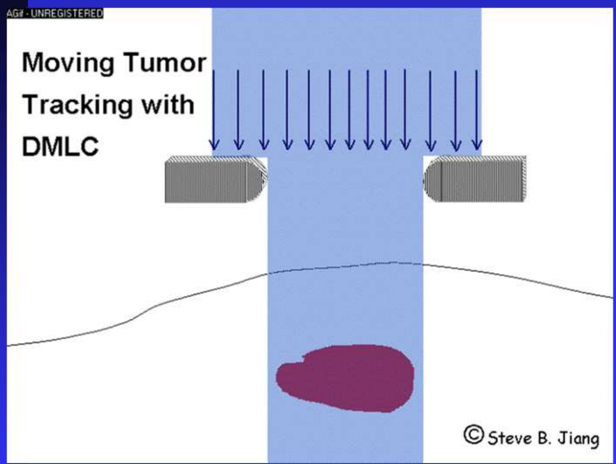
Robotic Arm

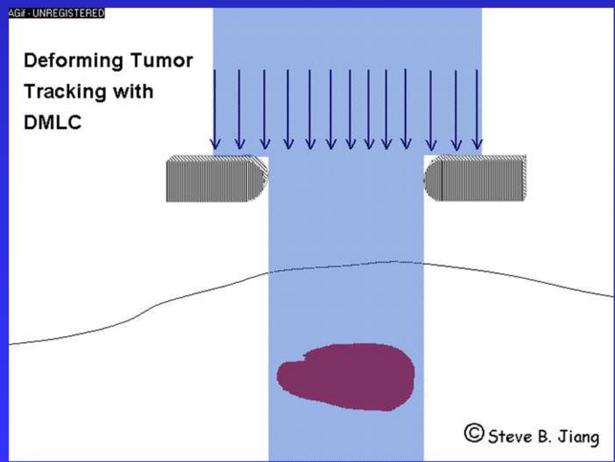


Methods of chasing the moving Tumor



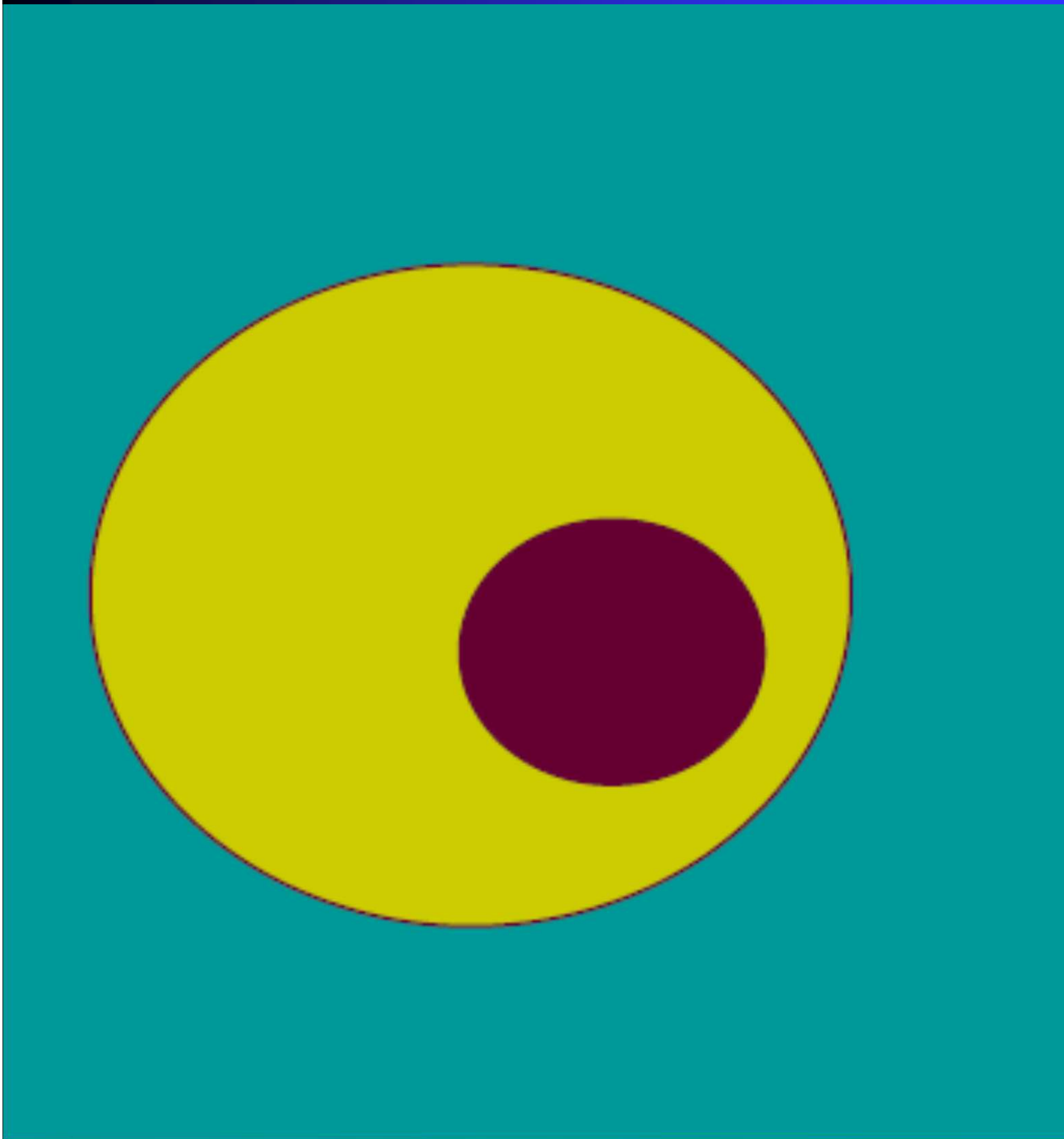


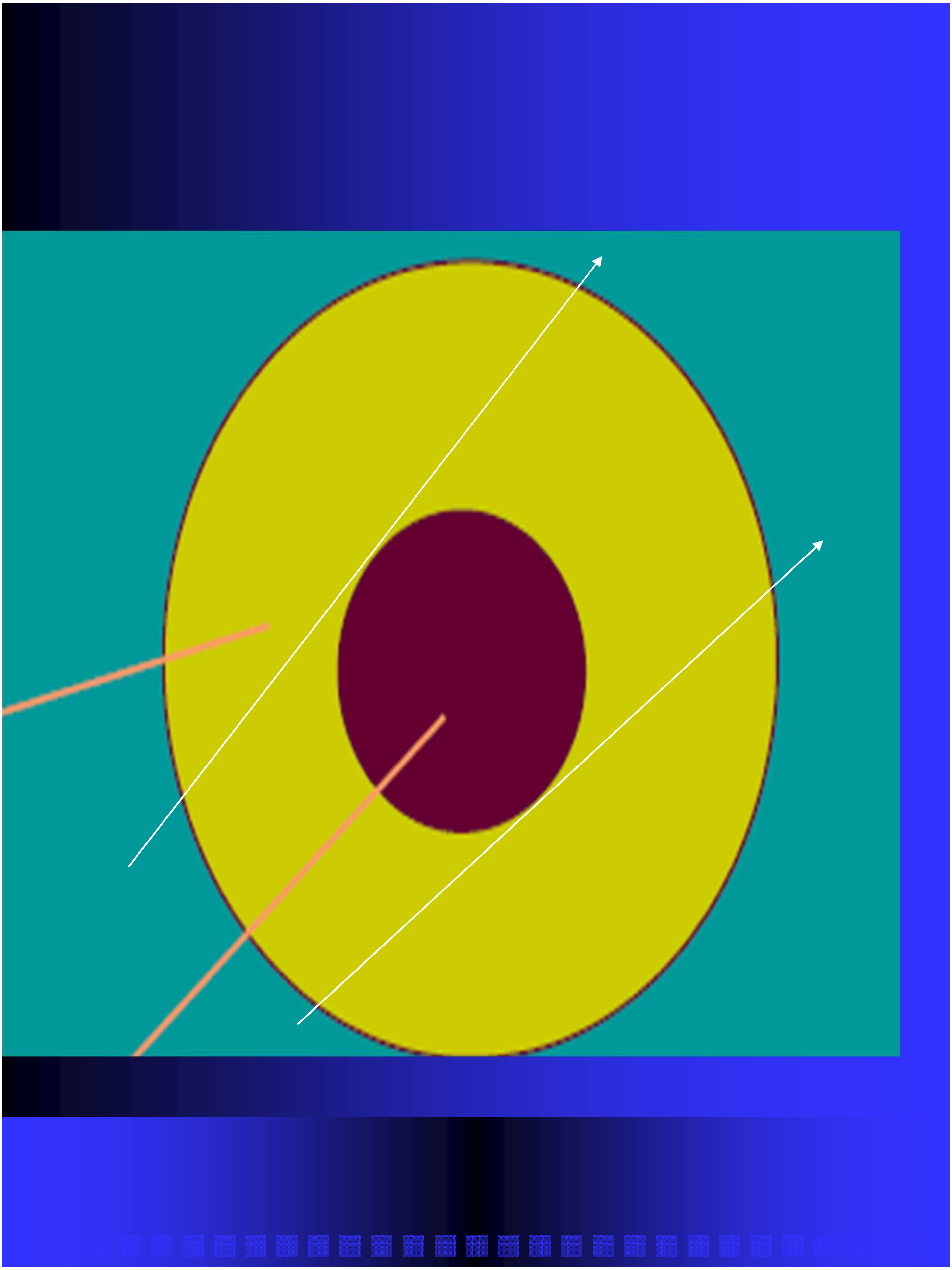


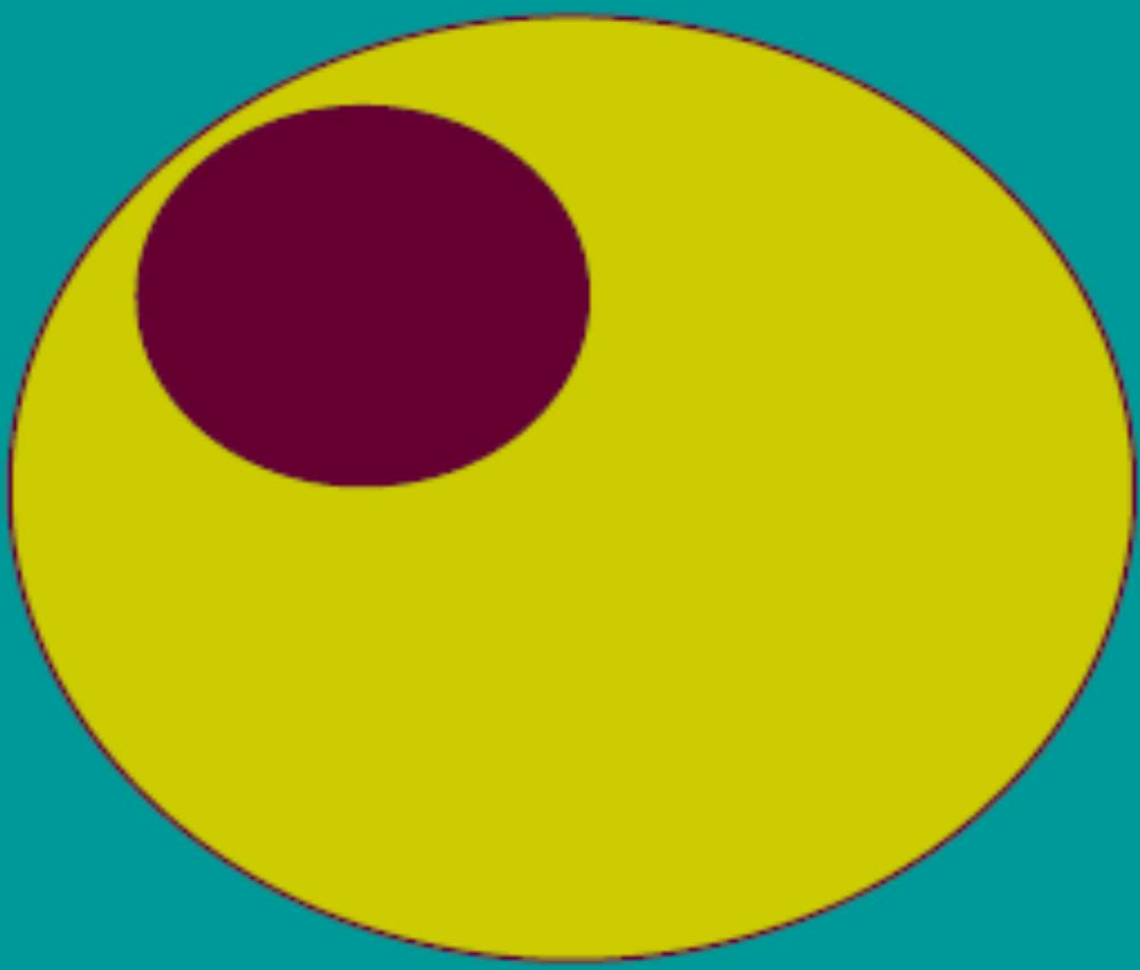


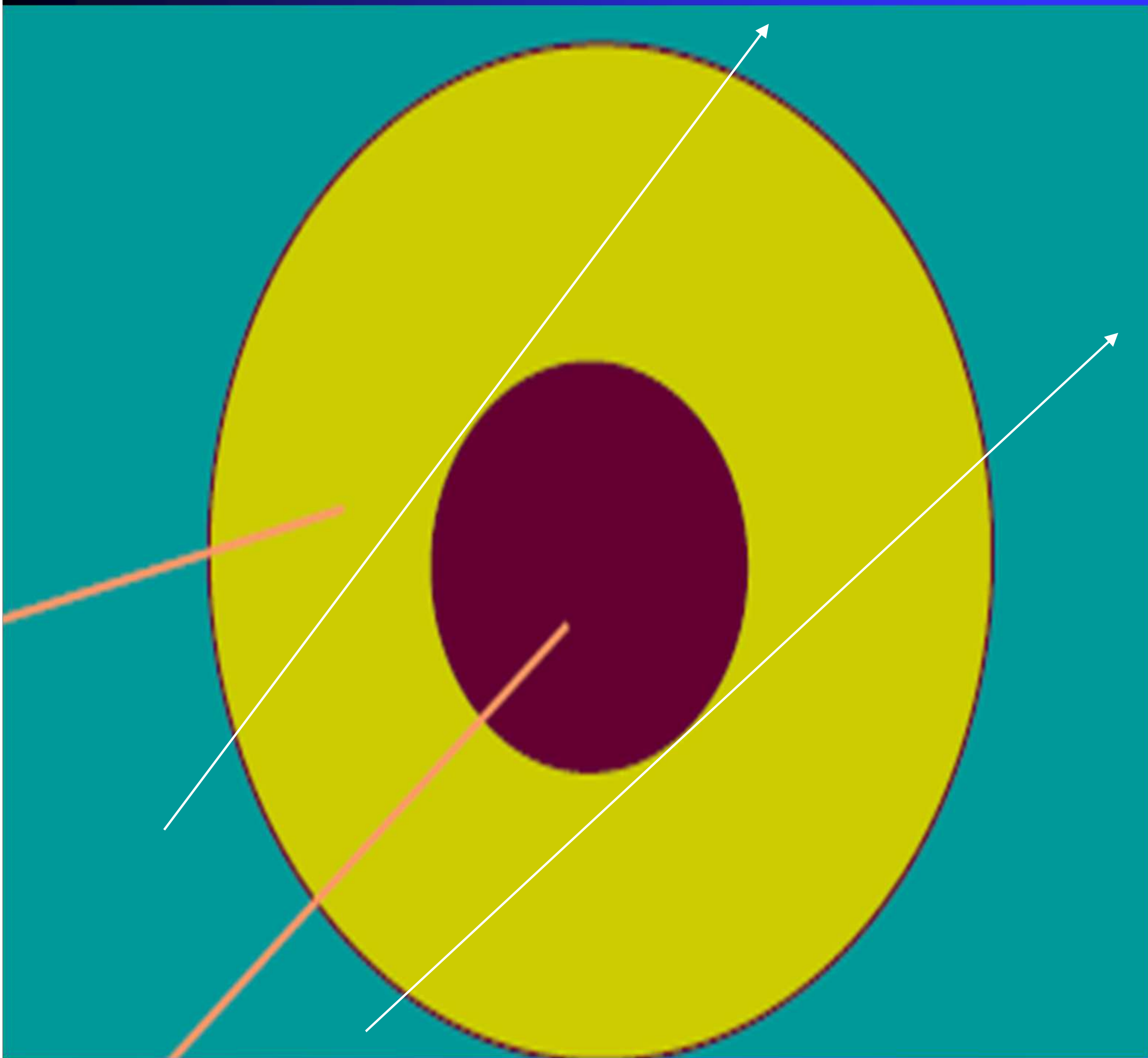
MOVING TUMOR

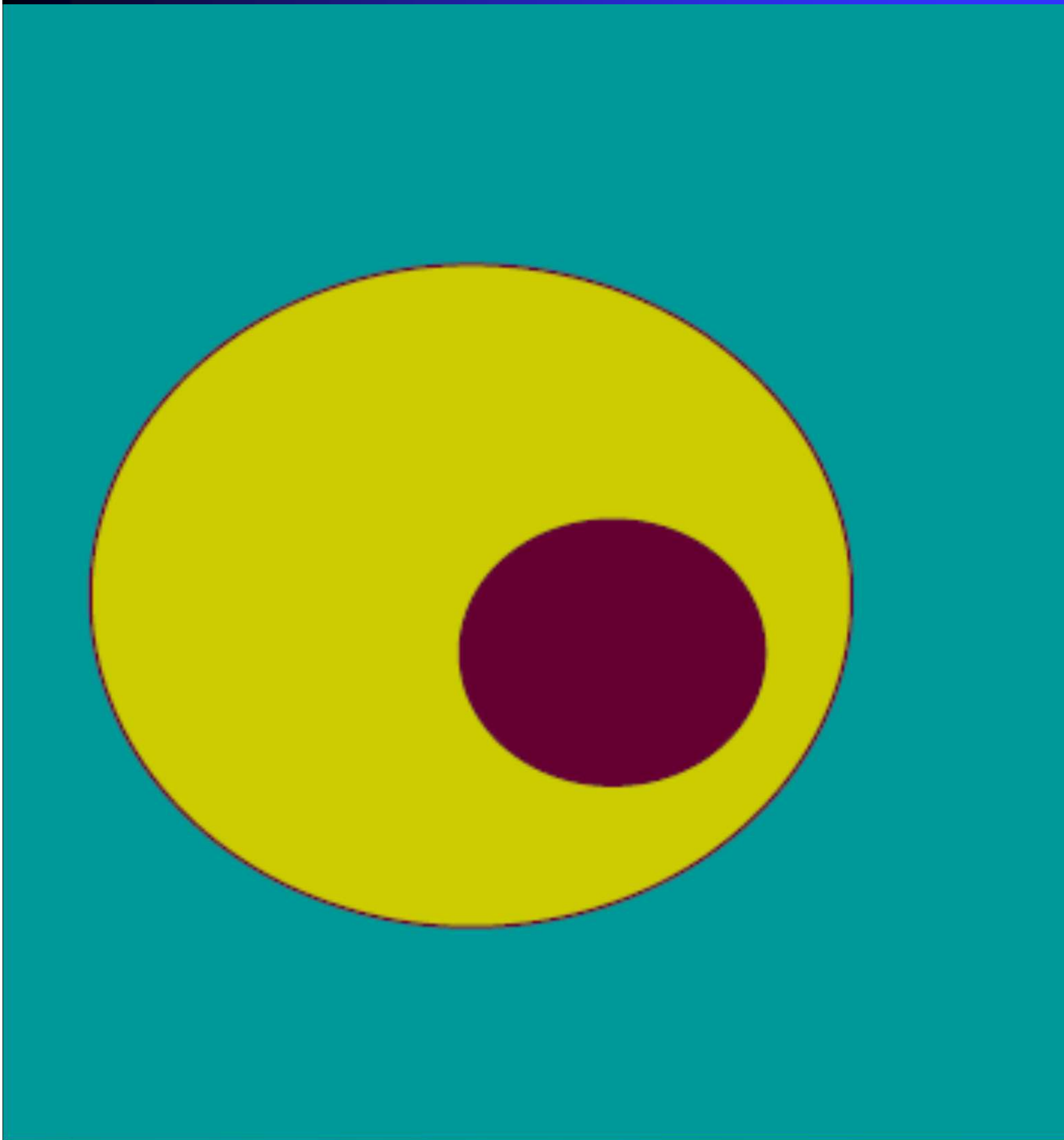
- **BY TREATING THE TUMOR IN A PARTICULAR PHASE OF MOVEMENT**

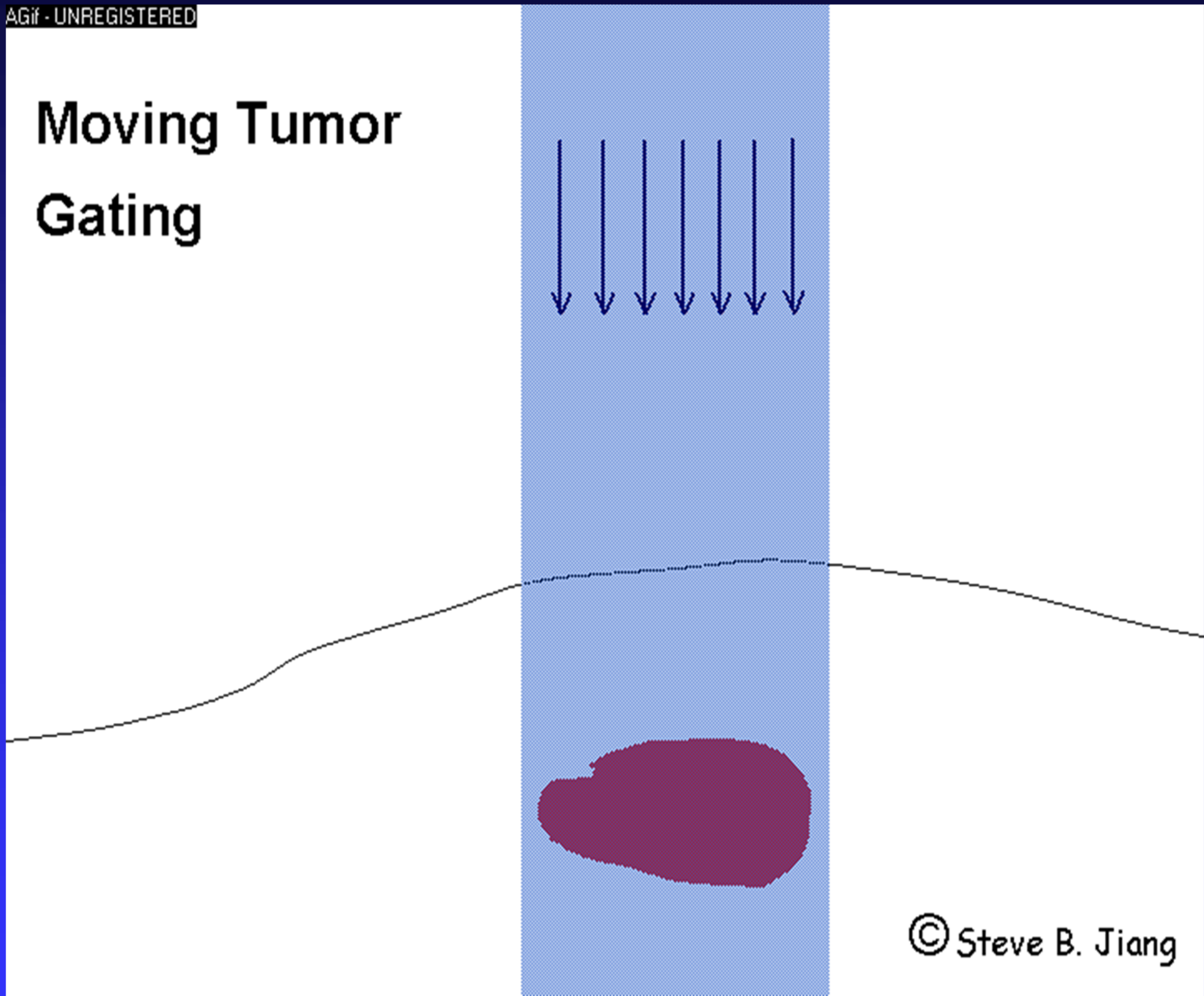











AGif - UNREGISTERED
Moving Tumor
Gating
© Steve B. Jiang

CyberKnife® Robotic Radiosurgery System

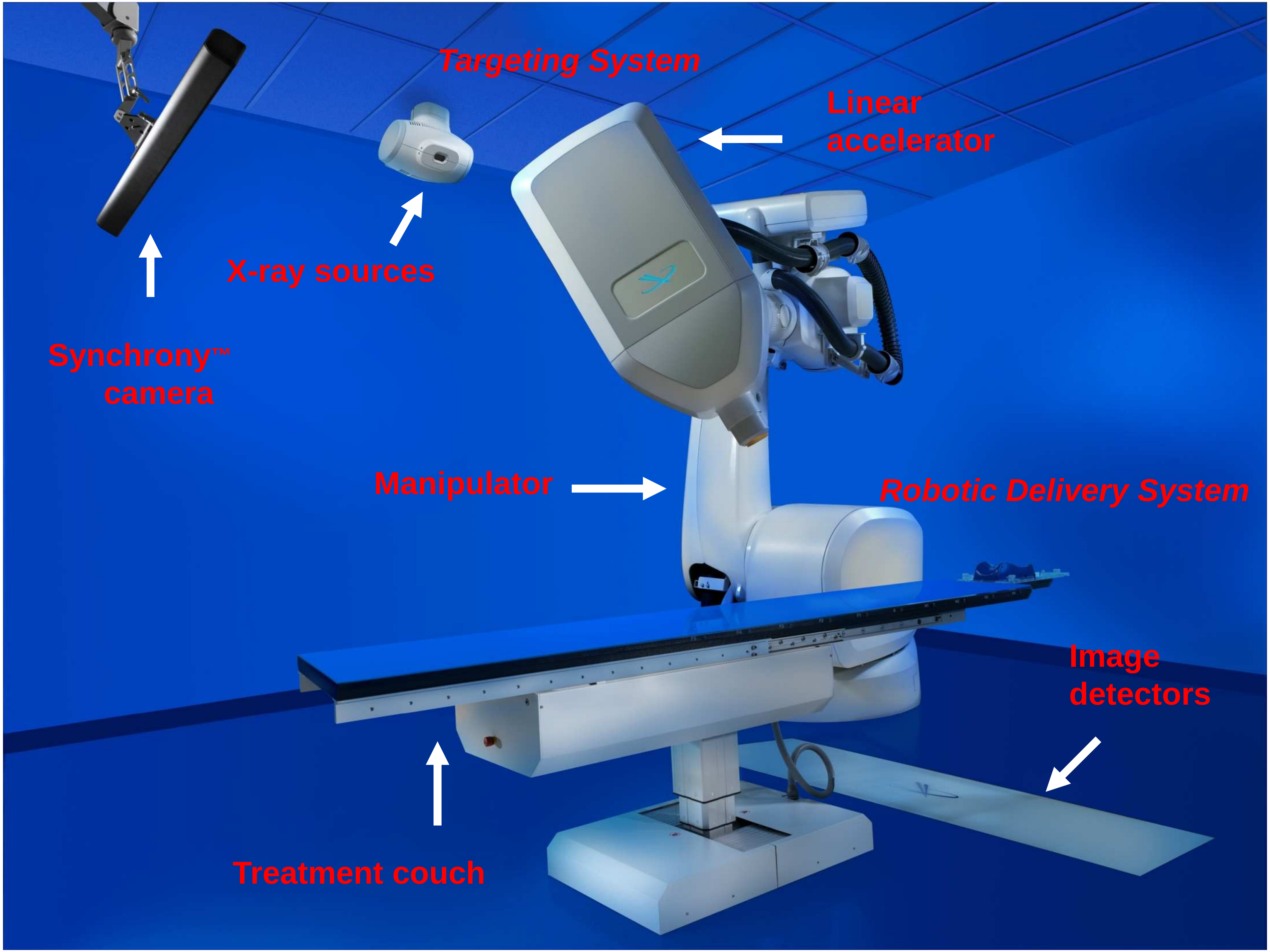
- Not a surgical knife
- Linear Accelerator mounted on a robotic arm
- Tracks, detects and corrects for tumor and patient movements throughout the treatment

CyberKnife® Robotic Radiosurgery System

- Broad clinical application
  - Intracranial radiosurgery
  - Extracranial radiosurgery
    - Spine
    - Lung
    - Liver
    - Pancreas
    - Prostate
    - Other

Hospital

- Staged/fractionated radiosurgery
- Proven clinical experience
  - Over 16,000 patients treated worldwide
  - Over 130 clinical and technical papers



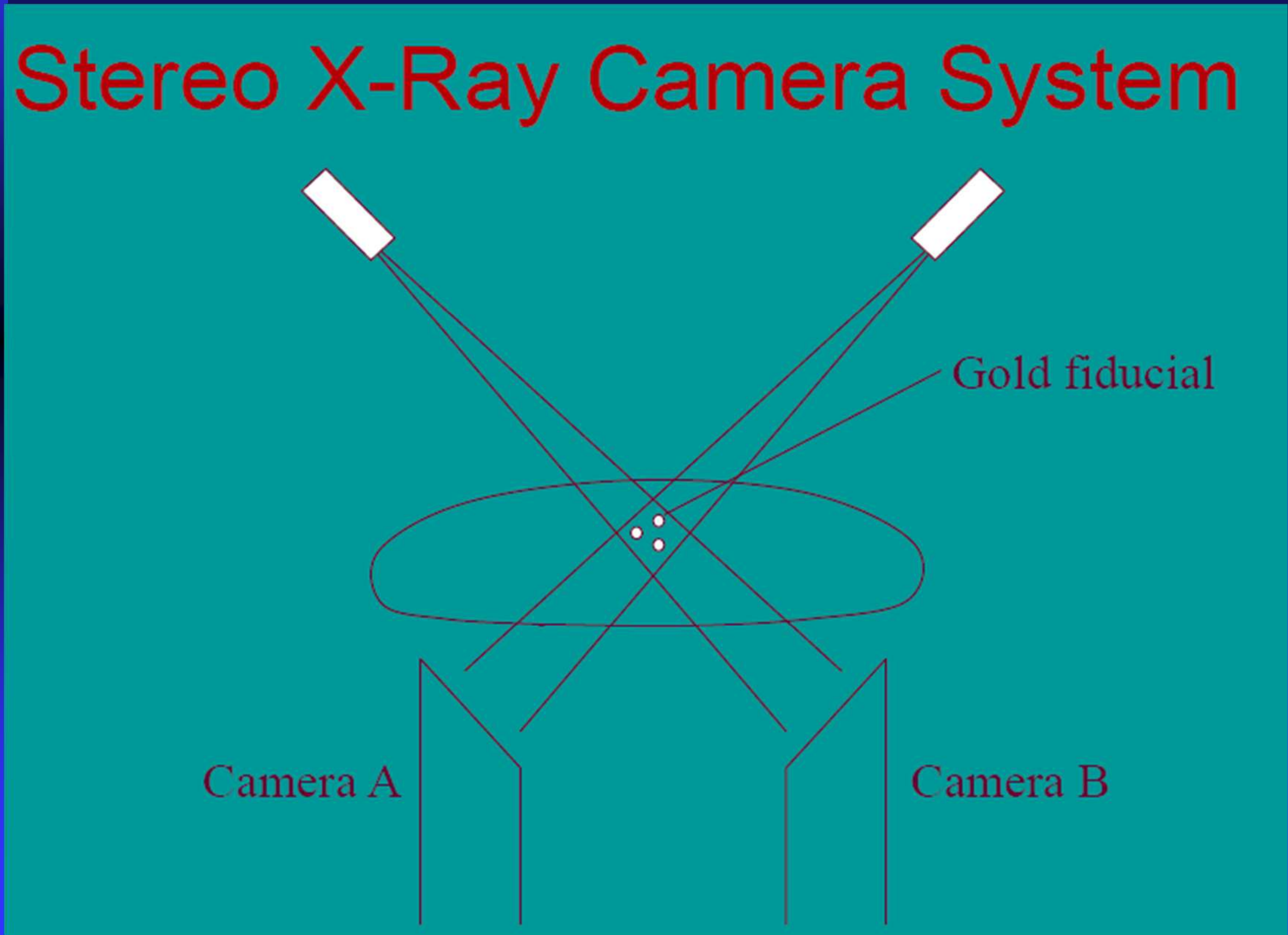
Targeting System
Linear accelerator
X-ray sources
Synchrony™ camera
Manipulator
Robotic Delivery System
Image detectors
Treatment couch

CyberKnife® Accuracy

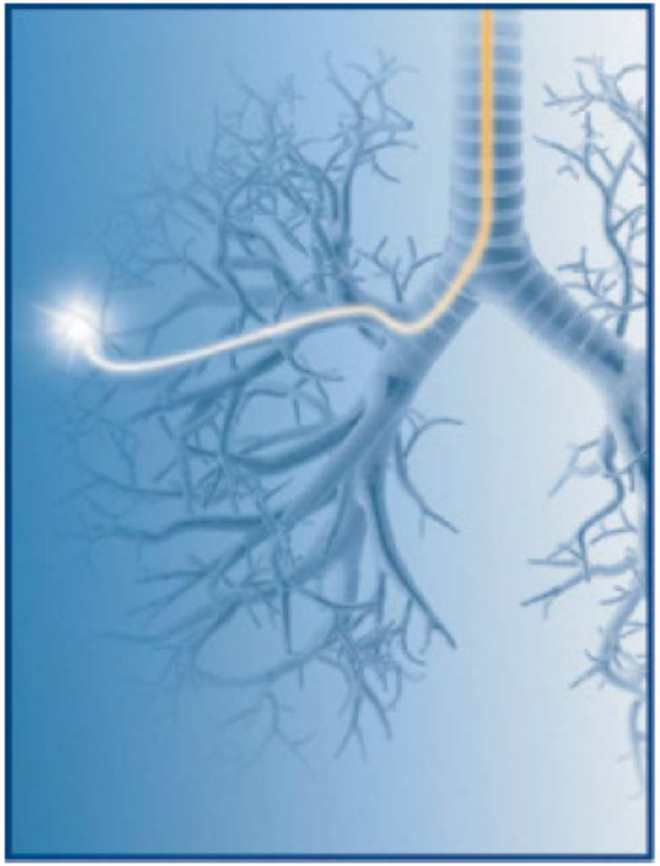
- Sub-millimeter accuracy
- Treats all parts of the body
- Treats lesions that were previously untreatable
- So accurate, head and body frames are not required

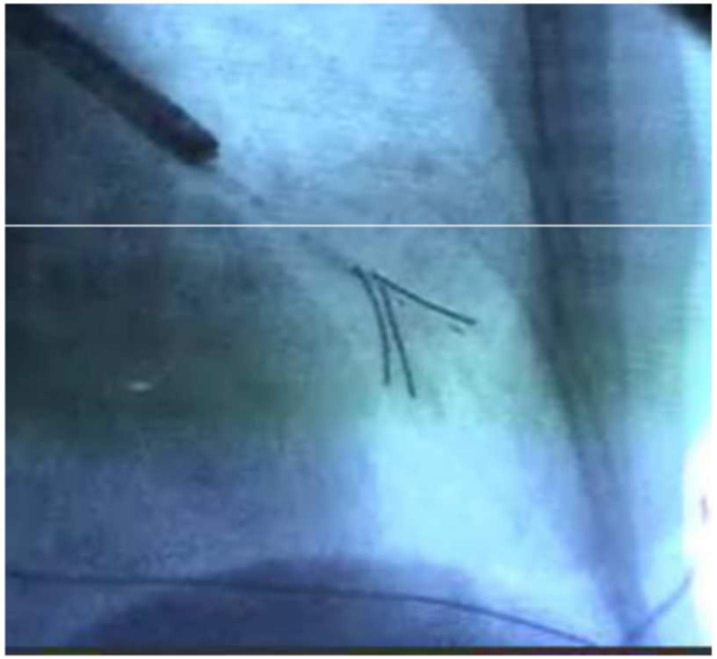
- How Cyber knife locate the target position during respiration with high accuracy.

Internal Tracking



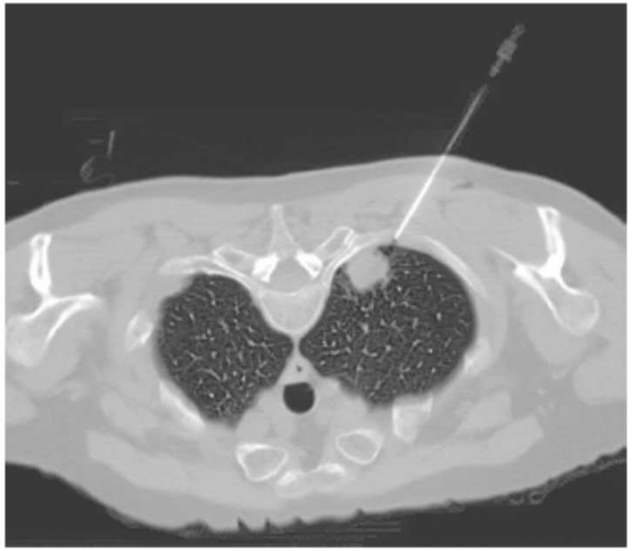
BRONCHOSCOPIC FIDUCIAL PLACEMENT





POTENTIAL ROLES OF PULMONOLOGISTS

If fiduicials are placed using CT guidance, the pulmonologists serve as back-up for the interventional radiologists in the event of a pneumothorax



Cyber Knife RT

- Is usually given in 1 to 4 fractions
- This treatment is called Steriotactic body Radiosurgery or Radiotherapy
    - SBRS
    - SBRT

"Radical Stereotactic Radiosurgery with Real-Time Tumor Motion Tracking in the Treatment of Small Peripheral Lung Tumors"

International Jounral of Radiation Oncology, 2007, Georgetown University

- 93 medically inoperable patients
- CyberKnife radiosurgery treatment with 45-60Gy in 3 fractions
- All patients had small (less than 3cm tumors)
- Excellent acute toxicity profile
  - Stage Ia NSCLC patients

100% Local Control at 2 years for medically inoperable patients

"Fractionated Stereotactic Body Radiation Therapy in the Treatment of Primary, Recurrent, and Metastatic Lung Tumors"

Clinical Lung Cancer August 2008,

University of Pittsburgh

- CyberKnife radiosurgery treatment with 60 Gy in 3 fractions
- Three patient groups (Patients with few other options)
  - Primary Stage Ia & Ib NSCLC (Medically Inoperable)
  - Patient with recurrent NSCLC who failed prior treatment
  - Patient with metastatic lung tumors
- Local control 85% NSCLC, 62% recurrent lung cancer, 92% metastatic lung tumor patients at 1 year
  - Local control with conventional radiation for similar patients is poor (10-40%)

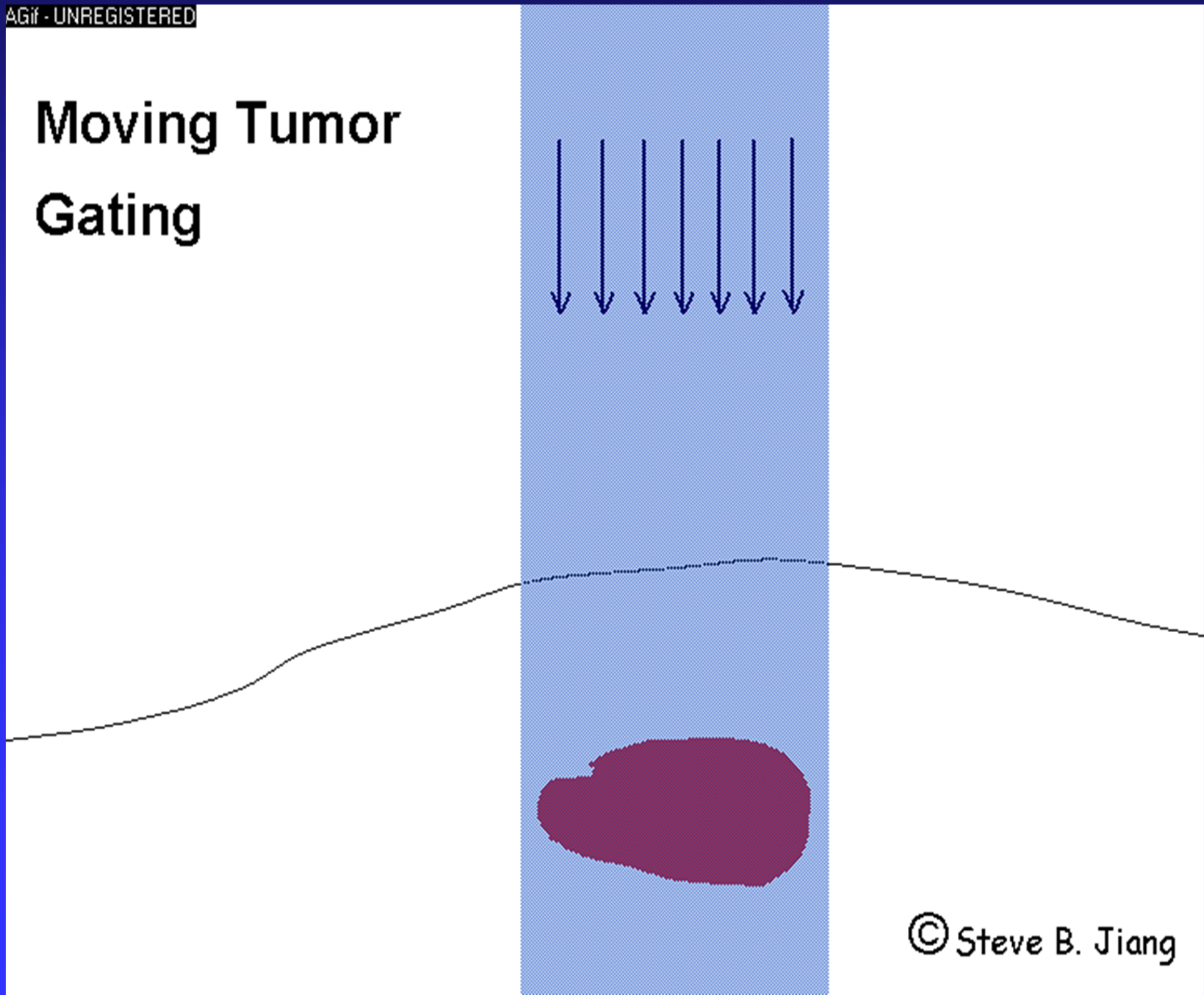
Excellent local control outcomes for patients with few other options

Prospective Evaluation of Radiosurgery Treatment for NSCLC Patients

- Operable Patients
  - Principal Investigator:
    - Jack Roth, MD (MD Anderson Cancer Center)
  - Study Population
    - Stage IA/B (<4cm) NSCLC Patients
  - Study Aims:
    - To Randomize patients to lobectomy vs. CyberKnife Radiosurgery
    - To Compare overall survival and outcomes at 3, 4, 5 years post treatment
  - Status:
    - Actively accruing patients since Fall 2008
      - Target of 1100 patients
    - Study to involve centers in the U.S., Europe, Asia

THE UNIVERSITY OF TEXAS
MD ANDERSON CANCER CENTER
Making Cancer History™

BY TREATING THE TUMOR IN A PARTICULAR PHASE OF MOVEMENT

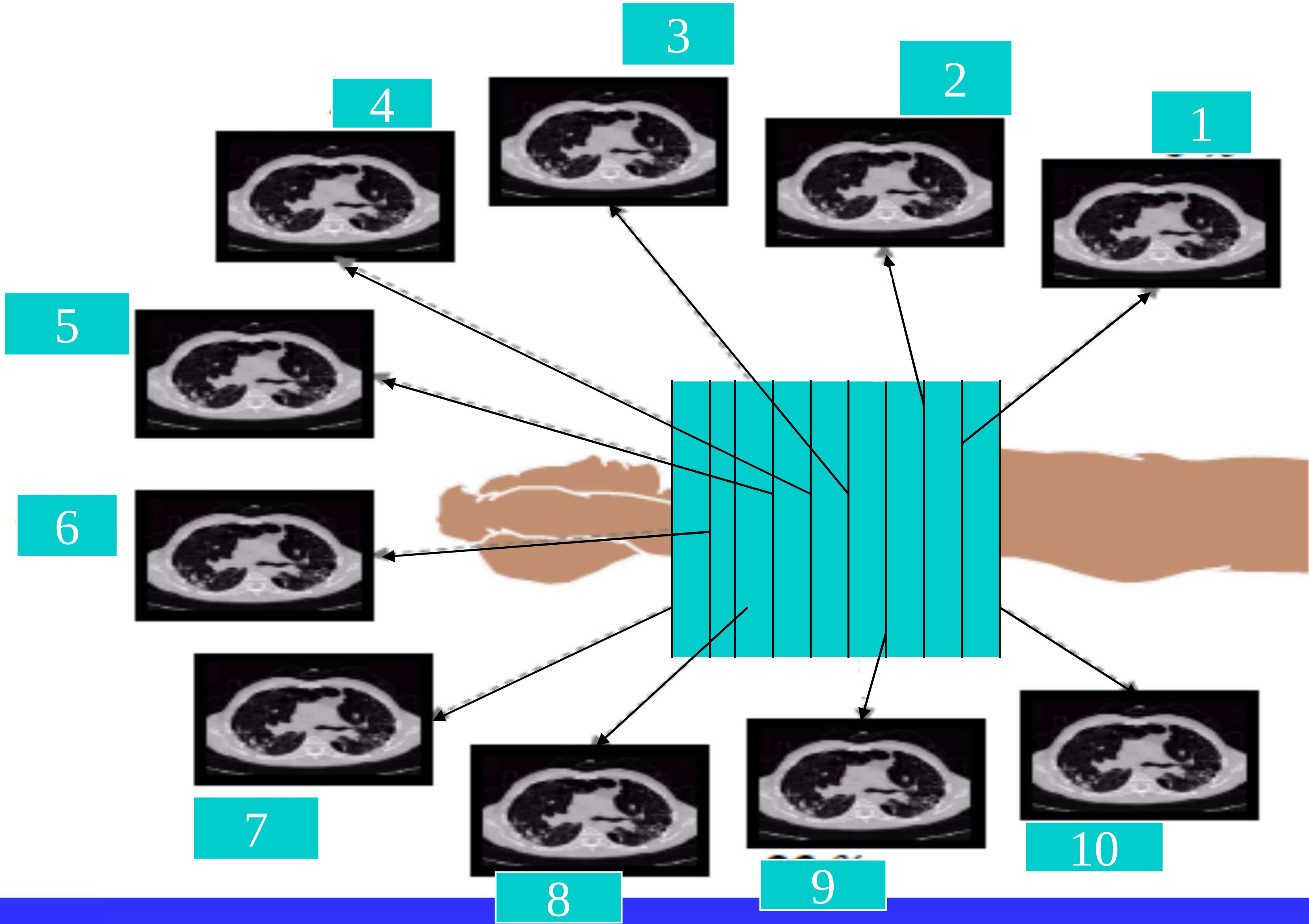


MOVING TUMOR

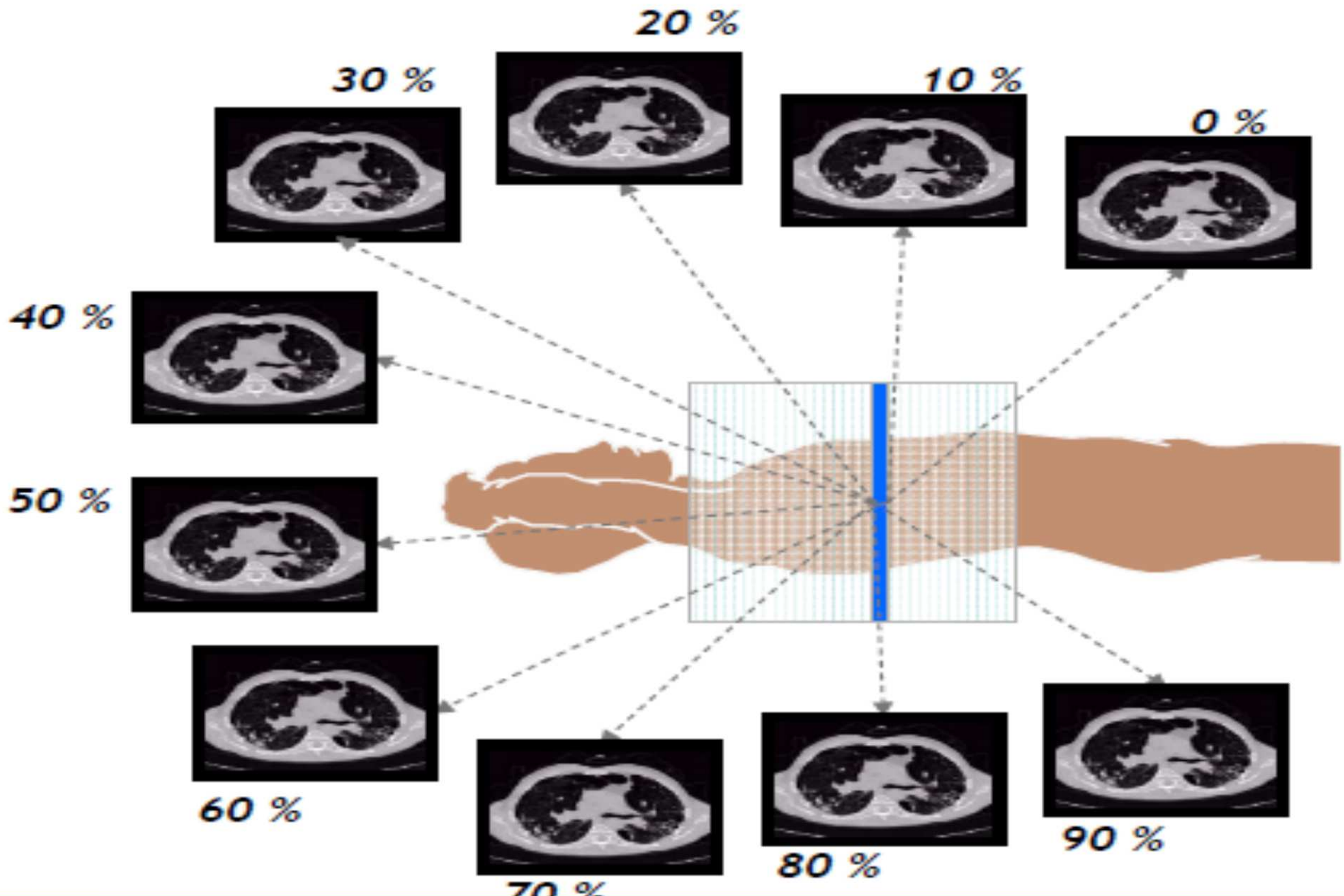
- To evaluate the exact movement and to find out the phase of respiratory cycle in which tumor to be treated----------

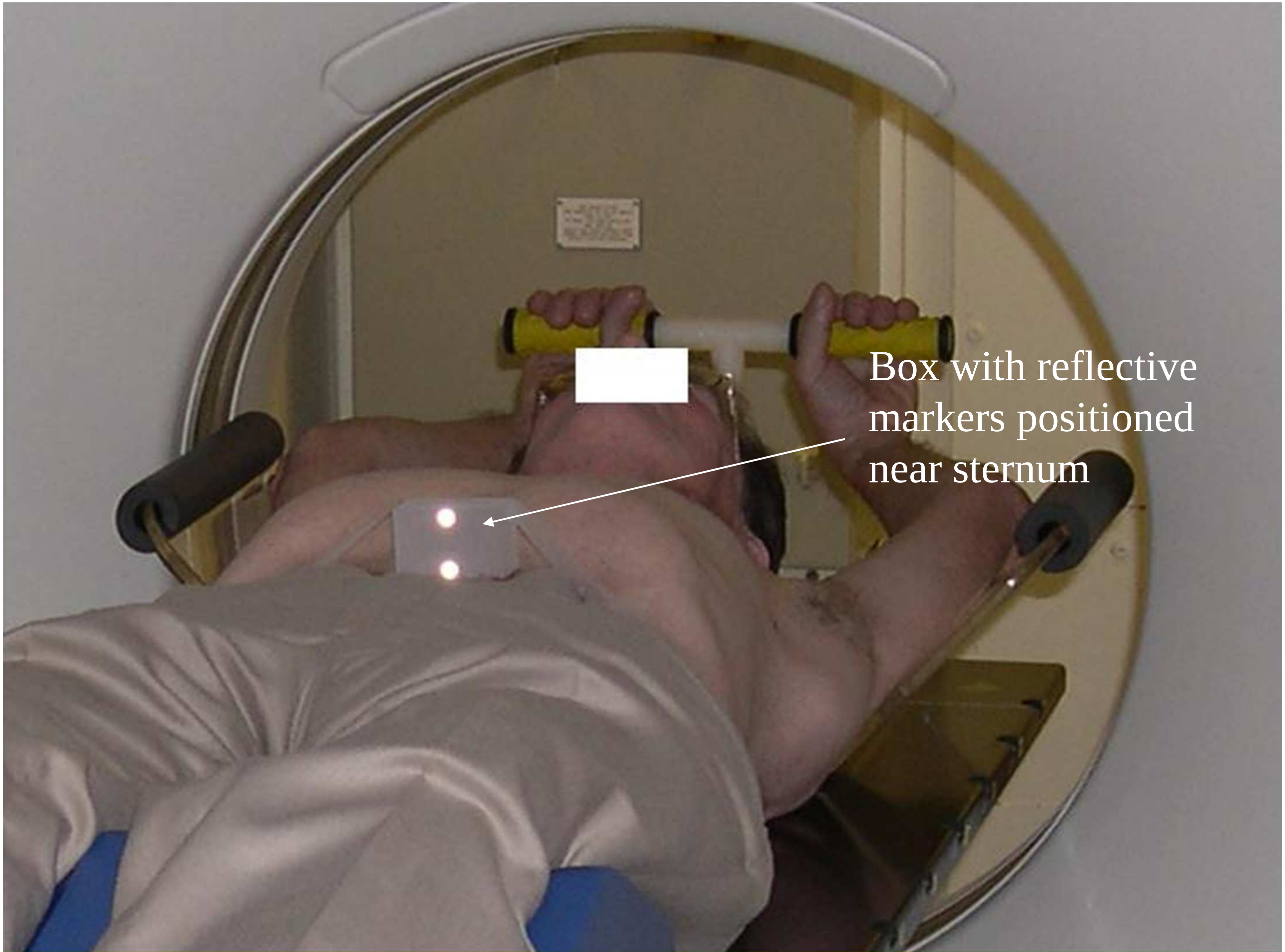
  - 4D CT Scan to be done

3 D CT SCAN



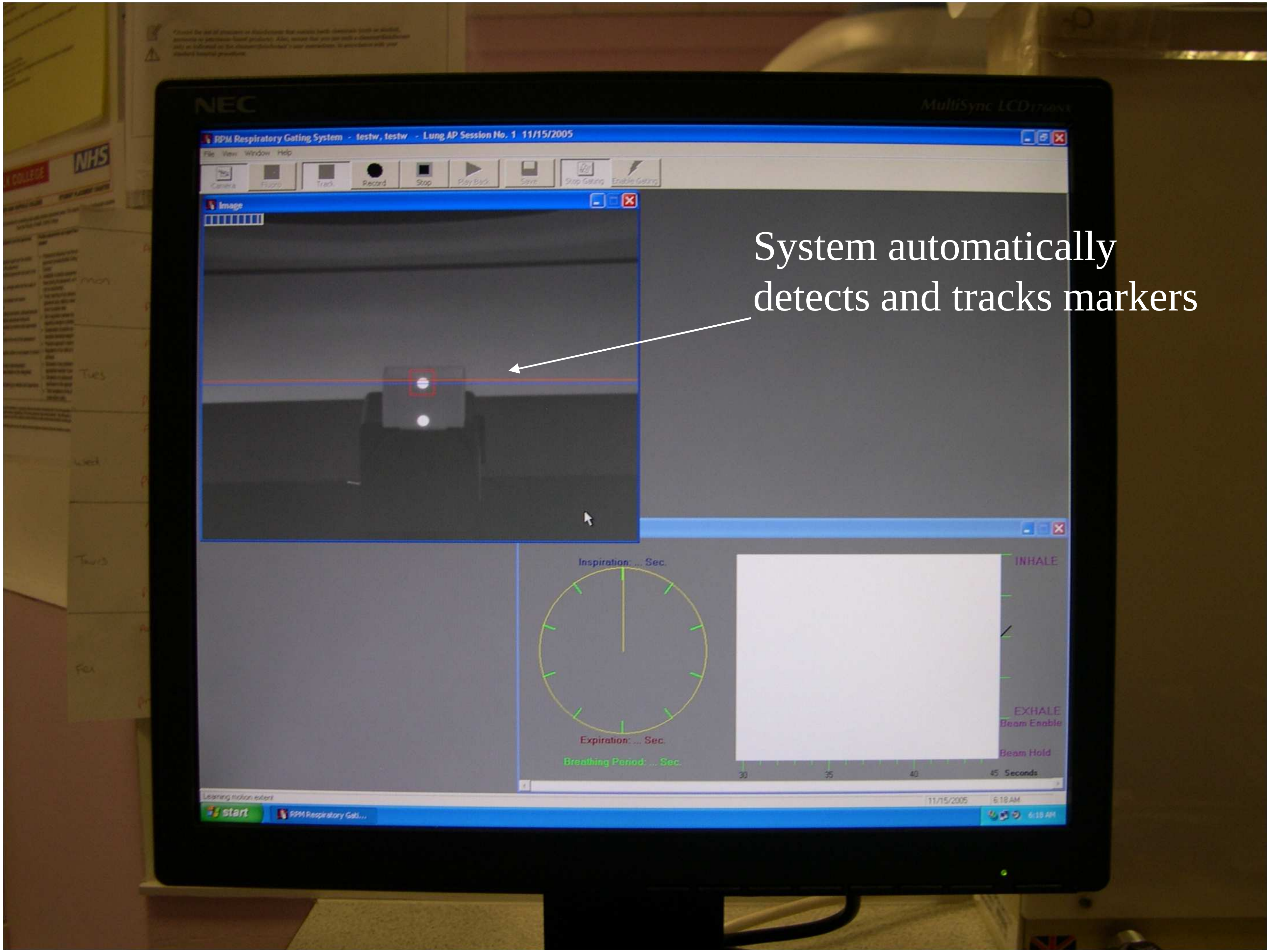
4D CT & Phase Sorting




Box with reflective
markers positioned
near sternum

4D CT SCAN

4D CT SCAN



System automatically detects and tracks markers

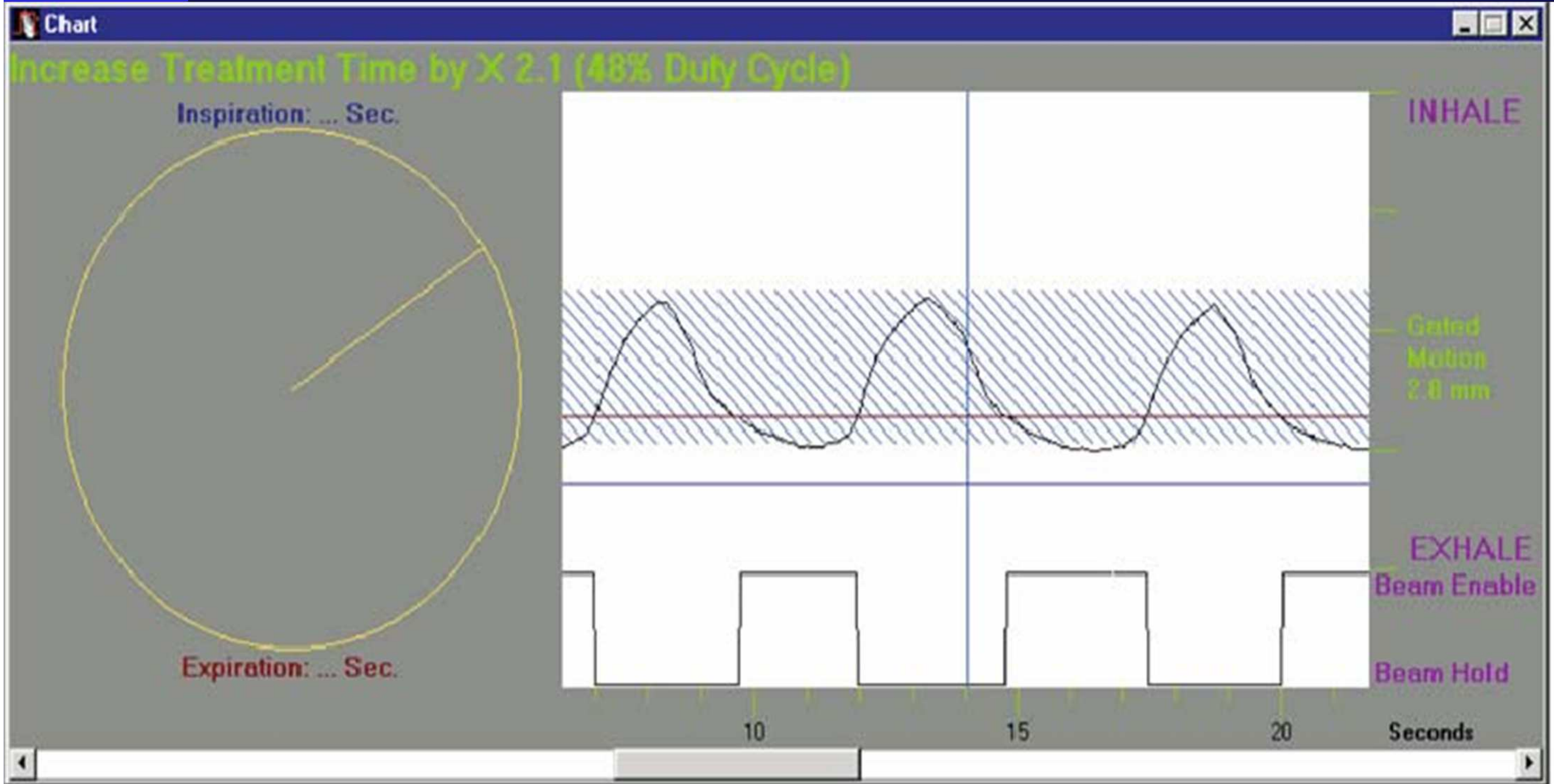
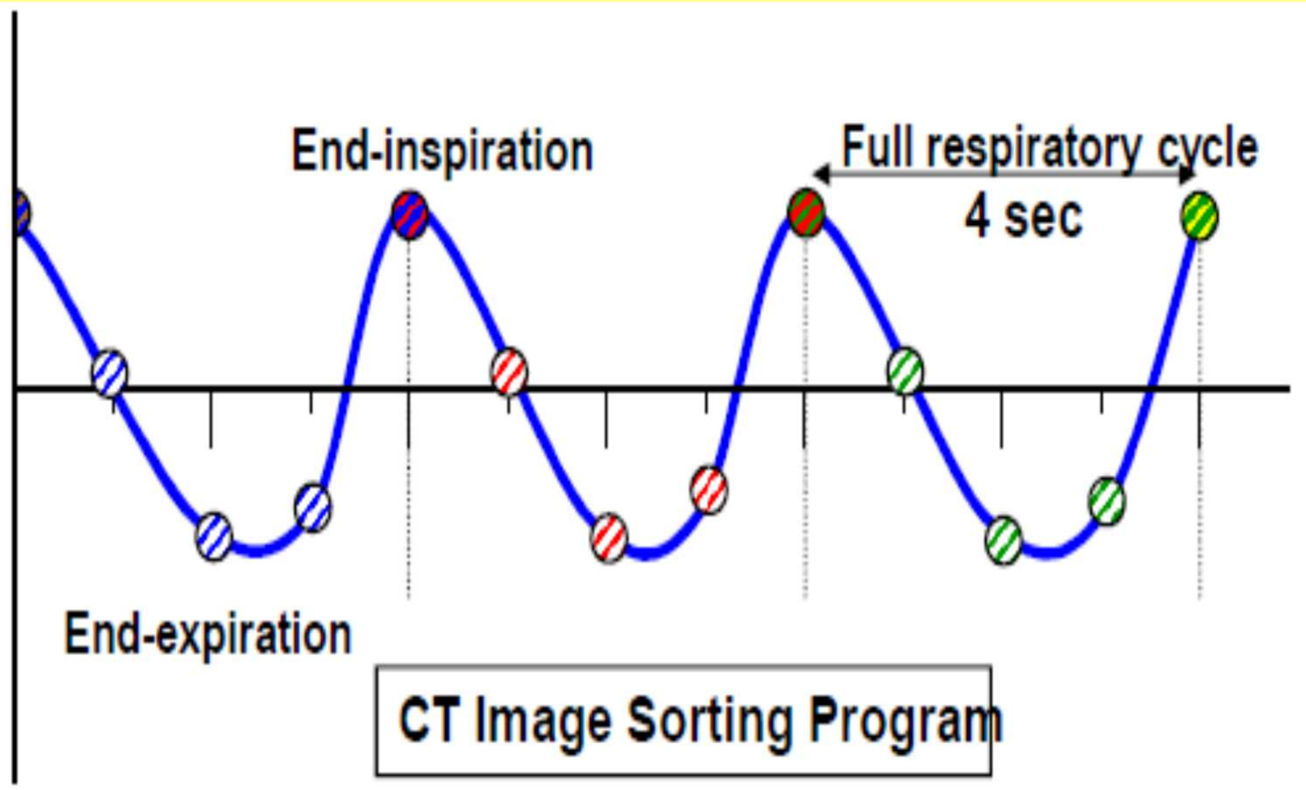
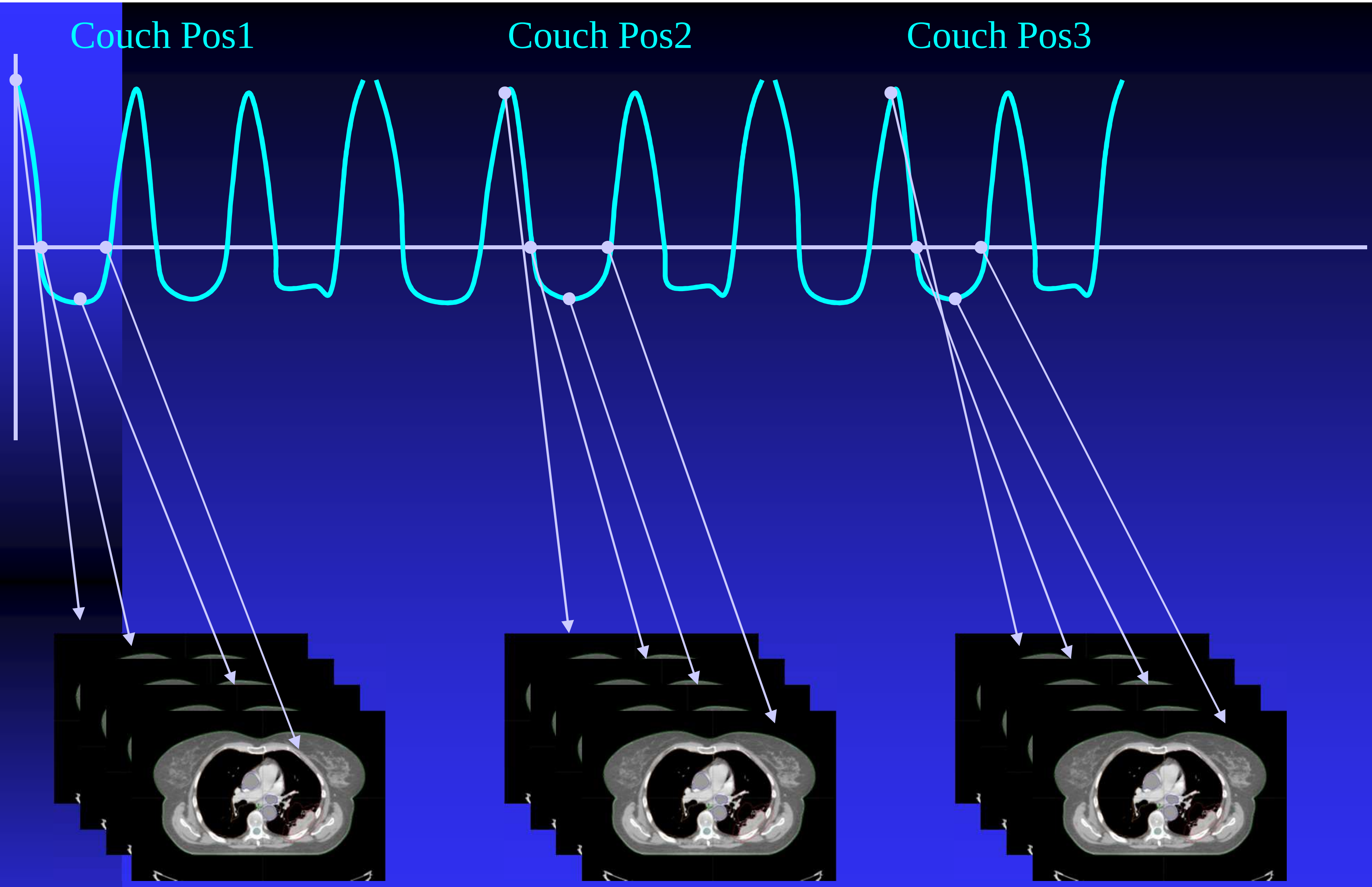


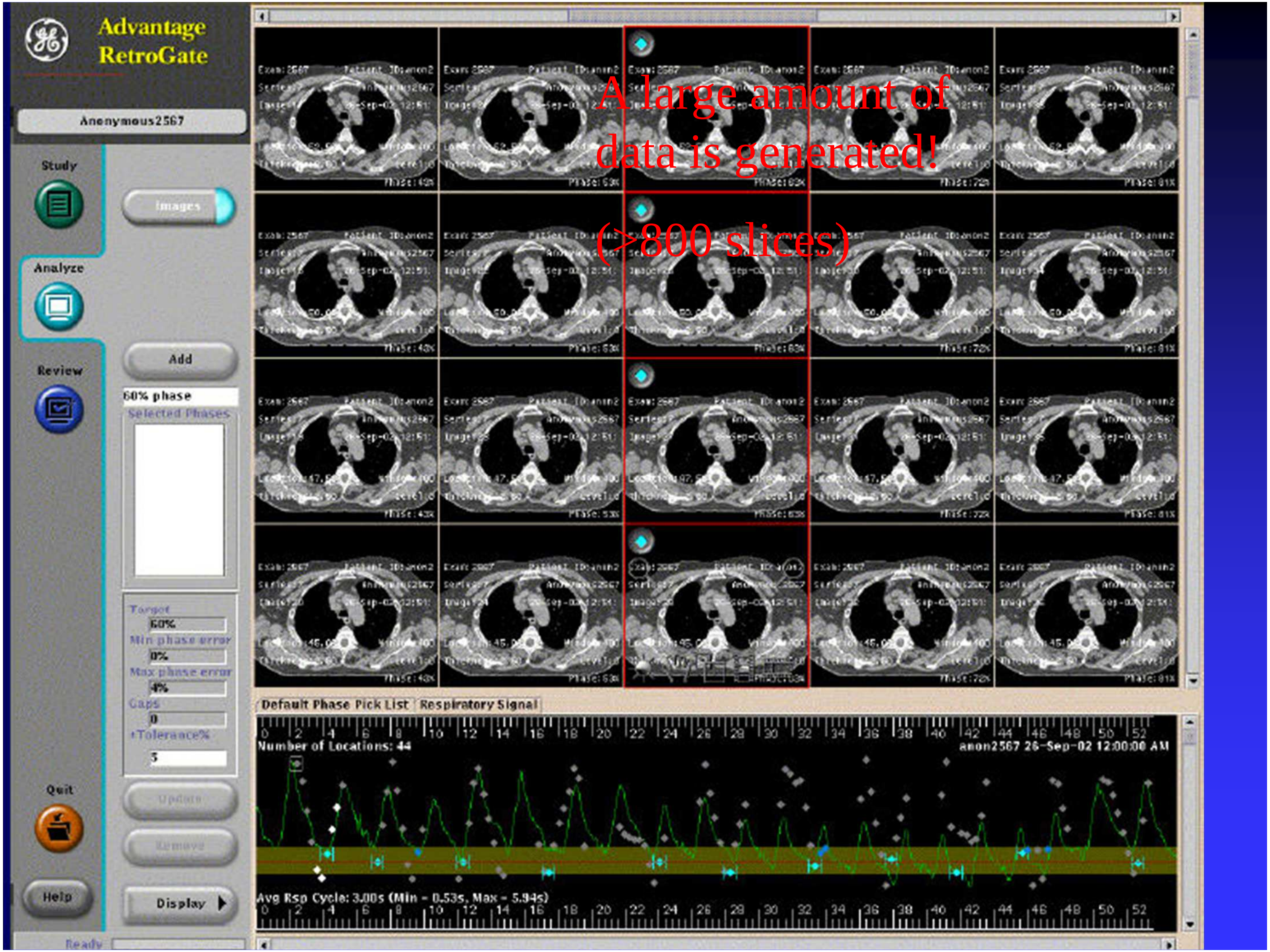
Chart
Increase Treatment Time by X 2.1 (48% Duty Cycle)
Inspiration: ... Sec.
Expiration: ... Sec.
INHALE
Gated
Motion
2.8 mm
EXHALE
Beam Enable
Beam Hold
10
15
20
Seconds


End-inspiration
Full respiratory cycle
4 sec
End-expiration
CT Image Sorting Program



Single Slice Scanner – 4 phase bins – Full Inhalation, Mid-Exhalation, Full Exhalation, Mid-Inhalation

3 Couch Positions = 3x4 = 12 slices



A large amount of data is generated!

(>800 slices)

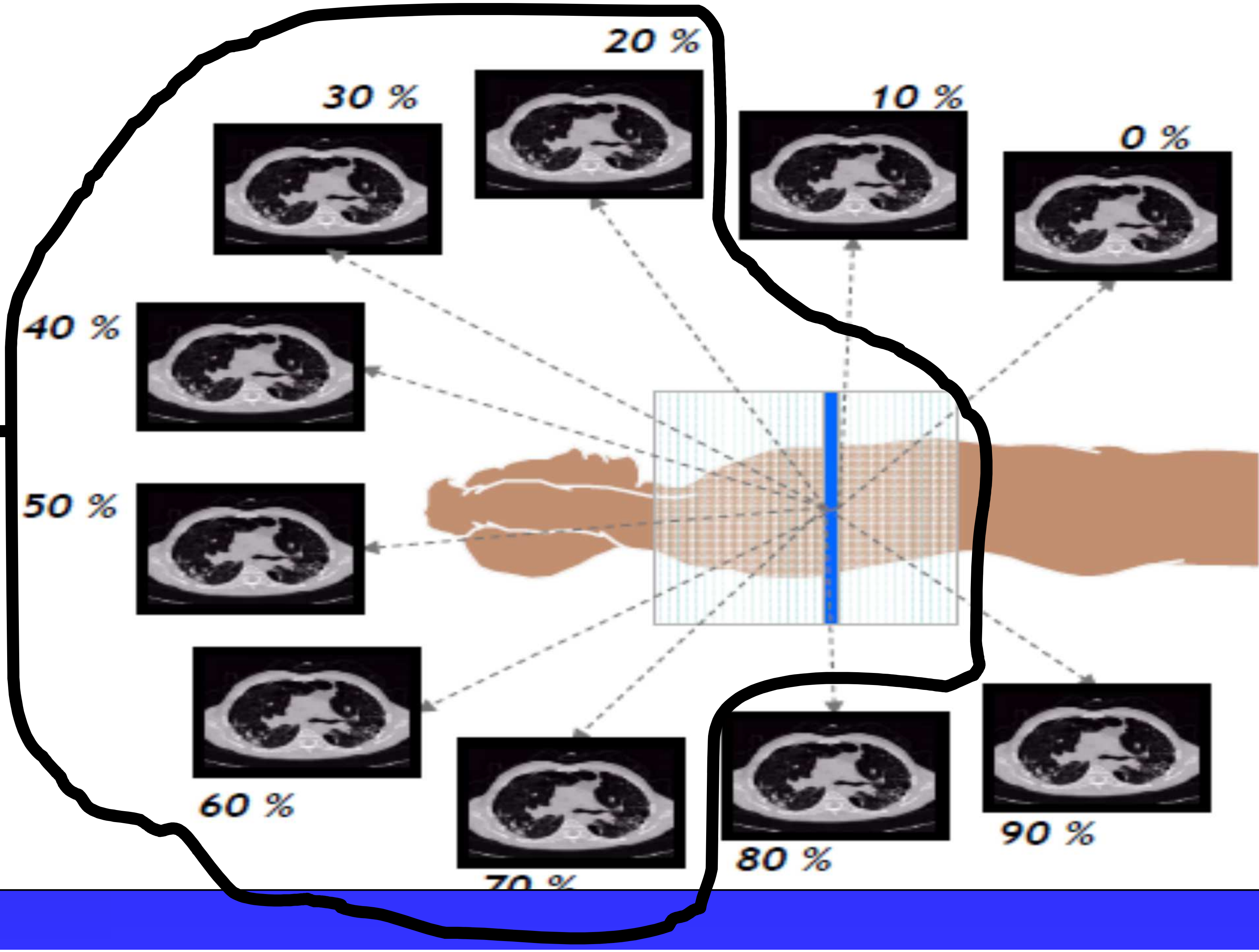
4D CT SCAN IN CA LUNG

- PUT THE CONSOLE IN MOVIE MODE.
- SEE THE MOVEMENT OF THE LUNG AND TUMOR.
- MEASURE THE RANGE OF THE MOVEMENT OF TUMOR IN ALL THE DIRECTIONS

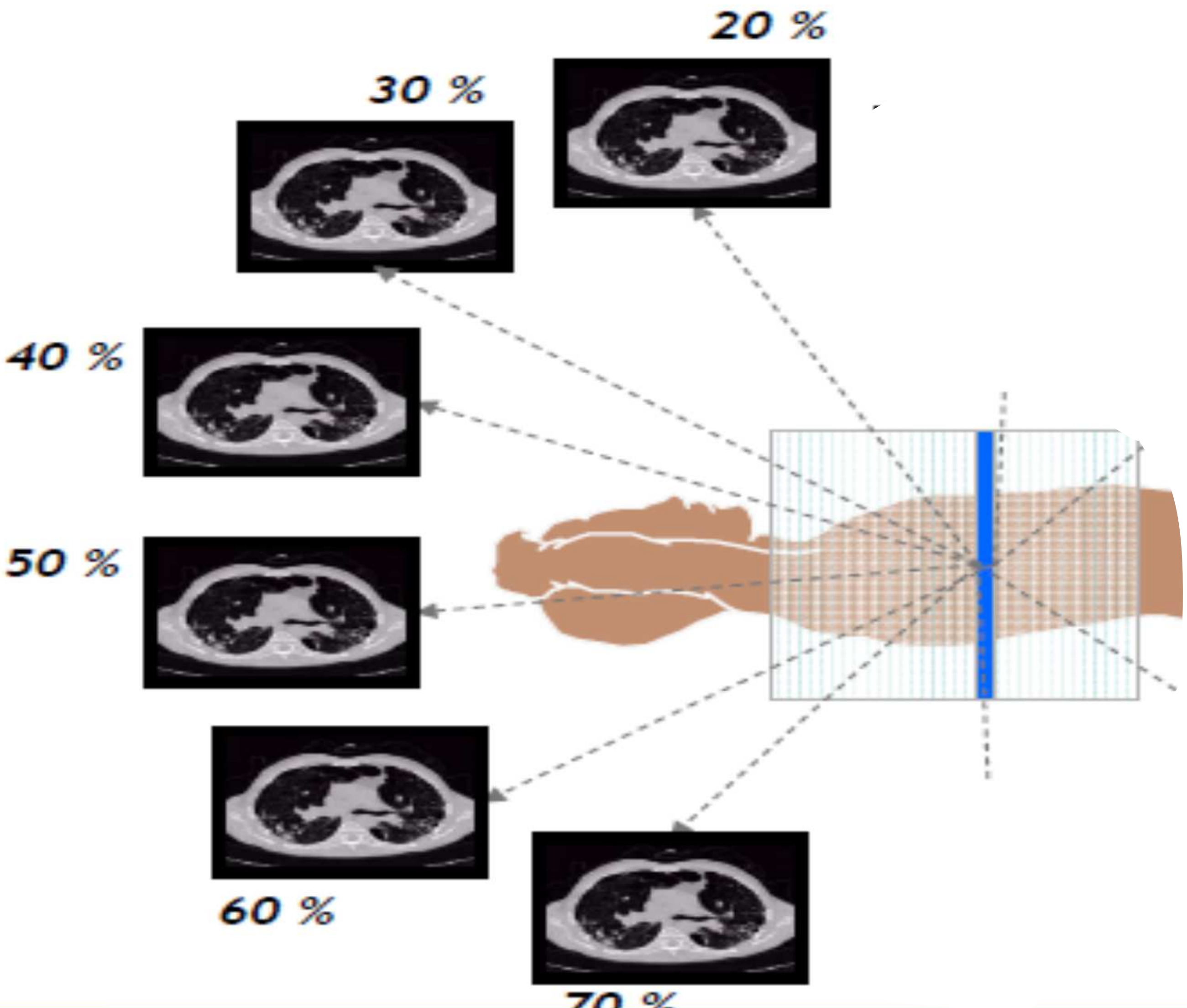
4D CT SCAN IN CA LUNG

- FIND OUT THE PHASES OF RESPIRAION IN WHICH THE MOVEMENT OF THE TUMOR IS LEAST
- THEN EXTRACT CT SLICES FROM THOSE PHASES ONLY

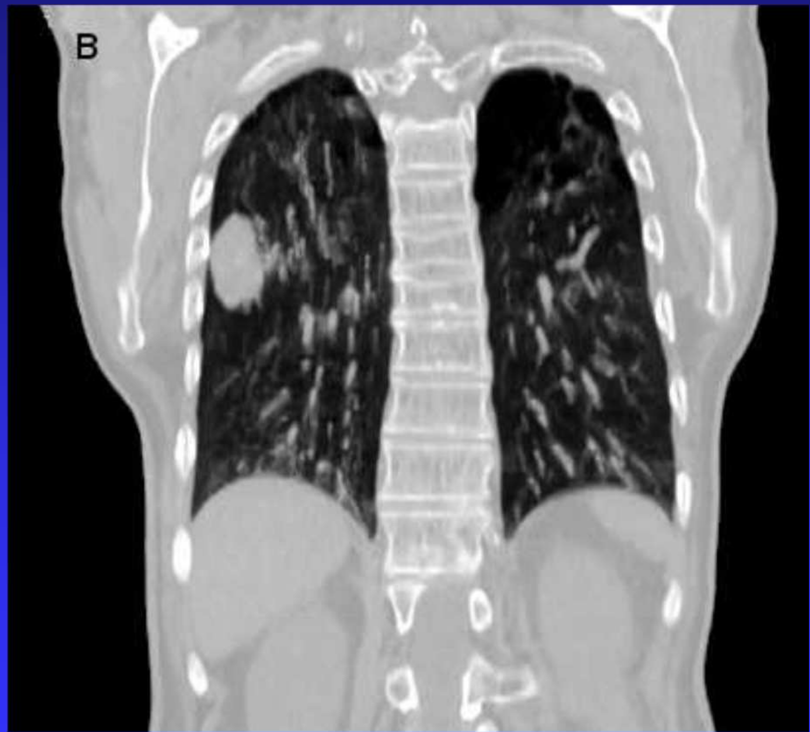
4D CT & Phase Sorting



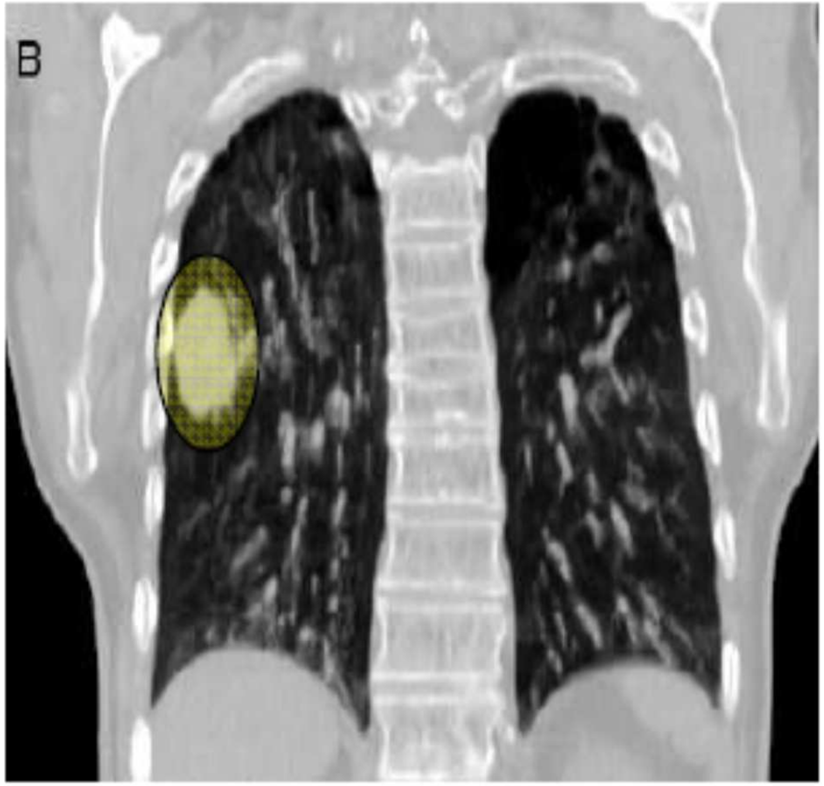
4D CT & Phase Sorting

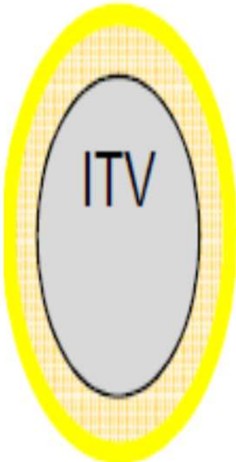


4D CT SCAN IN CA LUNG



4D CT SCAN IN CA LUNG





PTV derived by expanding the '*Internal Target Volume*' with margins for

- microscopic spread
- daily setup variations

4D RT DELIVERY

- ON MACHINE SAME BLOCK WITH IR BEADS ARE KEPT OVER ABDOME
- SAME PATTERN OF RESPIRATION IS REPRODUCED AS IN CT PLAN
- THE CONSOLE OF THE LINAC IS PROGRAMMED IN SUCH A WAY THAT THE RADIATION IS ON DURING 20% TO 70% PHASE OF THE RESP. CYCLE.

Typical eligibility criteria for lung SRT

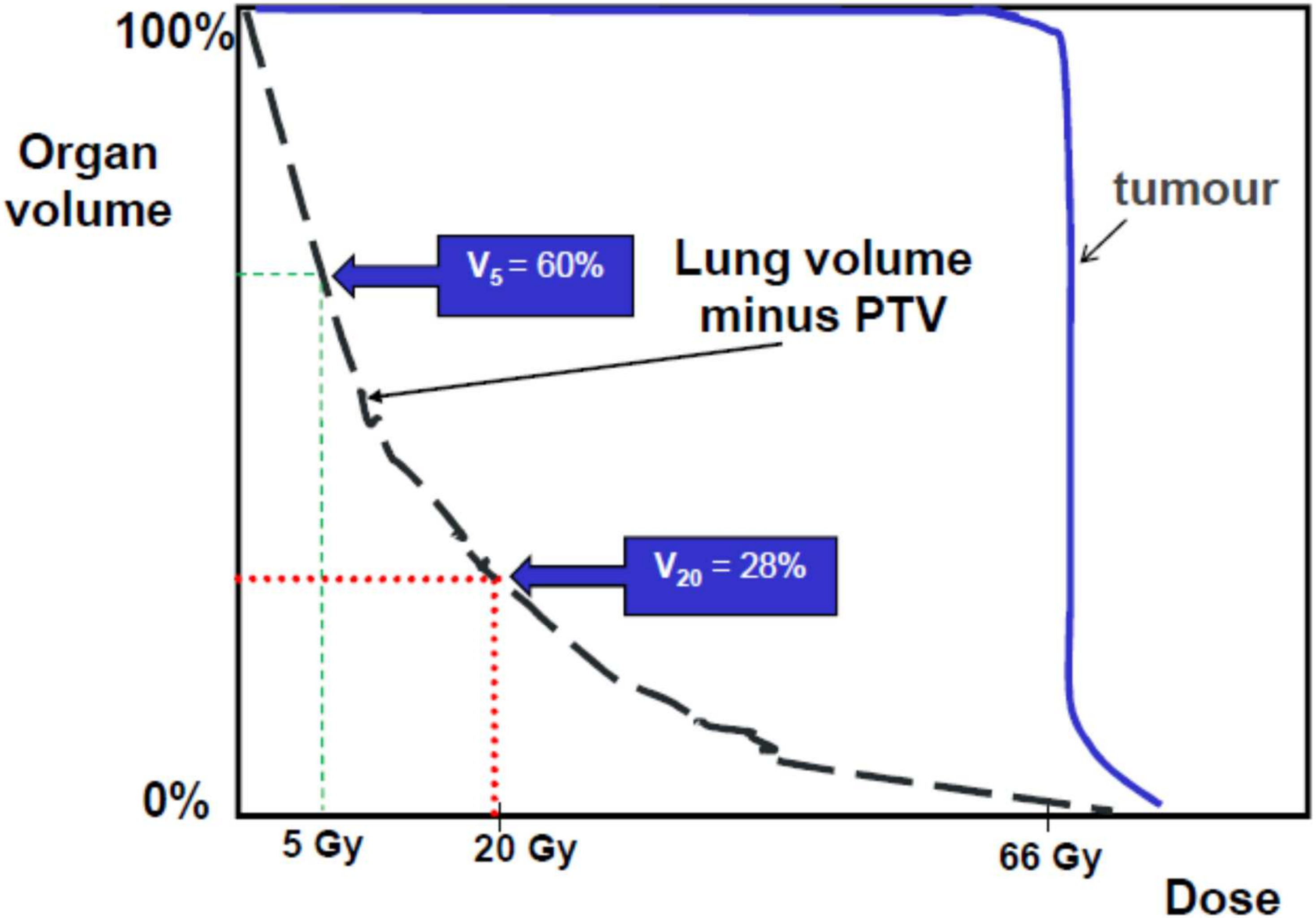
Lagerwaard FJ, 2008

- Maximum tumor size < 6 cm
- Medically inoperable or refusing surgery
- Regardless of pulmonary function
- FDG-PET confirmation of Stage I disease
- When no tissue diagnosis available, a new or growing PET-positive lesion with CT-characteristics of malignancy needed

SRT = stereotactic radiothera

Dose-volume histograms

For target coverage and risk prediction



V_{20} and outcomes after CT-RT

SWOG 0023 [Gaspar L, ASTRO 2006]

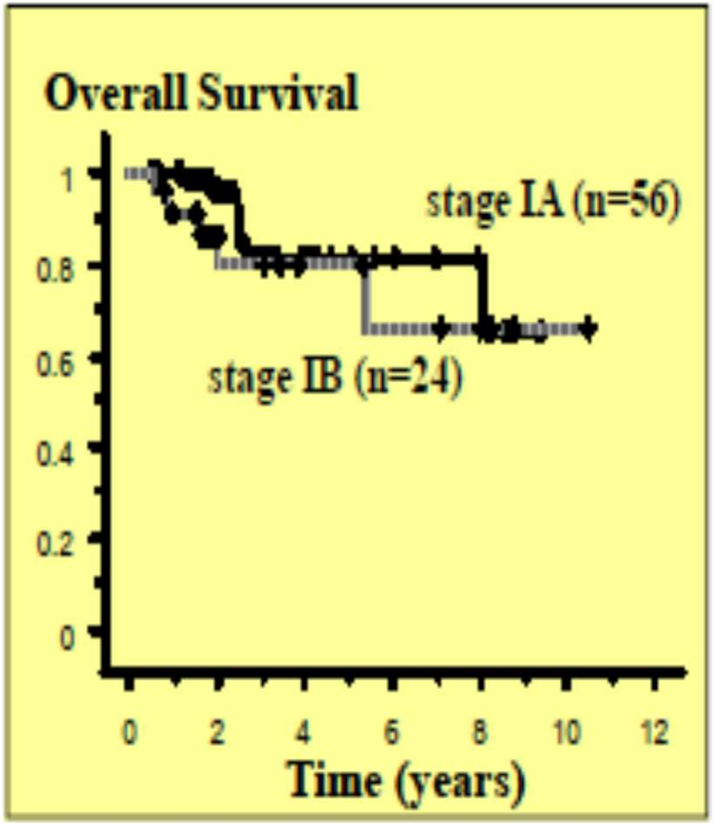
	$V_{20} \leq 35\%$	$V_{20} > 35\%$
Radiation pneumonitis ≥Grade 3 *	4%	10%
Median survival	24 months	12 months

Odds of incidence of $\geq$ Gr 3 pneumonitis increases by 5% for each percent increase in V_{20}

Local Control with SBRT

Series	Dose	Local control
North America/Europe		
Timmerman, 2006	20-22 Gy X 3	95% (2+ years)
Bauman, 2006	15 Gy X 3	80% (3 years)
Fritz, 2006	30 Gy X 1	80% (3 years)
Nyman, 2006	15 Gy X 3	80% (crude)
Zimmerman, 2005	12.5 Gy X 3	87% (3 years)
Timmerman, 2003	18-24 Gy X 3	90% (2 years)
Asia		
Xia, 2006	5 Gy X 10	95% (3 years)
Hara, 2006	30-34 Gy X 1	80% (3 years)
Nagata, 2005	12 Gy X 4	94% (3 years)

Stereotactic Body Radiation Therapy: Japanese Experience: Stage I NSCLC



Comparison of survival STI VS. surgery

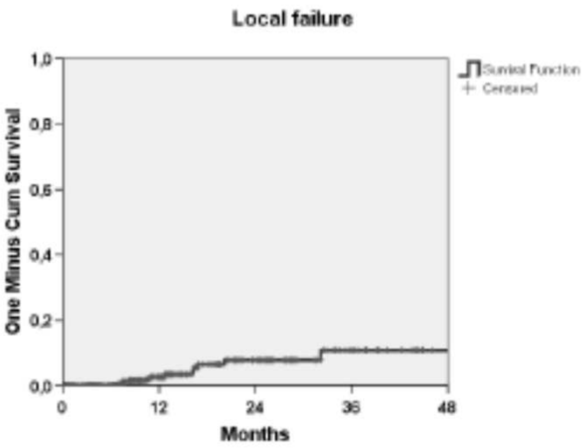
Mountain (US)*	JNCCH*	STI**
67%	74%	81%
57%	53%	79%

* surgery
** Stereotactic irradiation

Operable patients with
BED >= 100 Gy by stage

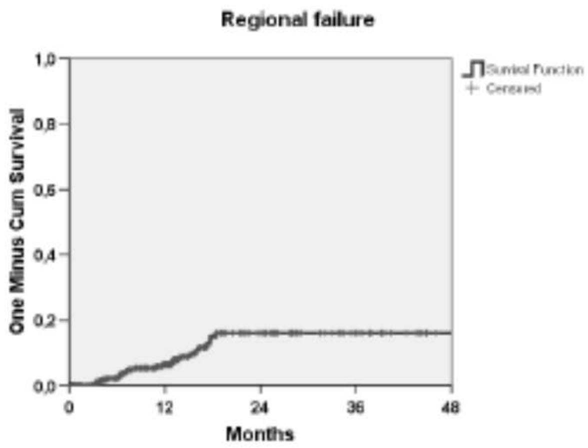
Stereotactic radiotherapy in stage I NSCLC

N= 341 patients (364 tumors)



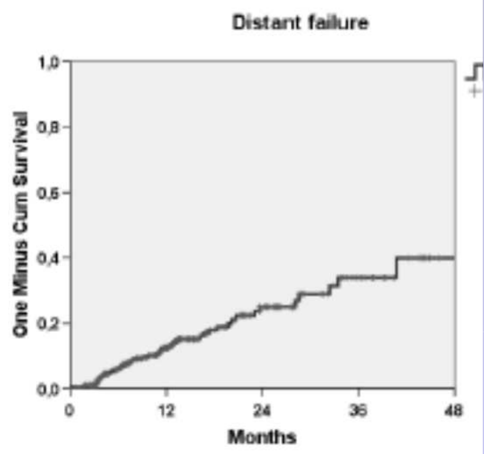
Local failure rate:
@1 year: 3%
@2 year: 8%
@3 year: 11%

Crude LF 3% (N=11)



Regional failure rate:
@1 year: 6%
@2 year: 16%
@3 year: 16%

Crude RF 8% (N=26)

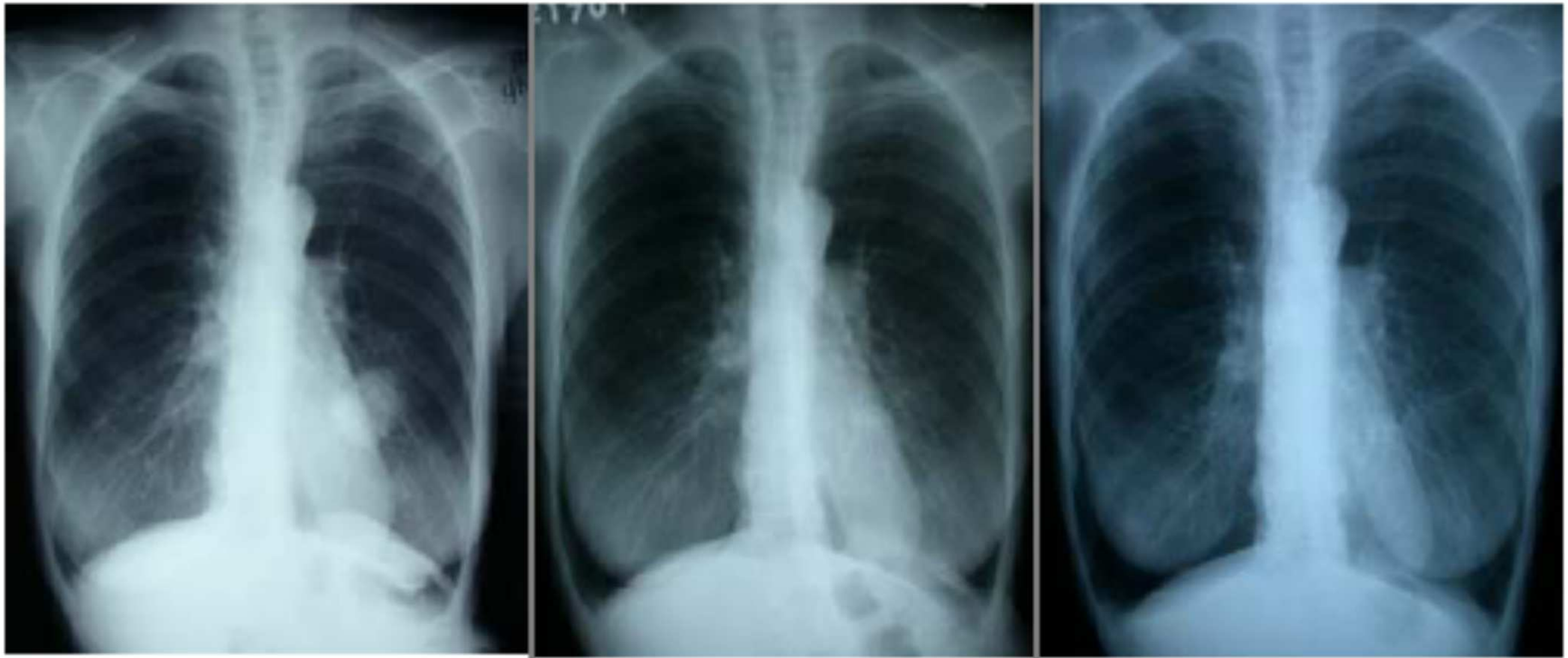


Distant failure rate:
@1 year: 12%
@2 year: 25%
@3 year: 34%

Crude DF 14% (N=48)

FJ Lagerwaard 2008 - Updated for ESMO-IASLC Lung Conference 2008

80 y/o, T2 tumor, 42 Gy



Pre-treatment | 6 weeks post-treatment | 3 years post-treatment

91 y/o, T2 tumor, 48 Gy

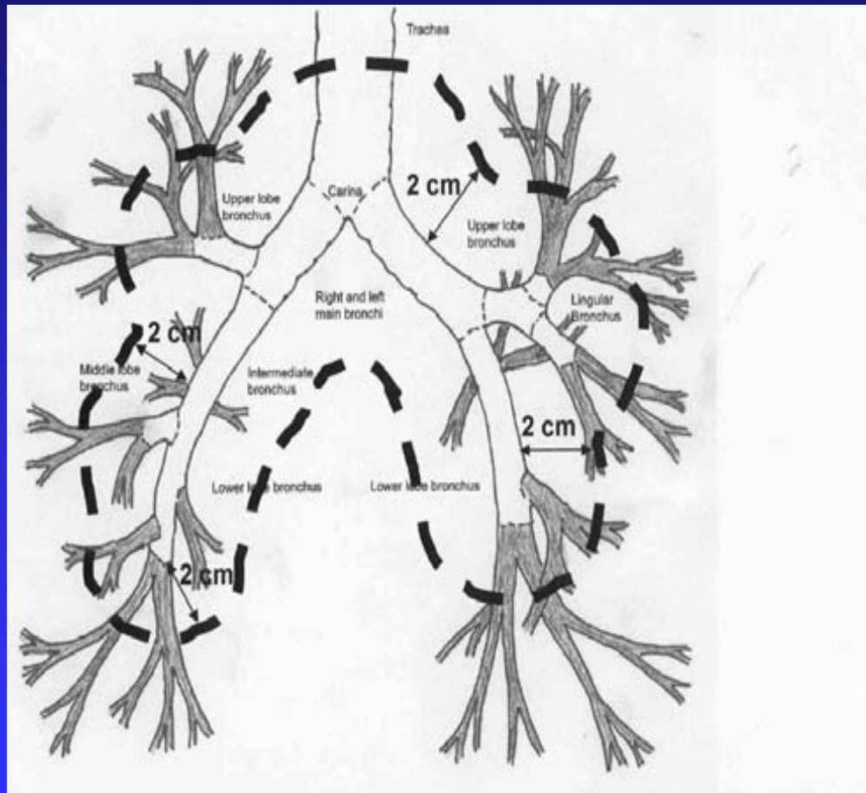
RTOG 0618

- A Phase II Trial of Stereotactic Body Radiation Therapy (SBRT) in the Treatment of Patients with Operable Stage I/II Non-Small Cell Lung Cancer

RTOG 0618

- **Schema:**
  - Stereotactic Body Radiation Therapy (SBRT), 20 Gy per fraction for 3 fractions over 1.5-2 weeks, for a total of 60 Gy
- **Eligibility:**
  - Patients with T1, T2 (≤ 5 cm), T3 (≤ 5 cm), N0, M0 operable non-small cell lung cancer; patients with T3 tumors must have chest wall primary tumors only; **no patients with tumors of any T-stage in the *zone of the proximal bronchial tree.*** Patients with T3 tumors based on mediastinal invasion or < 2 cm toward carina invasion are not eligible.

zone of the proximal bronchial tree



Defines *zone of the proximal bronchial tree*

DLCRG

Dutch Lung Cancer Research Group

ROSEL trial

PI: EF Smit and S Senan

Randomized clinical trial of radiosurgery (stereotactic radiotherapy) or surgery in patients with stage IA NSCLC who are fit to undergo primary resection

Design: Prospective, randomized phase III study

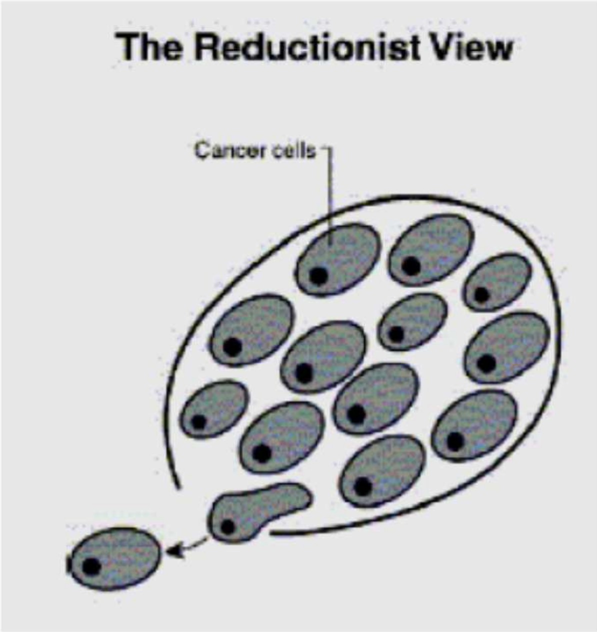
Outcome parameters

Primary: 2- and 5-year local and regional control, quality of life and treatment costs.

Secondary: Overall survival, quality adjusted life years (QALYs), pulmonary function, total costs (direct and indirect)

BIOLOGICAL ADAPTATION (5D RT)

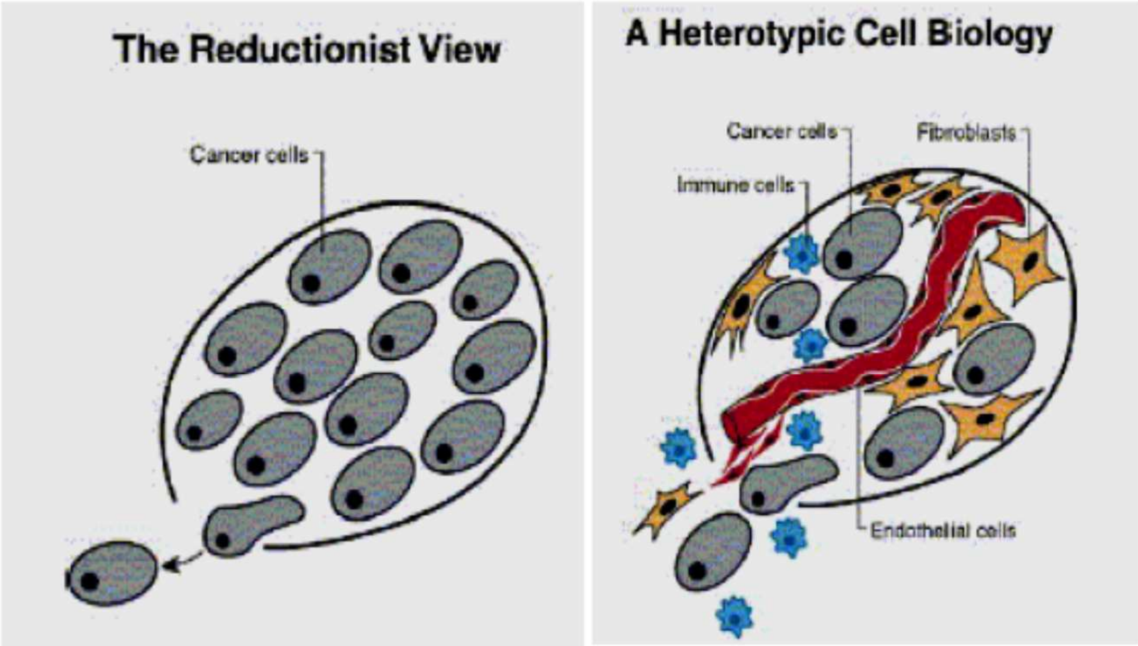
Biology



D. Hanaha, R. A. Weinberg, Cell,Vol. 100, 57-70,2000

BIOLOGICAL ADAPTATION (5D RT)

Biology



D. Hanaha, R. A. Weinberg, Cell,Vol. 100, 57-70,2000

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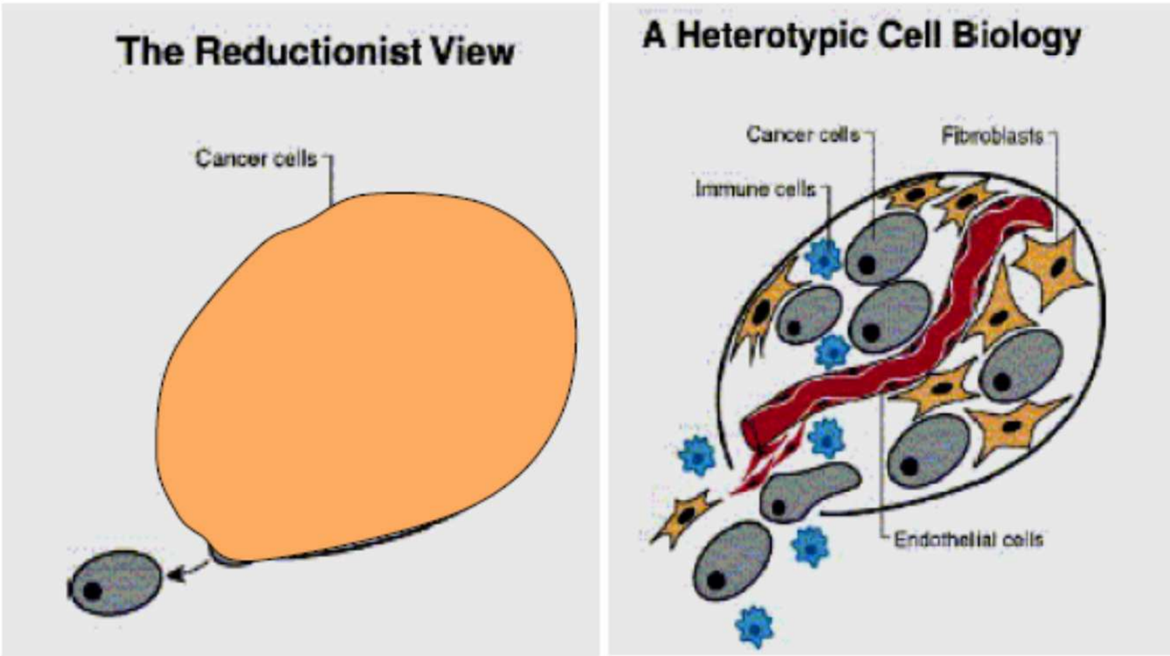
Biology



D. Hanaha, R. A. Weinberg, Cell,Vol. 100, 57-70,2000

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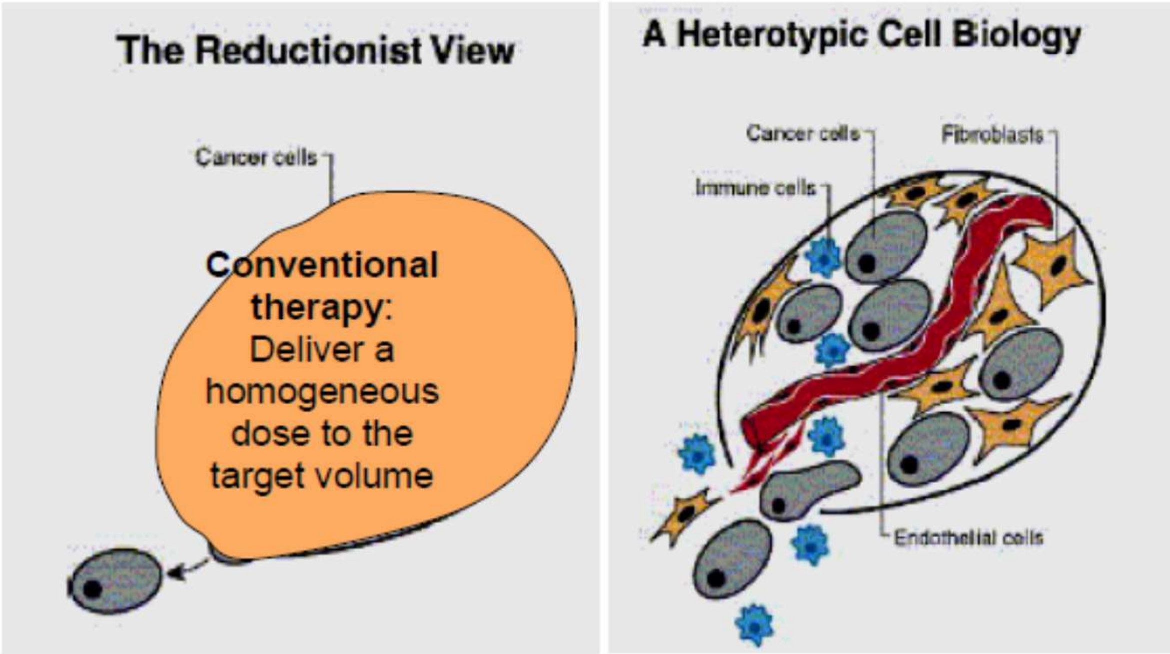

D. Hanaha, R. A. Weinberg, Cell,Vol. 100, 57-70,2000

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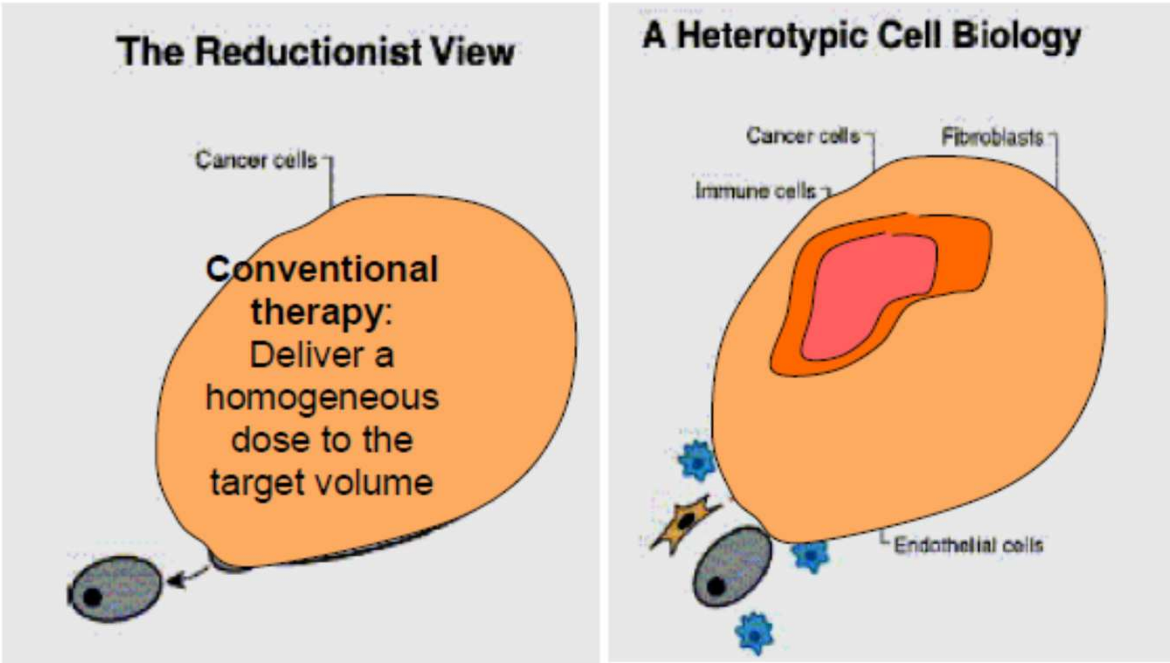

D. Hanaha, R. A. Weinberg, Cell,Vol. 100, 57-70,2000

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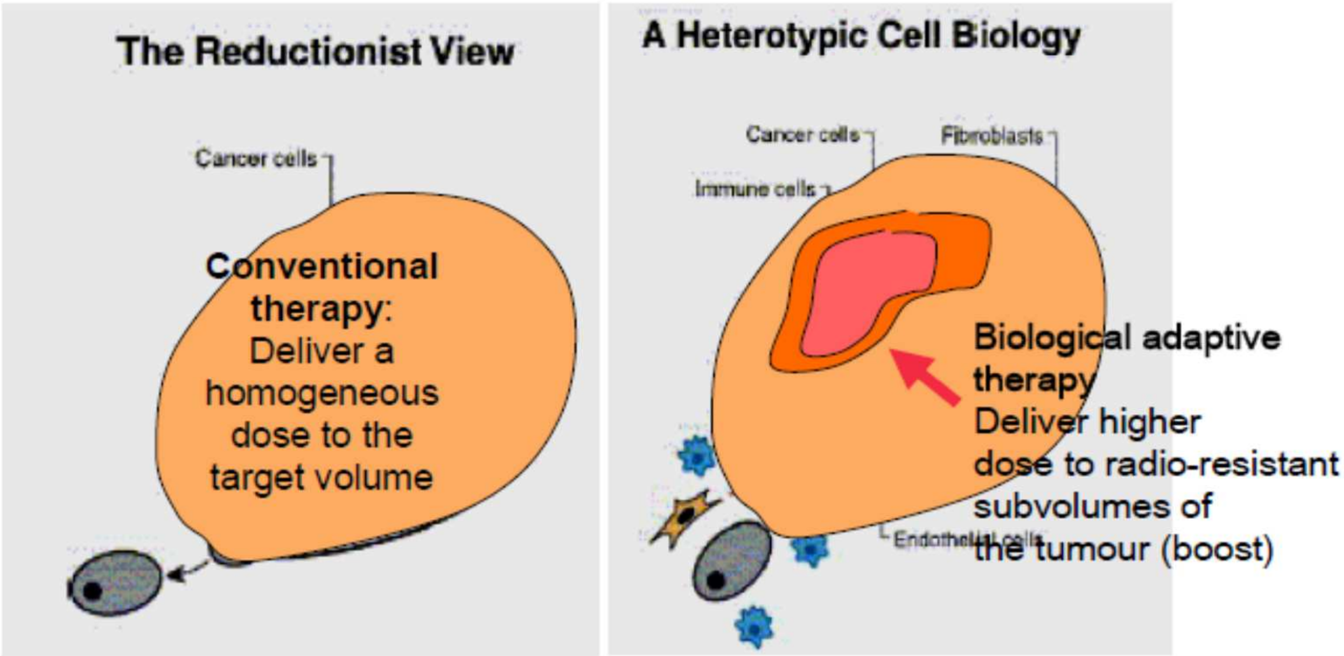


D. Hanaha, R. A. Weinberg, Cell,Vol. 100, 57-70,2000

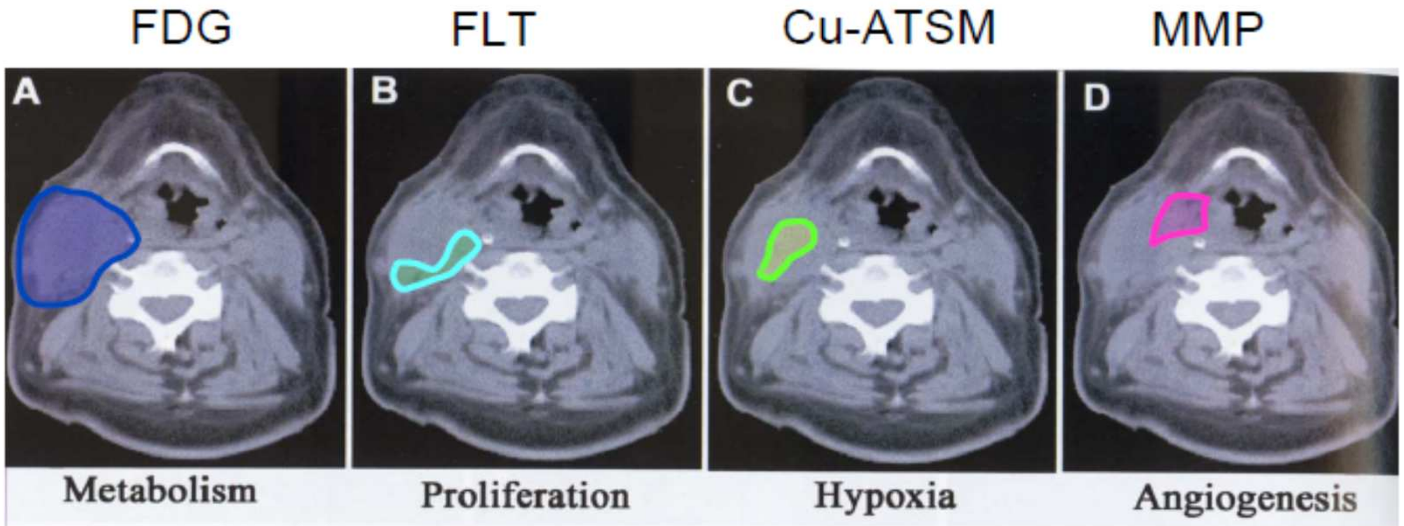
BIOLOGICAL ADAPTATION (5D RT)

Molecular Profiling	Most promising PET- or SPECT-markers[1]:	MRI/ MRS
Hypoxia	^{18}F-FAZA ^{60}Cu-ATSM	BOLD
Cellular Proliferation	^{18}FLT ^{11}C-Met Choline	^{1}H-Cholin-MRS
Apoptosis	Annexin 5	
Angiogenesis	^{18}F-Galacto-RGD	
Receptor status	^{18}F-FES	

1= see Apisarnthanarax 2005

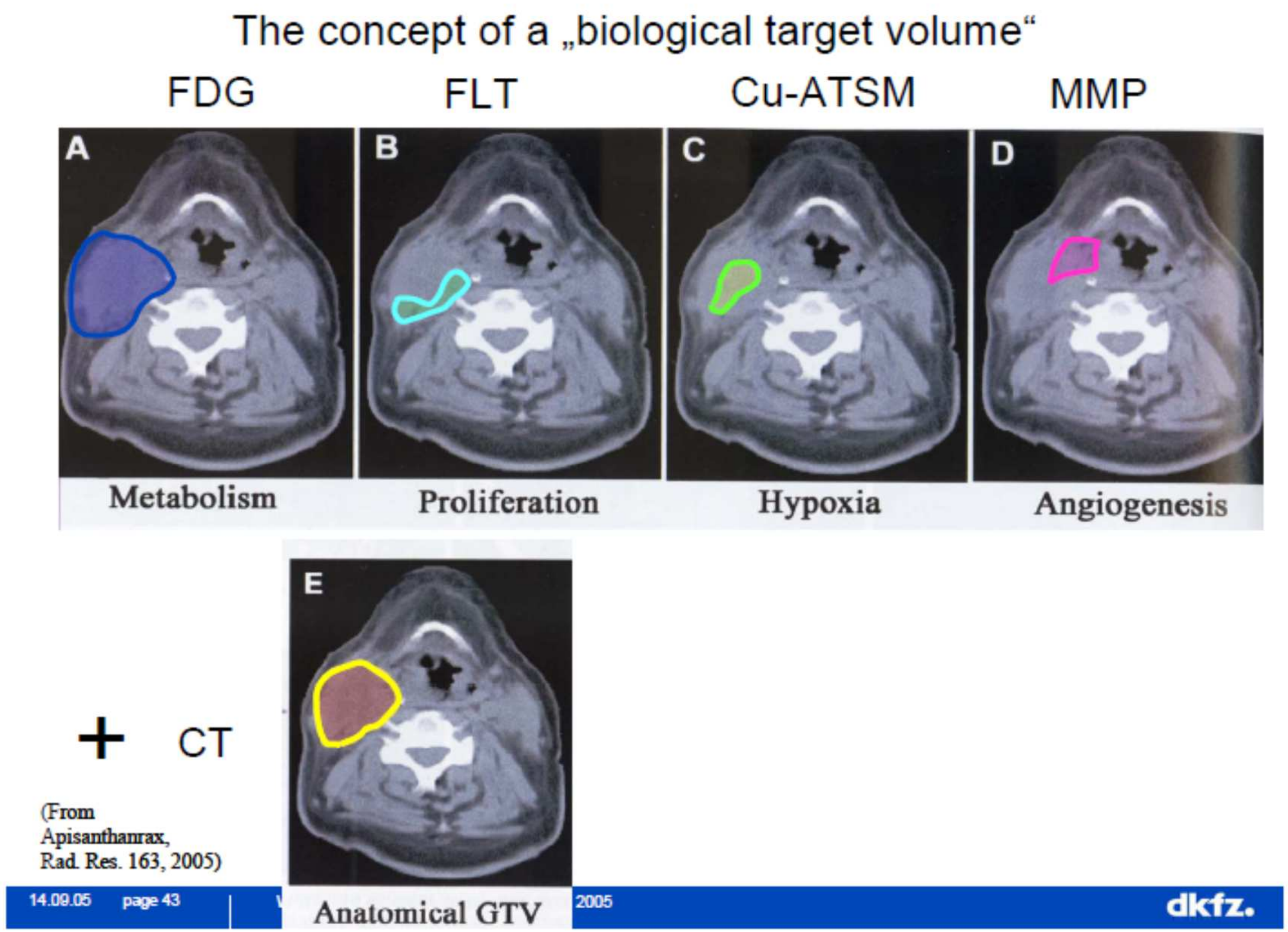
BIOLOGICAL ADAPTATION (5D RT)

The concept of a „biological target volume“

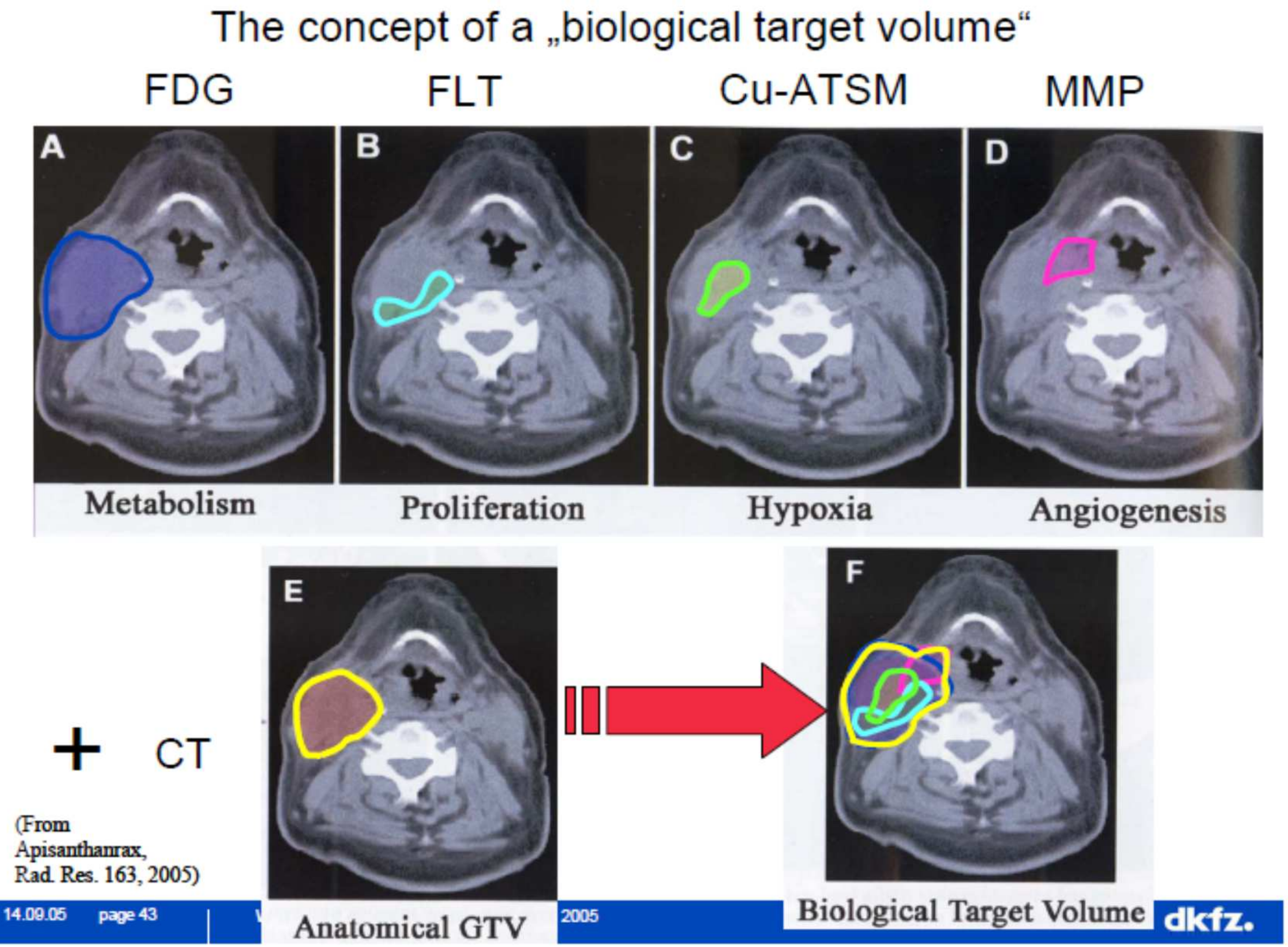


(From
Apisanthanrax,
Rad. Res. 163, 2005)

BIOLOGICAL ADAPTATION (5D RT)



BIOLOGICAL ADAPTATION (5D RT)



Conclusion

- With newer state of the art radiotherapy tools, very high dose of radiation can be delivered in early stage ca lung.
- Treatment finished in 1-2 wks time.
- Hospital visits reduced to 1-4.
- Results seems to be comparable to surgery
- Result of Randomized trial may change the standard of care in early stage NSCLC from surgery to SBRT.


Thanks for your attention