Stereotactic Ablative Radiotherapy for NSCLC: A New Hope

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Stereotaxy

- Refers to extremely accurate localisation of a point in space

- Stereotactic radiotherapy refers to a technique of extremely focused radiotherapy

- It is usually delivered in a small number of fractions (1-5), with large dose/fraction (>4Gy/#).

- Conventional radiotherapy is delivered using a large number of fractions, with small dose/fraction (1.8-2Gy),5 days a week, over 5-7 weeks

- Delivering a much higher dose over a shorter course of time, allows the radiation to be more effective biologically.

- The effect of stereotactic radiotherapy is akin to surgery.

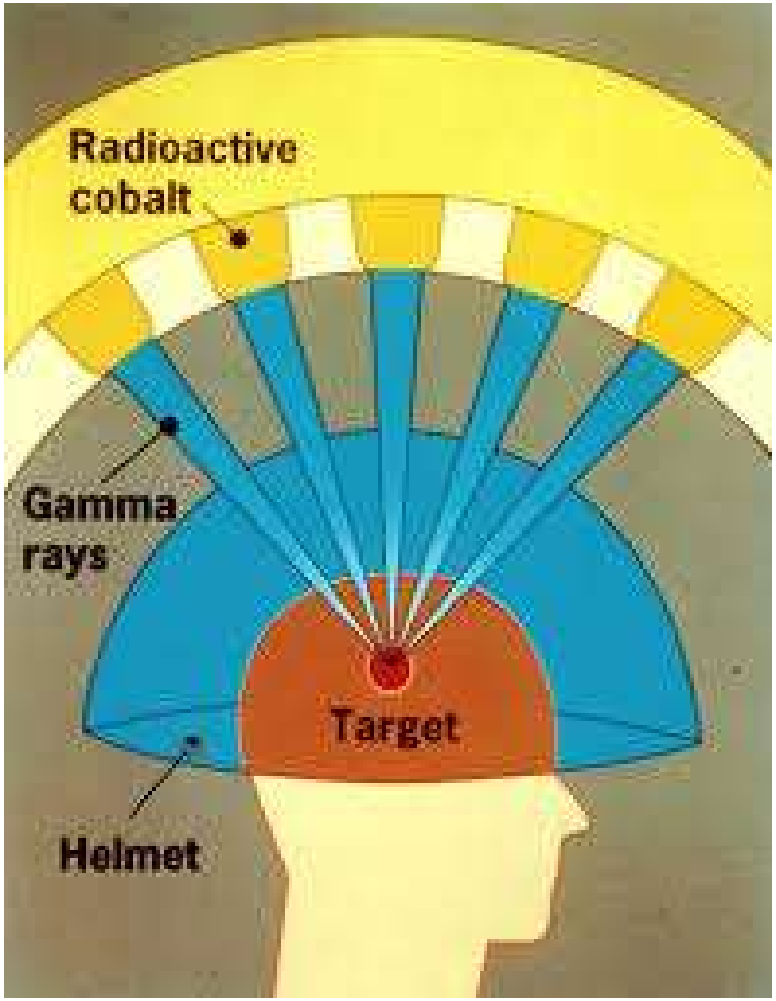
Cranial stereotaxy

- Stereotaxy was first achieved in cranial lesions, many of them benign, eg arterio-venous malformations, craniopharyngeoma, pituitary adenoma, acoustic neuroma.

- These all feature treatment of a small target, adjacent to vital areas, to a dose much higher than the tolerance dose of nearby structures.

- The first machine to deliver stereotactic radiotherapy was the Gamma knife, created by Lars Leksell (a neurosurgeon) in 1961. This machine uses 201 small telecobalt sources.

- Today, cranial stereotaxy can also be delivered by specially equipped linear accelerators (the so-called X-knife)

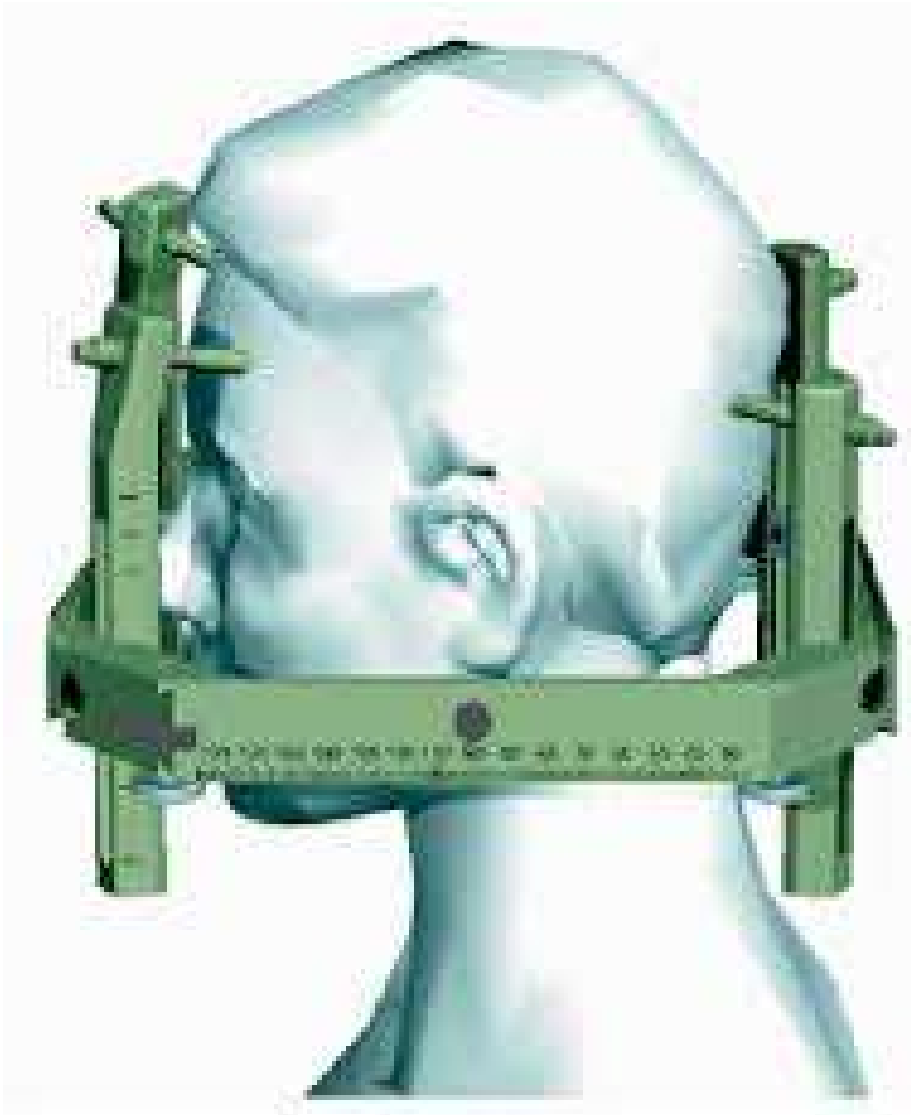


Gamma knife

Frame vs Frameless

- Cranial stereotaxy initially was based on physically & invasively fixing a rigid frame to the patient's cranium.

- The frame was required for the accurate localisation of the target on imaging.



- In the modern day, we have come to use non-invasive frames.

- Use of sophisticated pre-treatment imaging, such as in-room Cone Beam CT, has allowed us to do away with frames altogether.

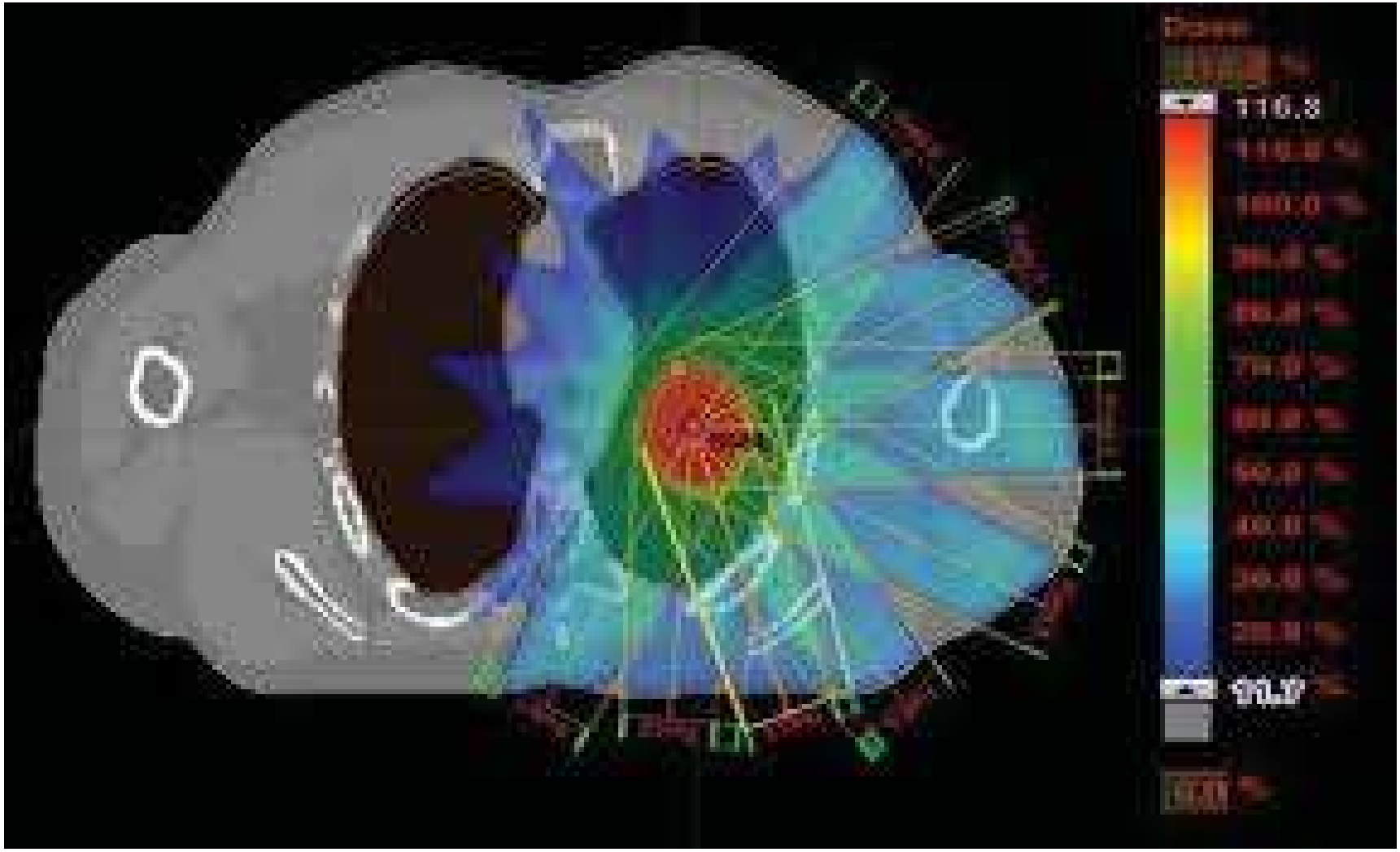
Stereotactic body radiotherapy (SBRT)

- Also called Stereotactic Ablative Body Radiotherapy (SABR)
- Extracranial stereotaxy has become possible because of Image Guidance in the treatment room
- SBRT is done for tumors of the lung, liver, pancreas, prostate & spine.

SABR for early NSCLC

- One of the most exciting recent developments in lung cancer therapy.
- Early lung cancers, though rare, are curable by surgery.
- However, many such patients have severe COPD & other medical comorbidities, precluding surgery.
- SBRT has provided an alternative to these patients.
- It has been shown to be as effective as surgery for local control.

SABR: Highly Conformal Dose Distribution



SABR: Biologically equivalent dose

- Ionising radiation acts by DNA damage

- With dose/fraction>8Gy, there is an additional benefit , which may be due to anti-angiogenic effects on vasculature of tumor micro-environment

Medical inoperability criteria

- Baseline FEV_1<40%
- Predicted post-op FEV_1<30%
- DLCO<40%
- Severe pulmonary arterial hypertension
- DM with severe end-organ damage
- Severe cerebral, cardiac & peripheral vascular disease

Surgery

- Significant variation in surgical outcome depending on setting & case-load of the institution
- 90-day mortality after surgery 5.4% (teaching) vs 7.8% (non-teaching)

5-year OS data:

- Stage I=45-79%
- Stage II=24-57%

Surgery vs SABR: Evidence

- ROSEL
- STARS
- RTOG 1021

3 RCTS of
Surgery
vs
SABR:
Failed due to
poor accrual

Meta-analysis (2014)

- 3 studies, N=864 patients
- 3-year OS was superior for surgery (80% vs 57%) , but not significantly so.
- Shorter-term survival stats were equivalent

Zheng et al. IJROBP 2014;90:603-11

SABR for Operable NSCLC: RTOG 0618

- Phase II trial
- N=33 (26 evaluable)
- Operable peripheral early stage NSCLC (T1-T3N0M0)
- Most cases were T1 (23) and 3 were T2

<u>2-year data:</u>

- Local failure rate=7.7%
- Involved lobe failure rate=19.2%
- Regional failure rate=11.7%
- Disseminated failure rate=15.4%
- PFS=65.4%
- OS= 84.4%

Timmerman et al. (Abstract) ASCO 2013

SABR vs conventional RT

- SABR is cost-effective as compared to sublobar resection & superior to conventional RT
- SPACE & CHISEL trials
- SABR (66Gy/3#) vs conventional RT (70Gy/35#)

Diagnosis of early NSCLC

- PET-CT based diagnosis : has been shown to be false+ve for between 1.3-25% cases (US data)

- Contrarily, as few as 40% of SABR cases have histopathology diagnosis

- Medical comorbidities may make tissue diagnosis difficult or even dangerous

Central vs peripheral

- Equivalent survival

Histology

- Difference in outcome between different subtypes of NSCLC have not yet been studied.

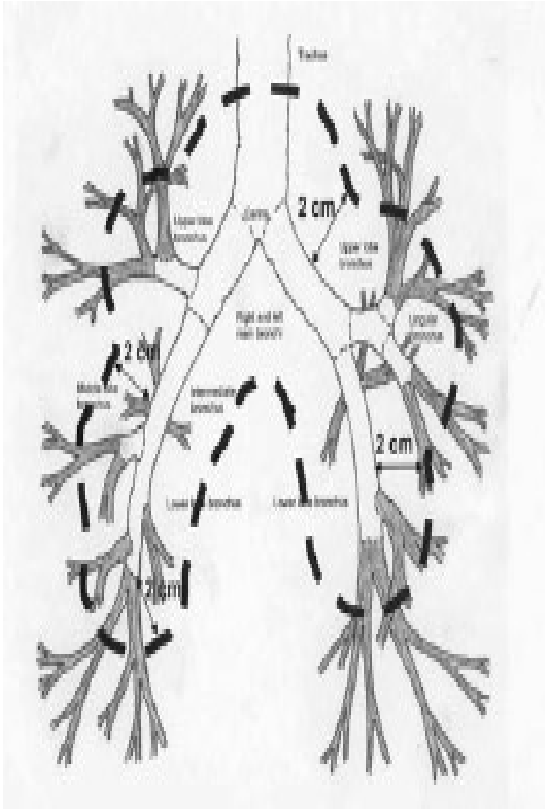
Doses

- Local control rates >85% with target dose >$100Gy_{10}$
- Mortality 1% with OAR doses < $210Gy_3$

Central tumors: No-fly zone?

- Initial trials showed significantly worse toxicity profile for central tumors
- 11-fold higher risk of death
- 54% vs 83% chance of freedom from severe toxicity at 2 years

- Gradually, a more fractionated approach has emerged



Excessive Toxicity When Treating Central Tumors in a Phase II Study of Stereotactic Body Radiation Therapy for Medically Inoperable Early-Stage Lung Cancer

Robert Timmerman, Ronald McGarry, Constantin Yiannoutsos, Lech Papiez, Kathy Tudor, Jill DeLuca, Marvene Ewing, Ramzi Abdulrahman, Colleen DesRosiers, Mark Williams, and James Fletcher

VOLUME 24 · NUMBER 30 · OCTOBER 20 2006

RTOG 0236 (2014 data)

- Phase II trial
- N=59 (55 evaluable)
- Stage I NSCLC, size <5cm, peripheral location
- Dose=18Gy x 3# (periphery)

<u>5-year data:</u>

- Local failure rate=7%
- Involved lobe failure rate=20%
- Regional failure rate=38%
- Disseminated failure rate=31%
- DFS=26%
- OS= 40%

Timmerman et al . (abstract) ASTRO 2014

SABR: Toxicities

Acute/Subacute

- Fatigue
- Chest wall pain
- Nausea
- Dyspnea
- Cough
- Erythema
- Hemoptysis
- Palpitations

- **Late (>3 months)**

- Chest wall pain
- Radiation pneumonitis
- Rib fracture
- Pleural effusion
- Atelectasis

Follow-up protocol

ESMO:

- CT scans q 6 months for 3 years
  q 1 year thereafter

Diagnosis of recurrence

- PET-CT is not always right!

- In fact, benigh lung injury post-SABR can have uptake on PET. However, SUVmax>5 suggests recurrence.

<u>High-risk features (HRF):</u>

- Enlarging opacity
- Sequential enlargement
- Enlargement after 12 months
- Bulging margin
- Loss of linear margin
- Loss of air bronchogram
- Cranio-caudal growth

SABR: Technology

The problem with lung motion

- The lungs are continuously moving with respiration.
- The extent of this movement can be blurred during a fast helical CT scan.
- Movement is maximum in lower lobe tumors (close to the diaphragm), & less in upper lobe tumors.

- **Average movement in normal breathing:**

Upper lobe = 0 - 0.5cm

Lower lobe =1.5 - 4.0cm

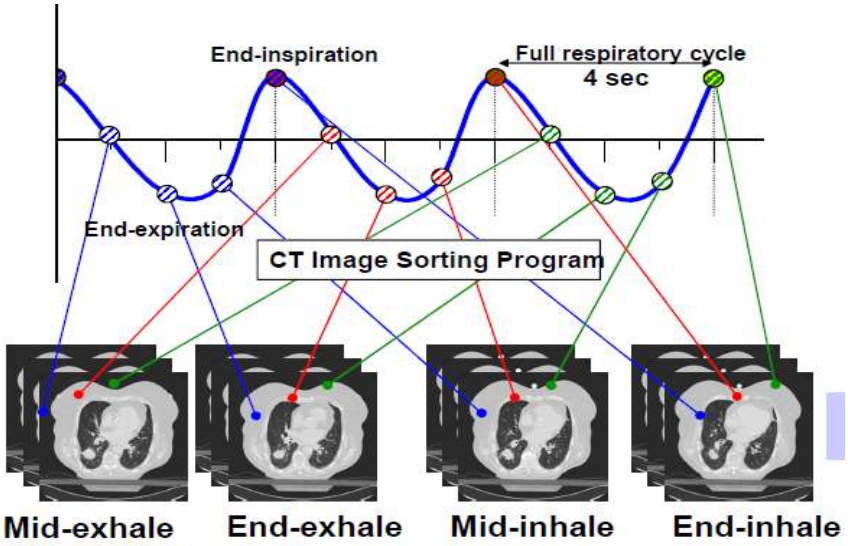
Middle lobe = 0.5 - 2.5cm

Hilum = 1.0 - 1.5cm

METHODS OF ASSESSING LUNG TUMOR MOTION DURING RESPIRATION

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

- Slow CT scans



•Take a succession of CT images across several respiratory cycles.
•Then the images are grouped according to the respective respiratory phase.
•Thus a composite image, over 10 phases, is achieved.

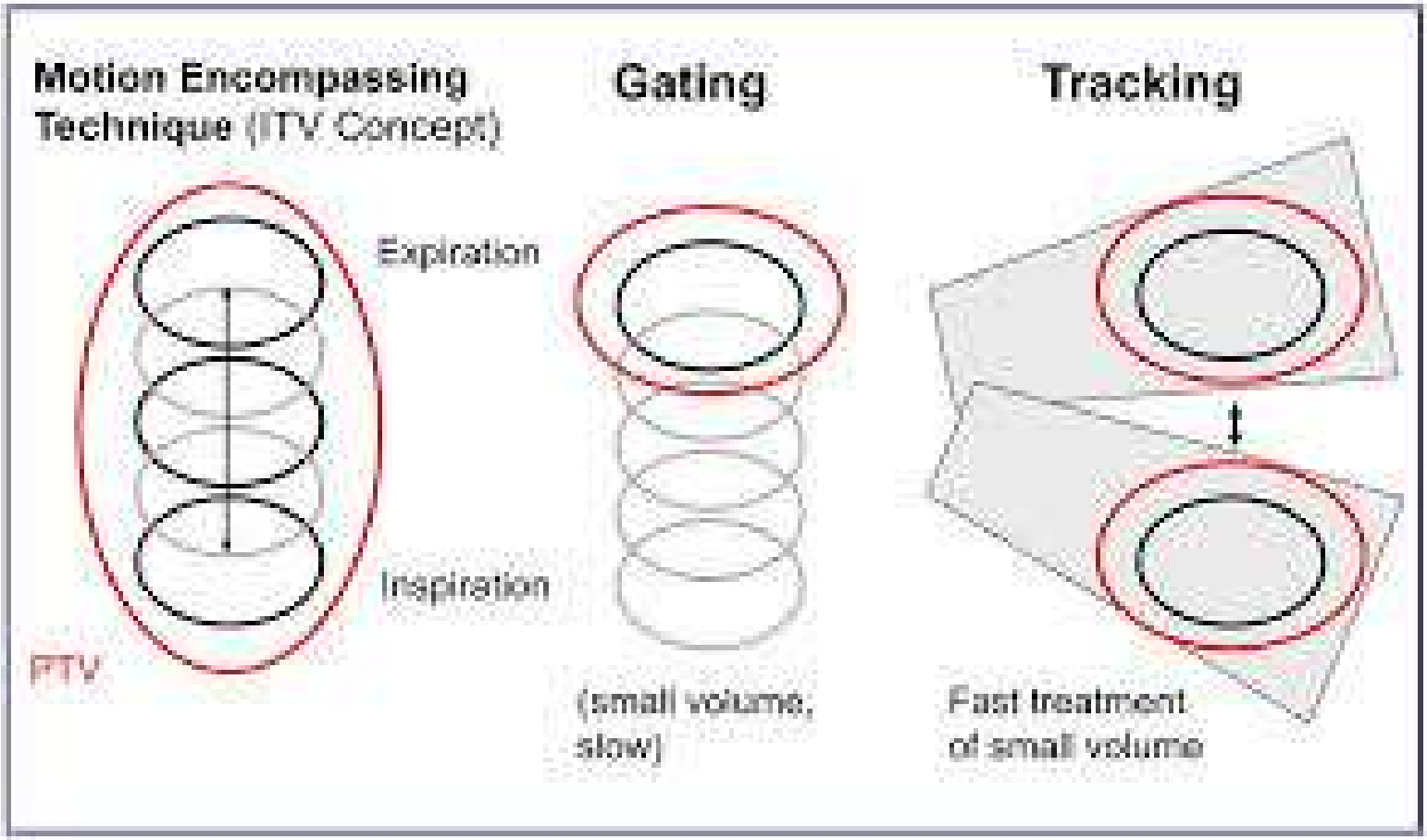
METHODS TO CONTROL / COMPENSATE FOR LUNG MOTION DURING RESPIRATION

Free breathing methods:

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

Breath-hold methods:

- Active Breathing Coordinator (ABC)


Motion Encompassing Technique (ITV Concept)
Expiration
Inspiration
ITV
Gating
(small volume, slow)
Tracking
Fast treatment of small volume

ITV-based treatment

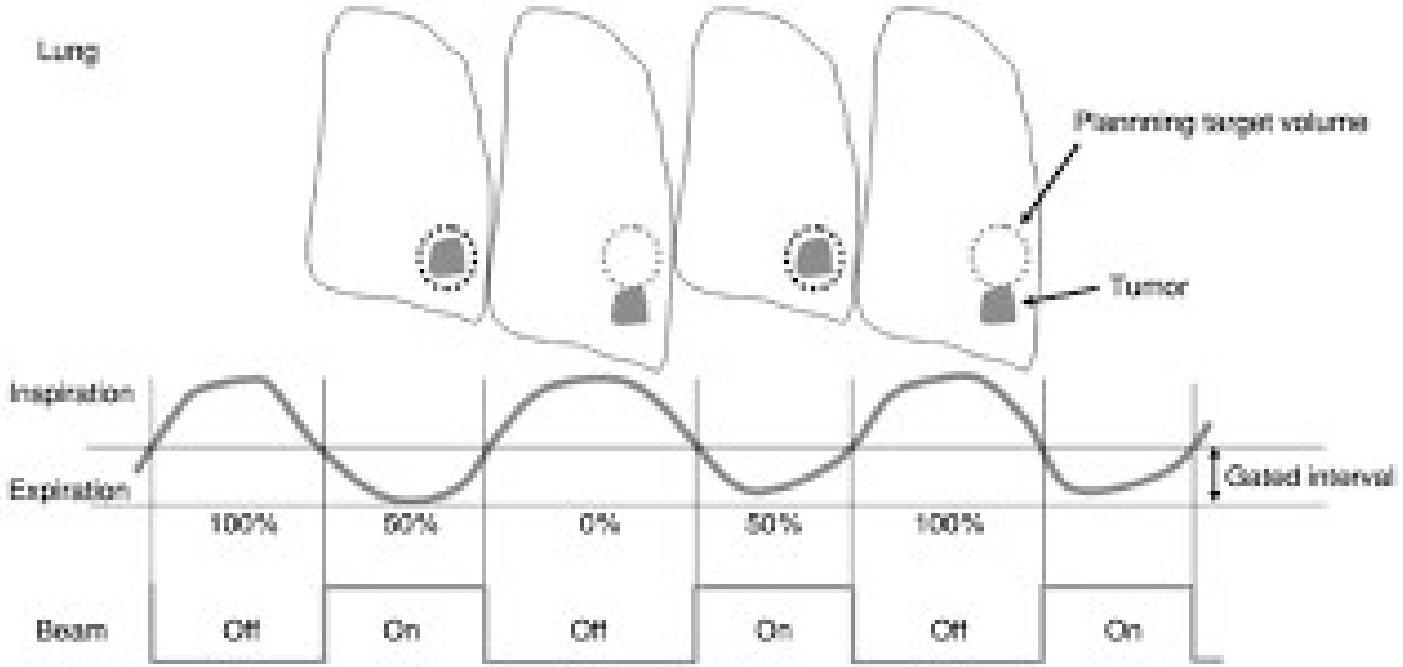
Generates a **composite target volume** for lung tumors, taking into account the different shape, size and position of the tumor in each phase of respiration

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

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.

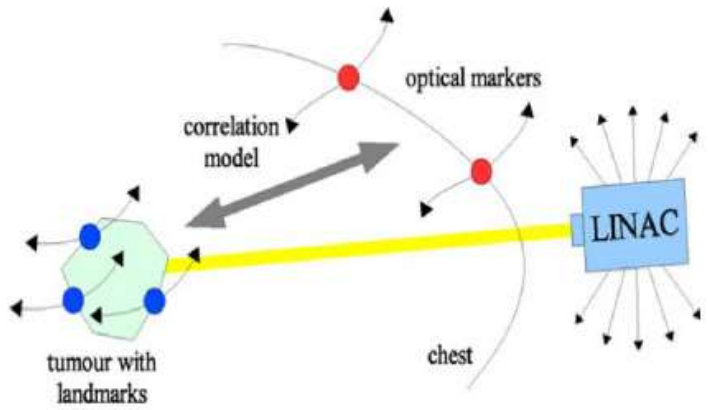
Usually requires an internal fiducial, implanted within the tumor.

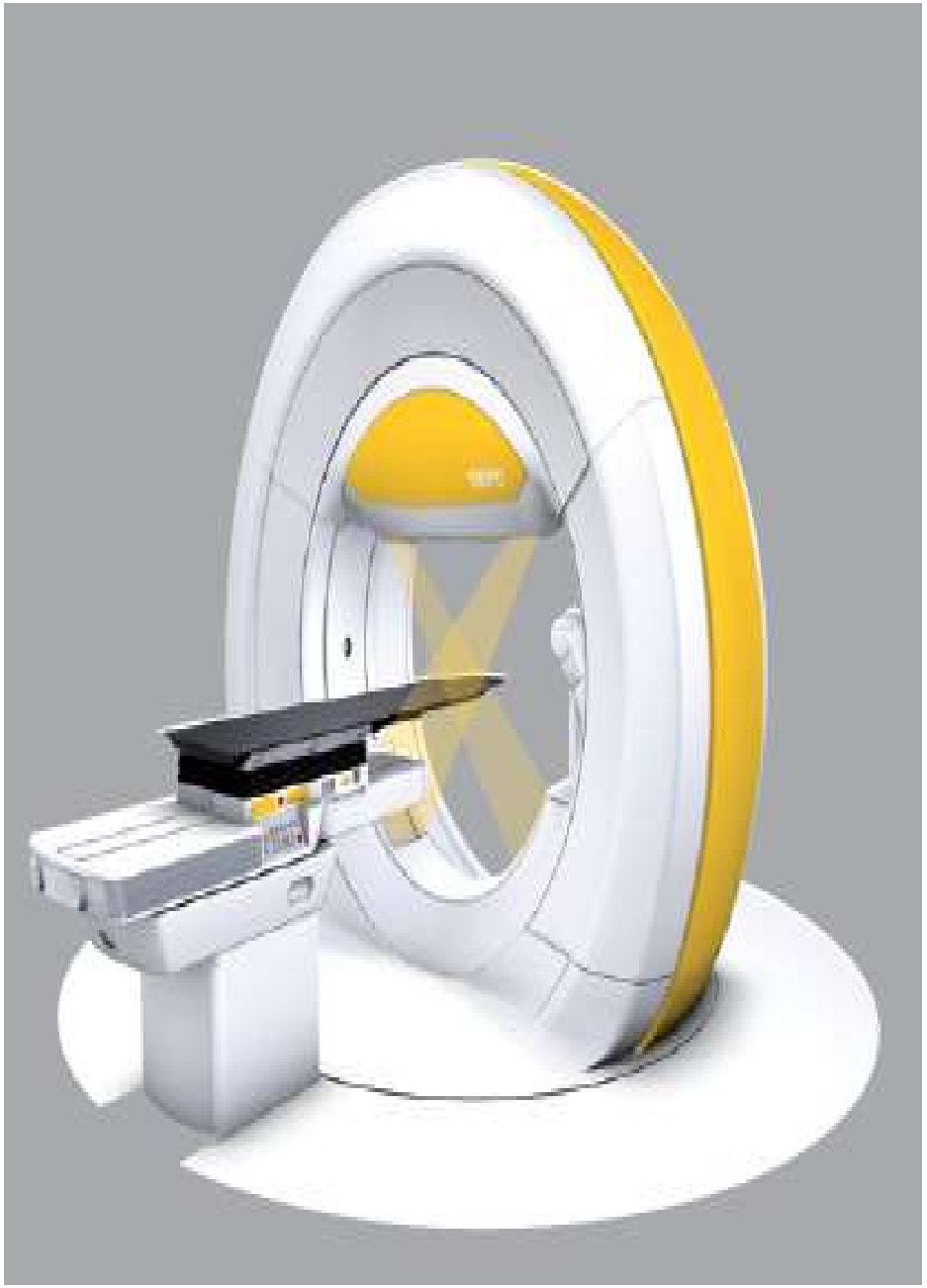
Can also be done non-invasively in some cases.

Real Time Tumor Tracking

- ExacTrac system (VERO)
- Cyberknife

Principle of RTT



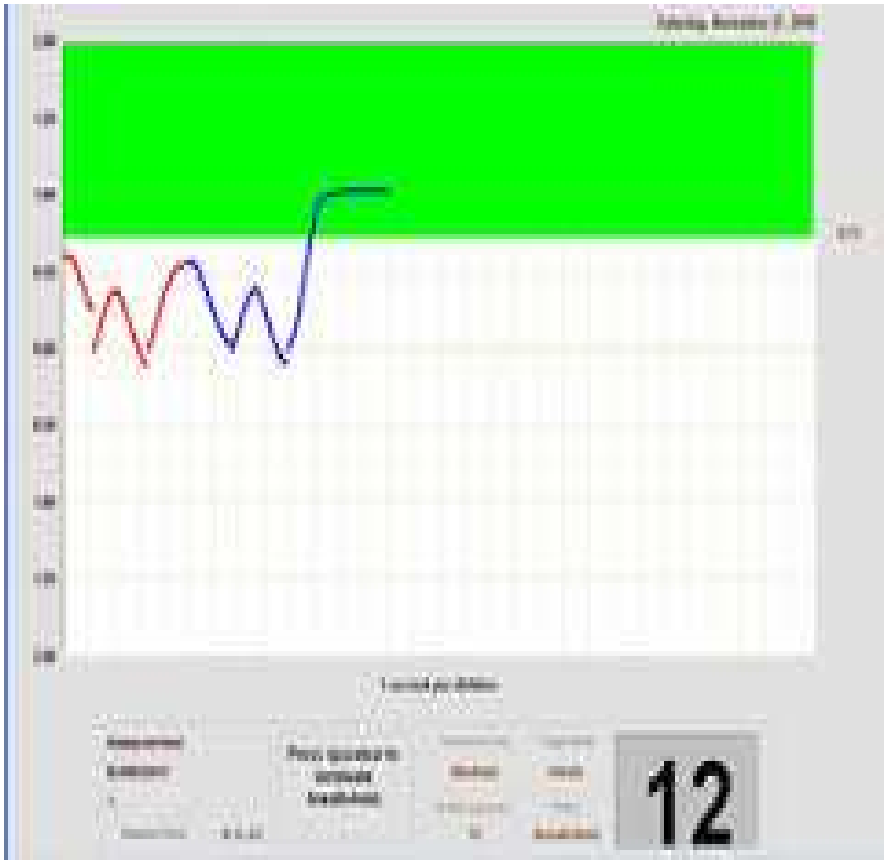


VERO

Cyberknife

Active Breathing Coordinator

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



SABR: Take Home Messages

- The success of SABR has opened up curative possibilities for medically inoperable NSCLC patients, many of whom would have otherwise died untreated

- Promising data with low-dose CT screening trials (NELSON) → may mean a higher pick-up rate for early stage NSCLC

- Central database & an organised system of referrals for medically inoperable cases→could see a higher % of such patients taken up for SABR

- A good surgical team→ more referrals for operative assessment→ may ironically mean more cases for SABR

- SABR may yet emerge as a viable alternative to surgery even in operable cases.