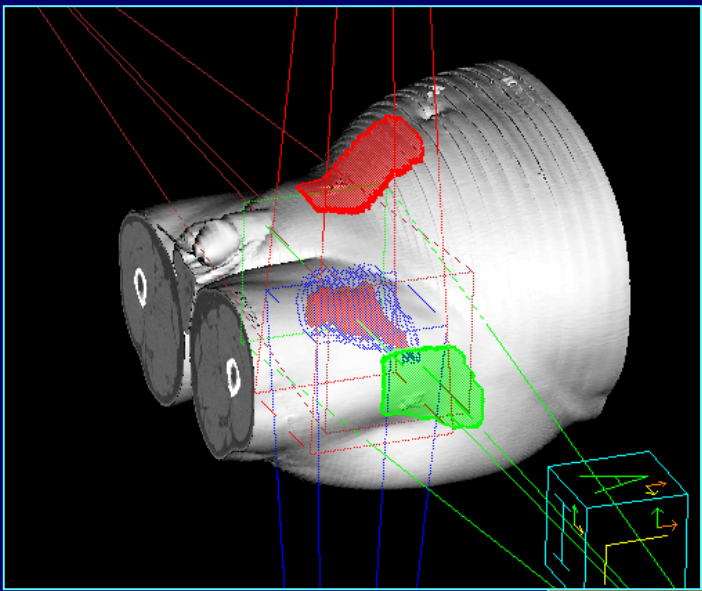
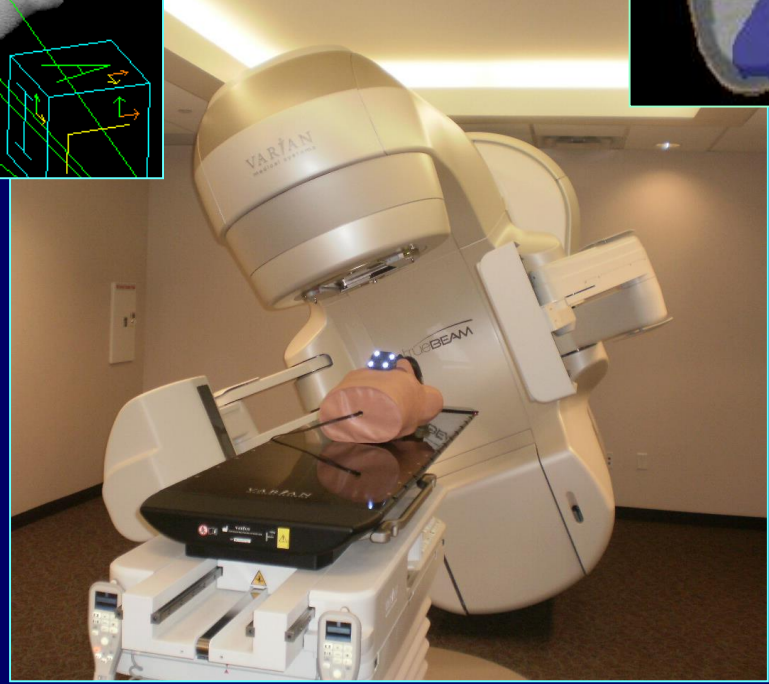


# Principles of radiotherapy and radio-chemotherapy of malignant tumours



Polgár Cs.<sup>1,2</sup> –  
National Institute of  
Oncology<sup>1</sup>,  
Chair of Oncology,  
Semmelweis  
University<sup>2</sup>



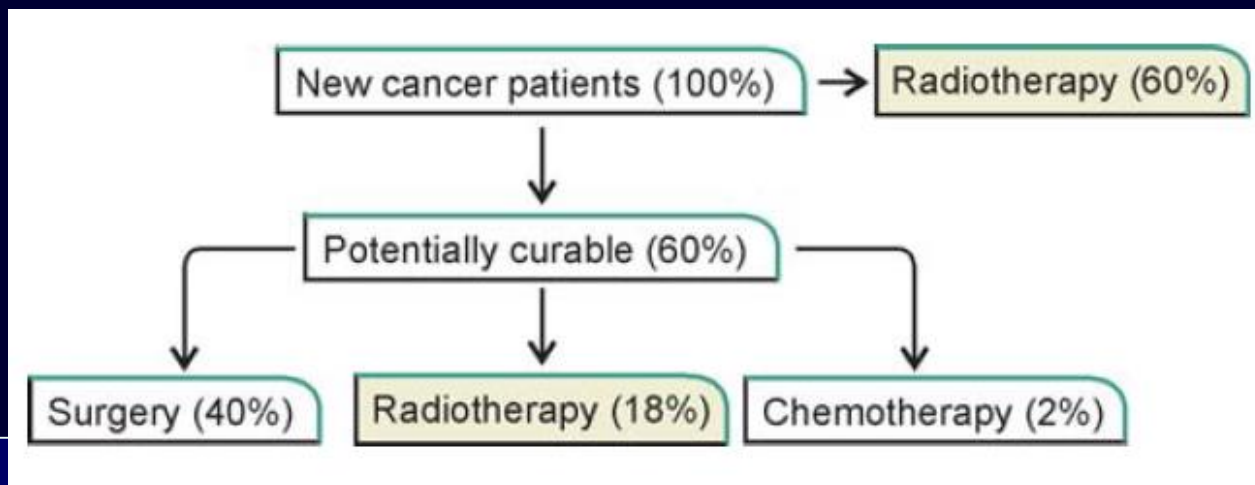
# Multidisciplinary treatment of malignant tumours

- Surgery (S)
- Radiotherapy (RT)
- Systemic therapy
  - Chemo-, hormone-, immuno-therapy + targeted therapies
- Combined (multidisciplinary) management:
  - S + RT
  - S + concomittant radio-chemotherapy (RCT)
  - Primary RCT
  - Preop. RT + S

- Radiotherapy: Clinical modality dealing with the use of ionizing radiation in the treatment of patients with malignant tumours.
- Aim: To deliver precisely measured dose of irradiation to a defined tumour volume with as minimal damage as possible to the surrounding healthy tissues, resulting eradication of the tumour.
- (selective killing of malignant cells)
- Teletherapy = external beam irradiation (EBI)
- Brachytherapy (BT) = irradiation with sealed radioactive sources placed close to or in contact with the tumour.

## Role of RT in the management of tumours

- New cancer cases/year in Hungary: 76.000 → 2030 ≈ 100.000 new cases
- In 60% of cancer patients RT is mandatory!
- In 20-25% of RT patients a 2<sup>nd</sup>. course of RT (reirradiation) is needed.




## Annual number of RT patients in Hungary

	1993	2012	2013	2014	2015	2016	2017
RT patients#	12.685	31.097	32.194	33.162	28.359	33.376	33.024

+ 20.339

# Intention of radiation therapy

- Intention to treat:
  - Curative (total dose: 50-80 Gy)
  - Palliative (total dose: 20-60 Gy)
- Preoperative RT (down-staging & down-sizeing, devitalisation of tumour cells before surgery  organ preservation surgery)
- Postoperative RT (eradication of microscopic residual tumour cells)
- Definitive or primary RT
- RT alone
- Combined RCT (head & neck, cervical, bladder, anal canal, rectal, lung)
- Combined radio-biotherapy (head & neck: cetuximab + RT)

# Preoperative RT

- Rectal ca.
  - T1-2 N0 - preop. RT
  - T3-4 N1-2 – preop. RCT
- Esophageal ca.
  - preop. RCT
- Cervical and endometrial cancers
  - preop. brachytherapy

# Postoperative RT

- **Prostate ca.**
  - T3-4, N1
- **Breast ca.**
  - After breast-conserving surgery (All pts.)
  - After mastectomy (T3-4, ill. N+)
- **Gastric ca.**
  - Postop. RCT
- **Head & Neck cancers**
  - Postop. RT
  - Postop. RCT (R1 resection, >1 pos. LNs)
- **Brain tumours**
  - Glioblastoma – Postop. RCT
- **GYN cancers**
  - Endometrial ca. (postop. RT: G3, pT1b, N+)
  - Cervical ca. (postop. RCT: R1 resection, pos. LNs, infiltr. parametria)
  - Vulvar ca.

# Primary (Definitive) RT/RCT

- Anal canal cc.: Curative RCT
- Prostate ca.
  - Low risk: Brachytherapy (BT) OR external beam irradiation (EBI) alone
  - EBI + BT boost
- GYN cancers
  - Endometrial ca. – RT alone (EBI + BT)
  - Cervical ca.
    - St. I/A-I/B1: RT alone (EBI + BT)
    - St. I/B2, II/A-B, III/A-B, IV/A: concomitant RCT + BT
  - Vaginal ca.: RT or RCT
- Head & Neck tumours
  - T1-2 N0 – RT alone
  - T3-4 N1-2 – RCT
- Lung ca.: Curative RT or RCT
- Bladder ca. (muscle invasive;  $\geq T2$ ): TUR + curative RCT



# Palliative RT

- Cerebral metastases – Whole brain irradiation (WBI)
  - Stereotactic radio-surgery (SRS)
- Spinal compression
- Bone metastases (pain and/or danger of fracture)
- Vena Cava Superior (VCS) syndrome (decompression)
- Palliative brachytherapy
  - GYN cancers – stop bleeding
  - Lung and esophageal tumours – avoid obstruction

# Cutaneous lymphoma – Primary RT



Before RT



After RT

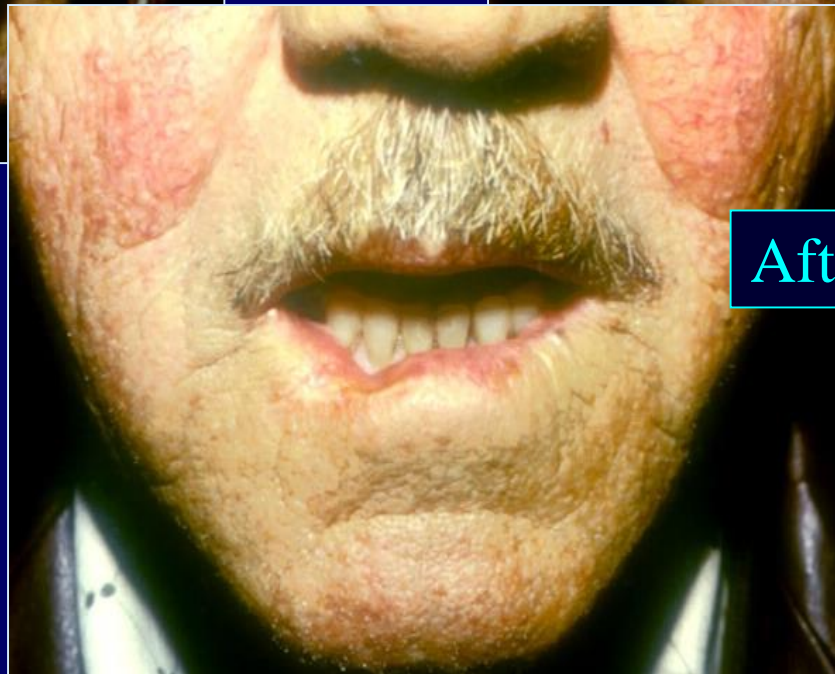
# Ca. of the lip – Primary RT



Before RT



After RT



# Squamous cell ca. of the nose – Primary RT



Before RT



After RT

# Dosimetric principles

- Only the energy of ionizing radiation absorbed by the tissues has biological effect!
- The absorbed energy is quantified with the term "absorbed dose")

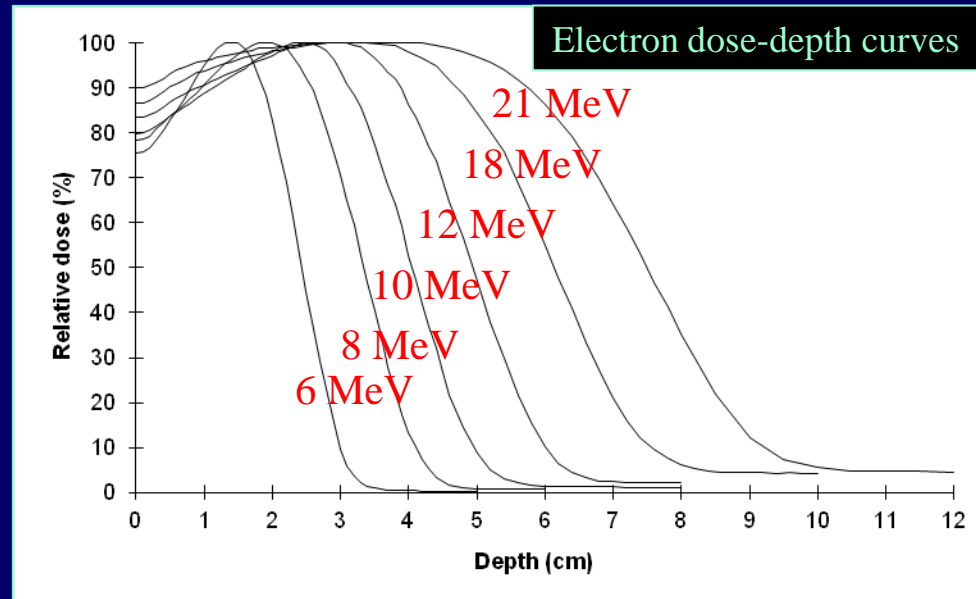
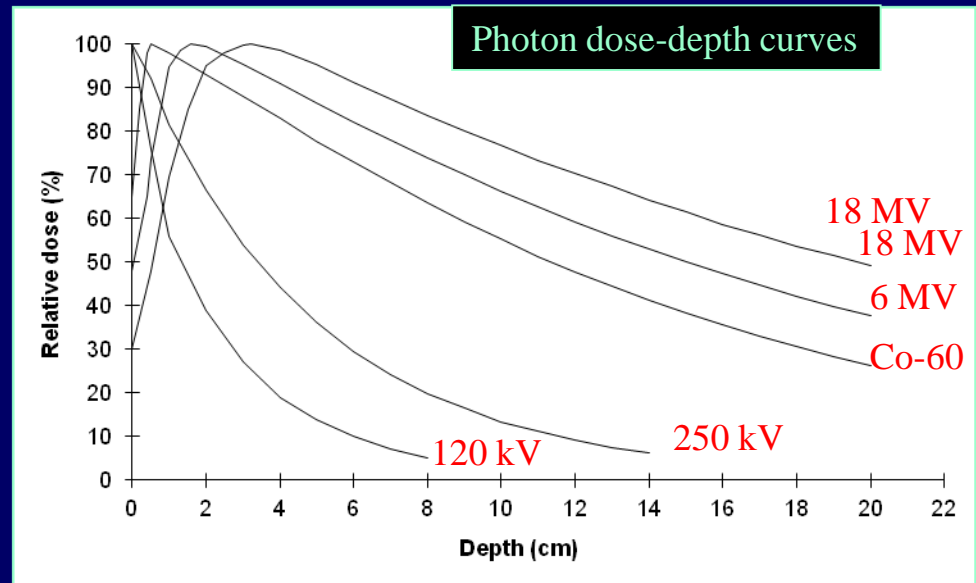
Absorbed dose: absorbed energy by a unit of tissue mass.  
SI unit: Gray (Gy)

$$1 \text{ Gy} = 1 \text{ J/kg} \quad 1 \text{ Gy} = 100 \text{ cGy}$$

Dose rate: absorbed dose by time unit.  
SI unit: Gy/min, Gy/h

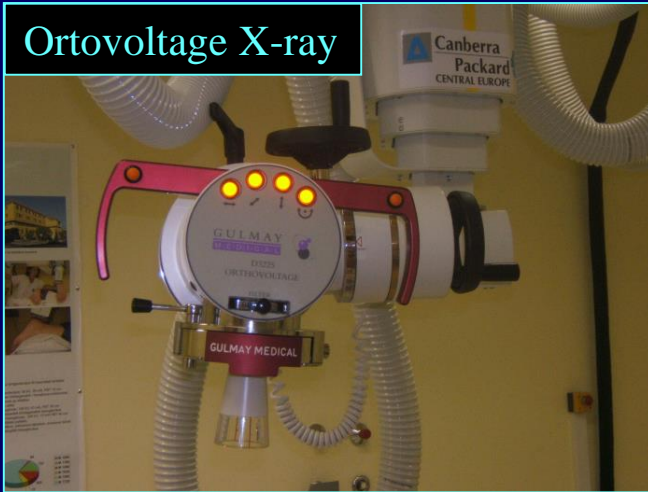
# Modifying factors of the biological effects of RT

- Radiation quality (photons, electrons, protons)
- Energy
- Total dose
- Fractionation
- Radiosensitivity of tumours and normal tissues
- Irradiated volume
- Radiosensitizers (hyperbaric O<sub>2</sub>, RCT, hyperthermia)
- Radioprotective drugs (e.g. Salagen – protection of salivary glands)



# Teletherapy equipments

Ortovoltage X-ray



- Kilovoltage equipments:
  - X-ray therapy machines: 40-300 KV Roentgen-photons
- Megavoltage equipments:
  - Telecobalt unit: 1.25 MV gamma-photons
  - **L**INear **A**Ccelerators (**L**INAC): 4-29 MV photons OR electrons

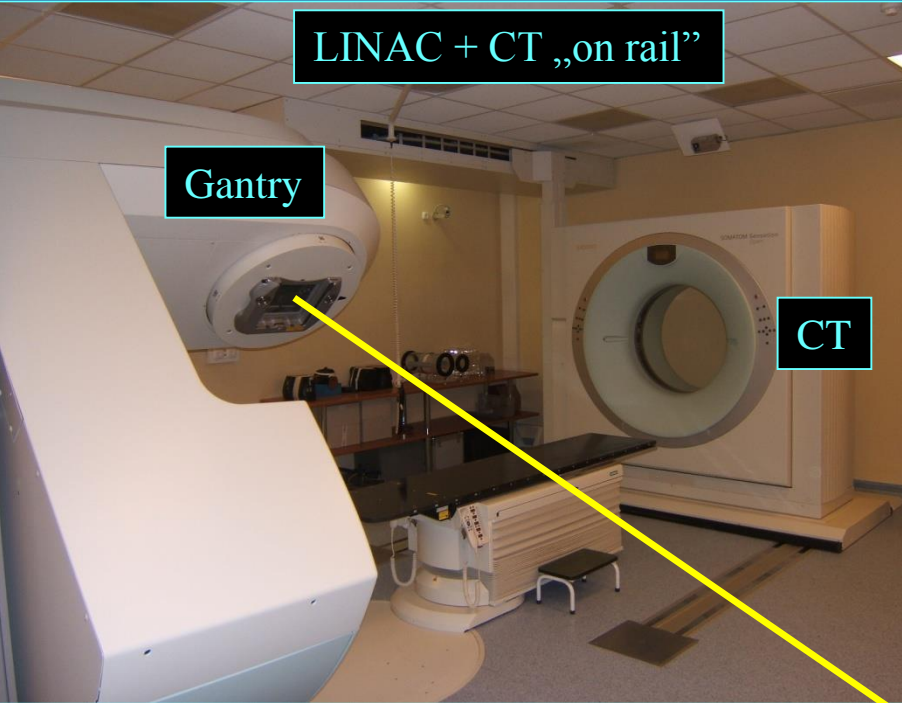
Telecobalt



LINAC



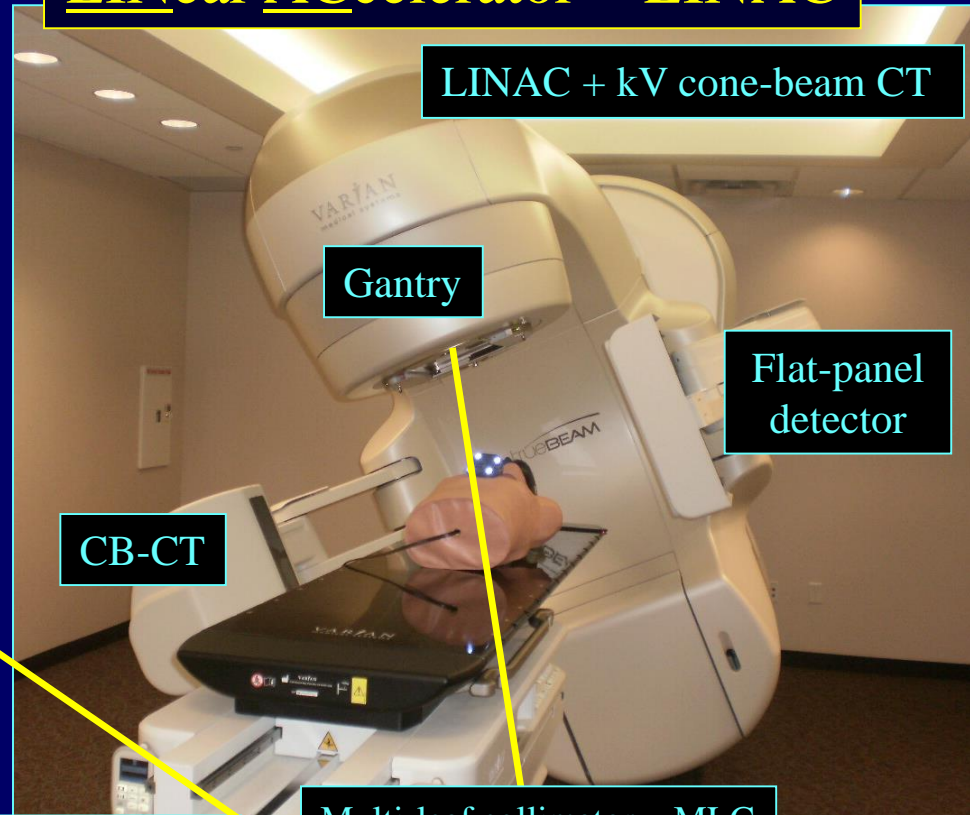
LINAC + CT „on rail”



Gantry

CT

LINear ACcelerator = LINAC



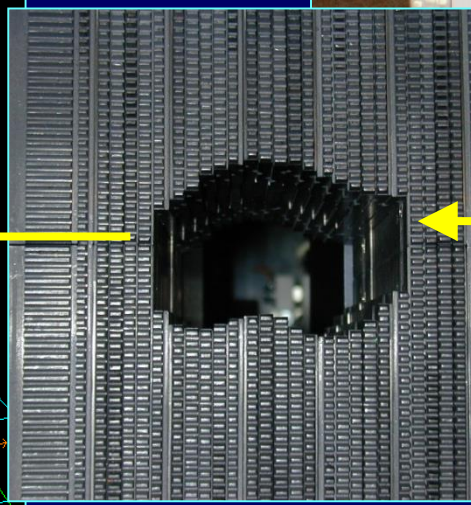
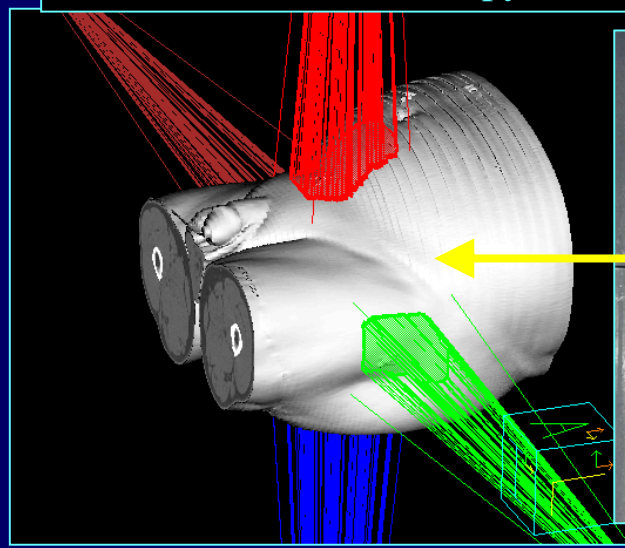
LINAC + kV cone-beam CT

Gantry

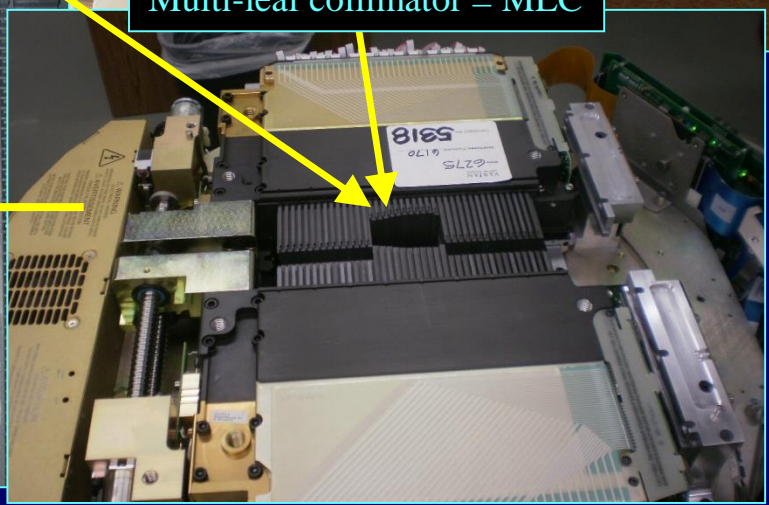
Flat-panel detector

CB-CT

3D conformal radiotherapy = 3D-CRT



Multi-leaf collimator = MLC



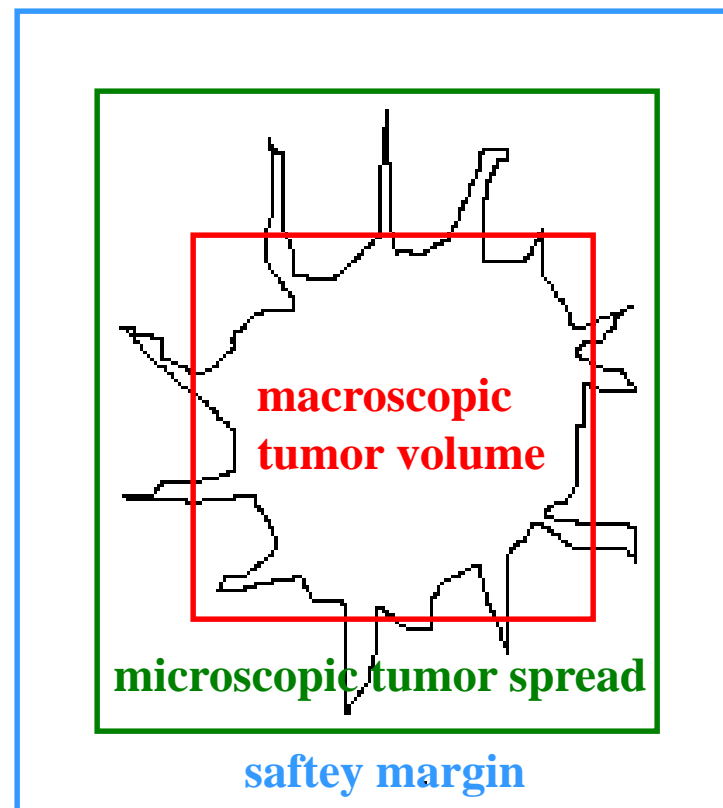


# Definition of target volumes for radiotherapy treatment planning

**GTV = Gross Tumor Volume** ← CT, MRI, US

**CTV = Clinical Target Volume**

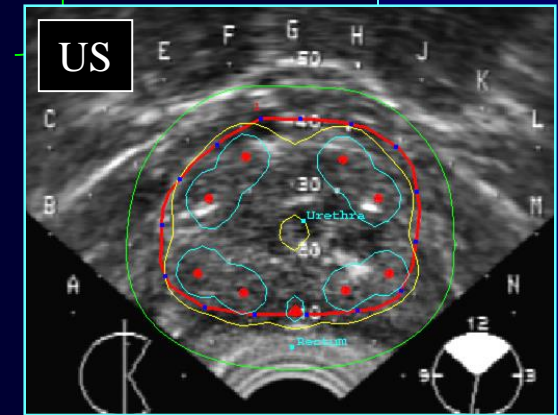
**PTV = Planning Target Volume**



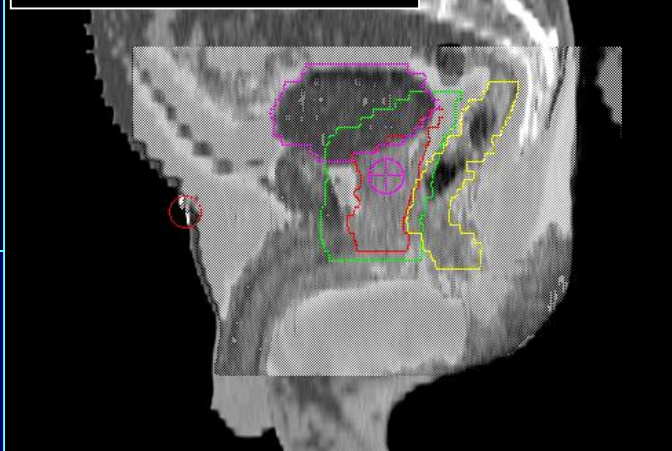
# Informations needed for radiotherapy treatment planning

- Data on tissue density – for dose calculation (CT)
- Anatomic information (CT, MRI, US)
- **Biological information (PET)**
- 4D information (3D + change in time)

PET/CT

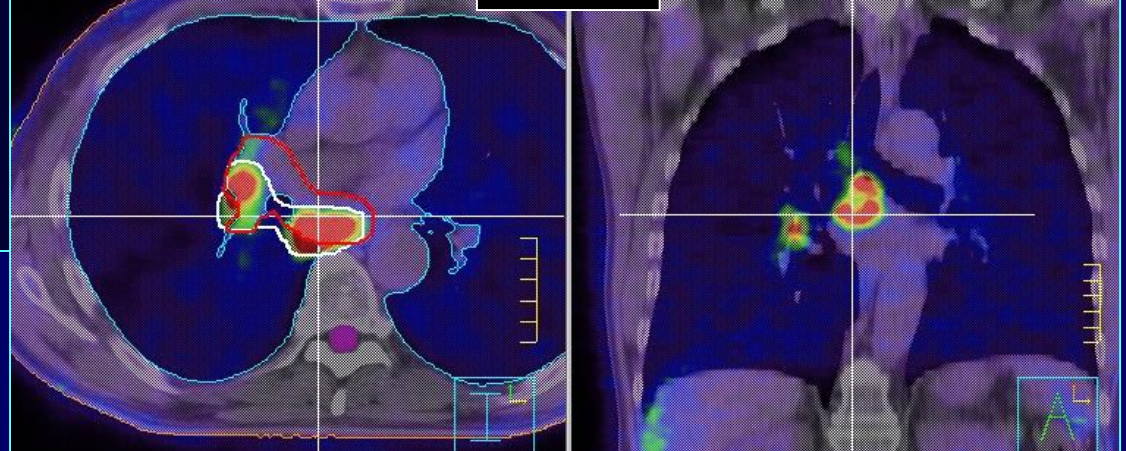


CT-MR image fusion



Trial\_1

PET/CT

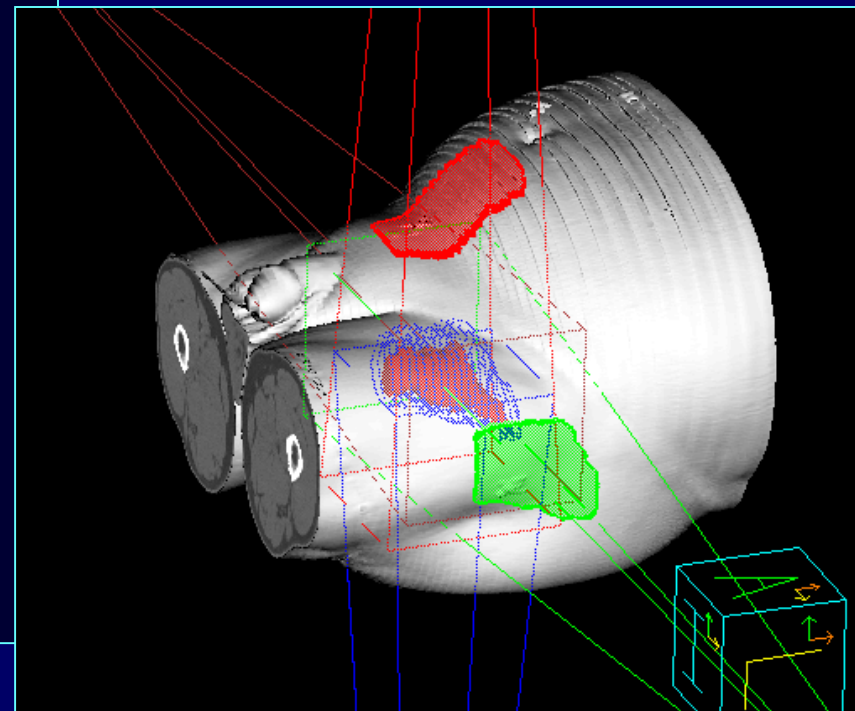
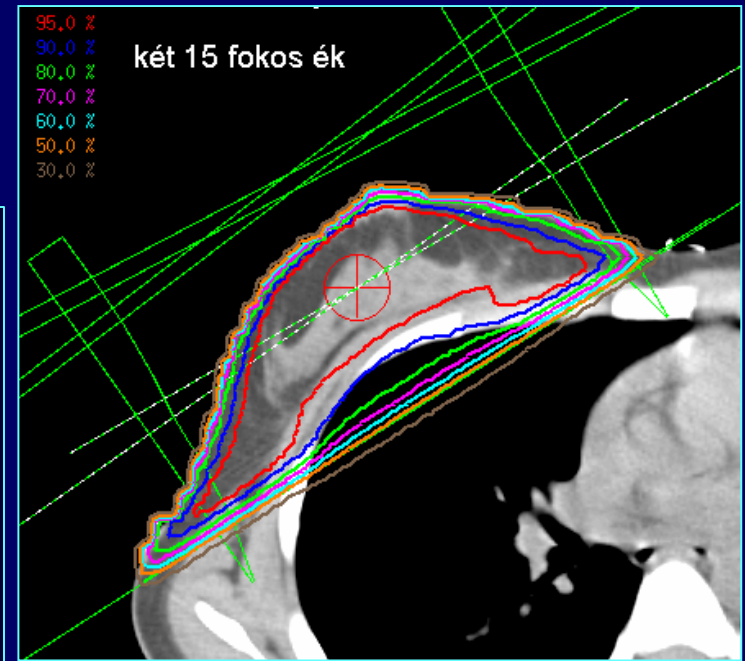


# Treatment planning

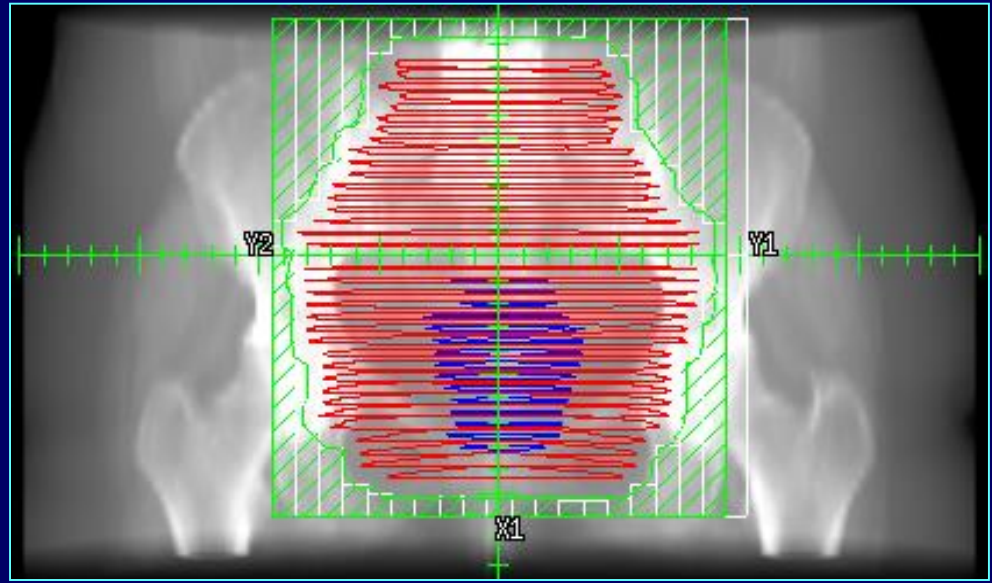
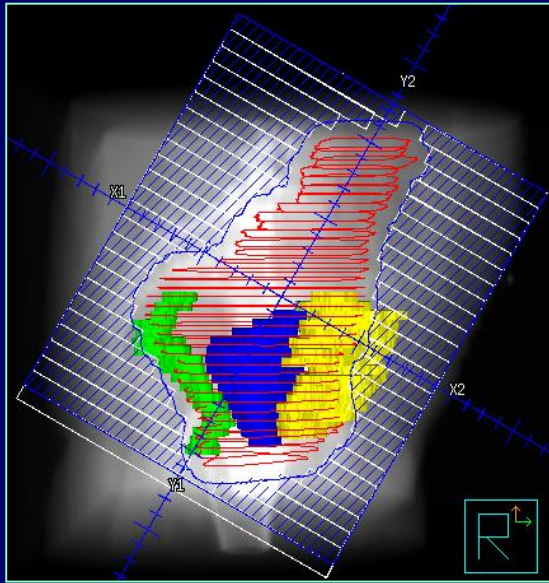
- Reproducible patient positioning + CT-based treatment planning



- 3D-CRT: use of individual, irregular fields conforming to the 3 dimensional shape of the target volume - “multi-leaf collimator”

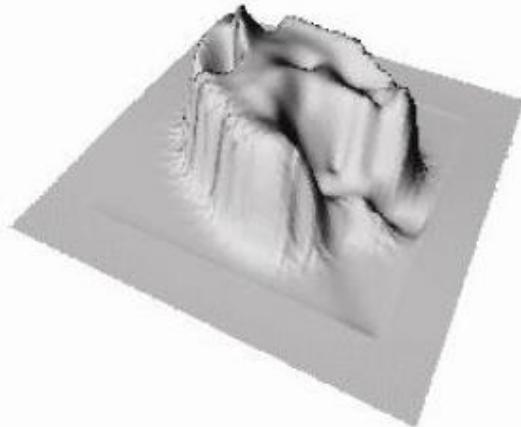


3D-CRT = individual, irregular fields conforming to the 3D shape of the target volume

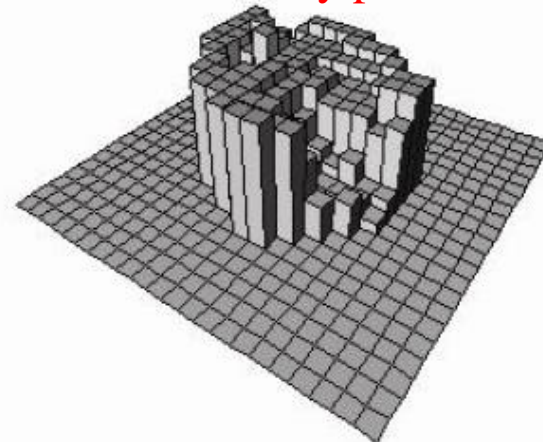


Intensity modulated RT (IMRT) = modulation of intensity within the radiation field

Ideal intensity profile

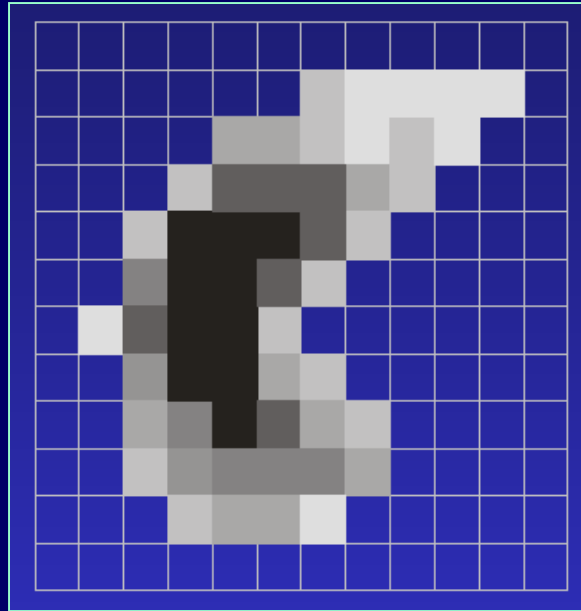


Achievable intensity profile using MLC

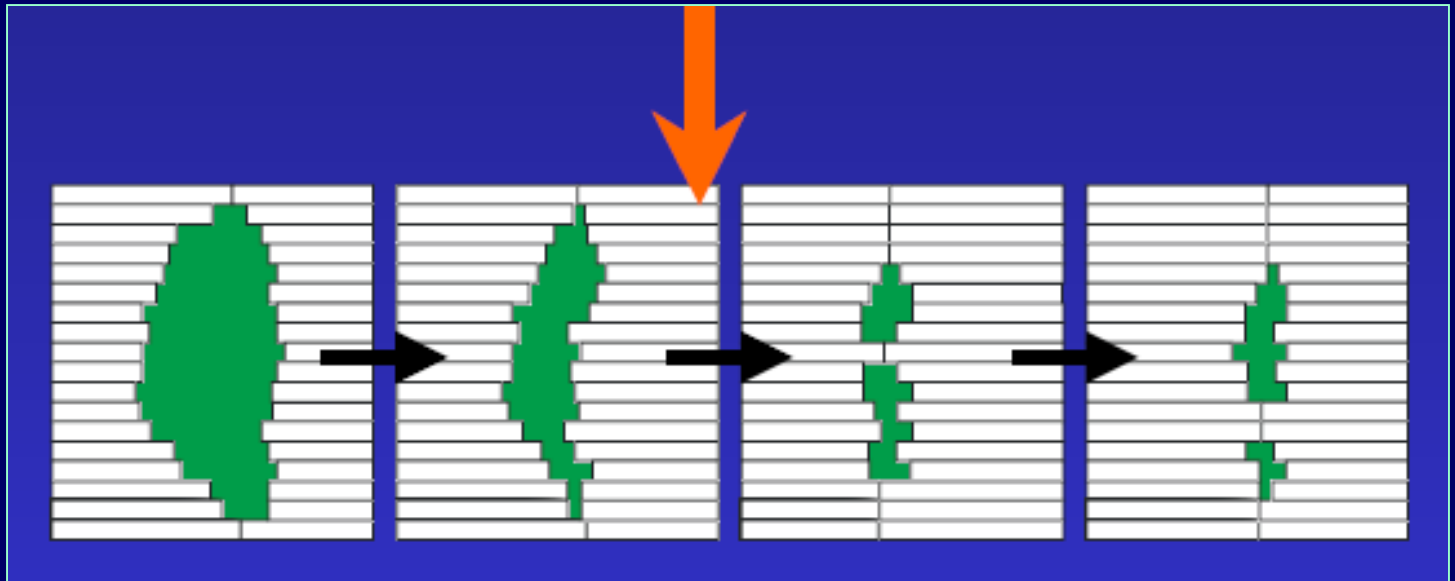


# Intensity modulated radiotherapy (IMRT)

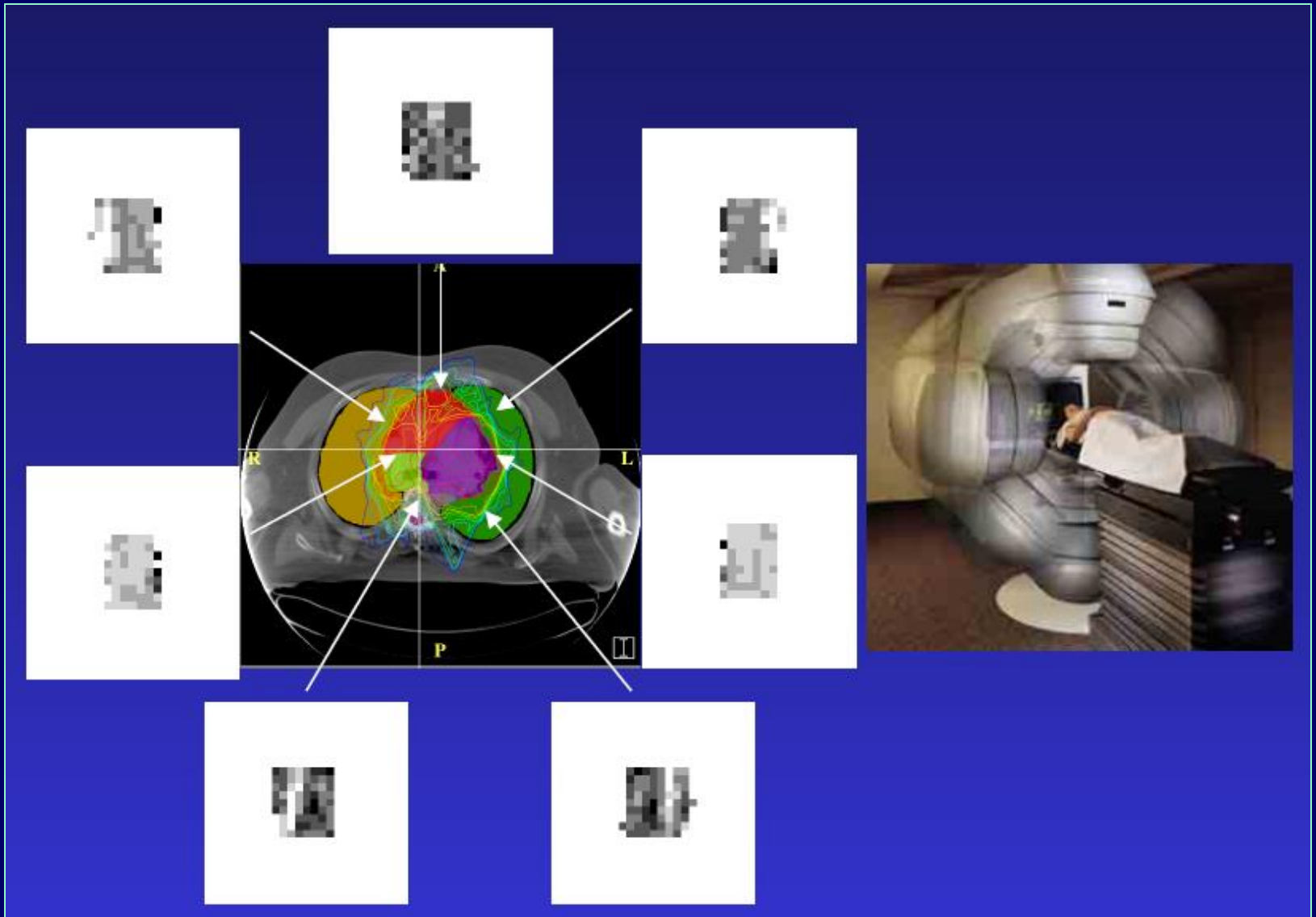
- Step-and-shoot IMRT
- Dinamic IMRT
  - Sliding window
  - IMAT (arc therapy)



Intensity profile builds up as the sum of individual radiation field segments.



# Intensity modulated radiotherapy (IMRT)



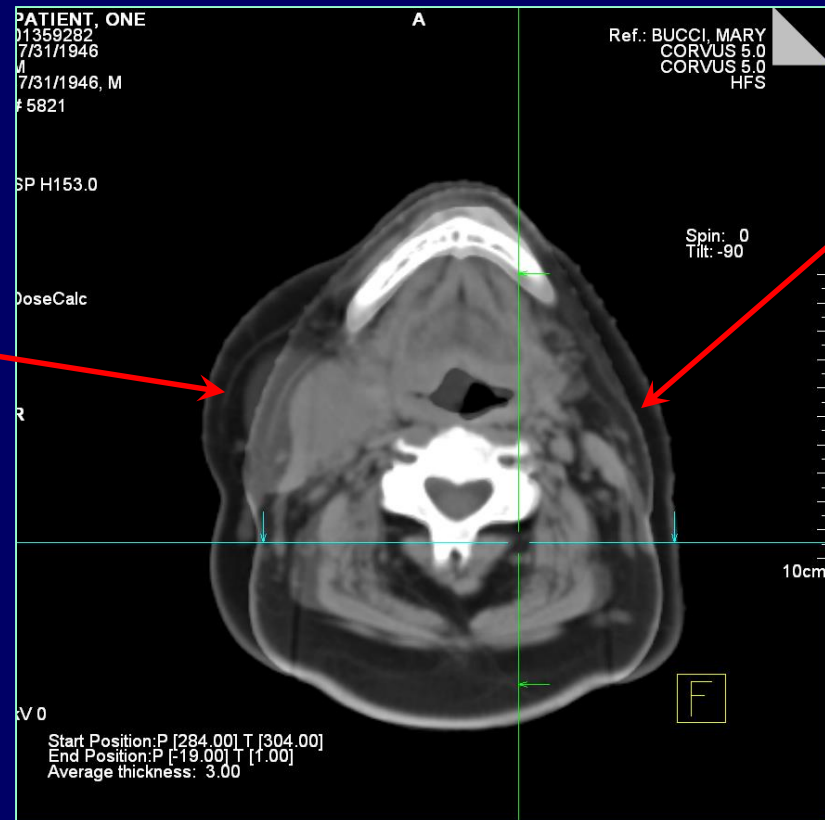
# Image-guided radiotherapy = IGRT

Goal: to avoid inaccuracies caused by daily set-up error, change of patient anatomy, and internal organ motions

## Head & Neck tumour:

Change of patient anatomy during the course of RT:

- tumour shrinkage
- loss of weight



# IGRT using LINAC + integrated CT on-rail





# IGRT using LINAC + integrated CT on-rail

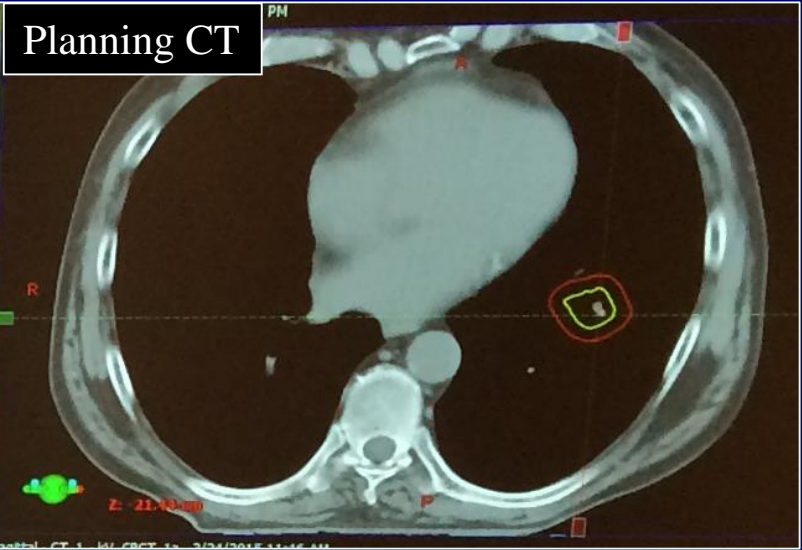
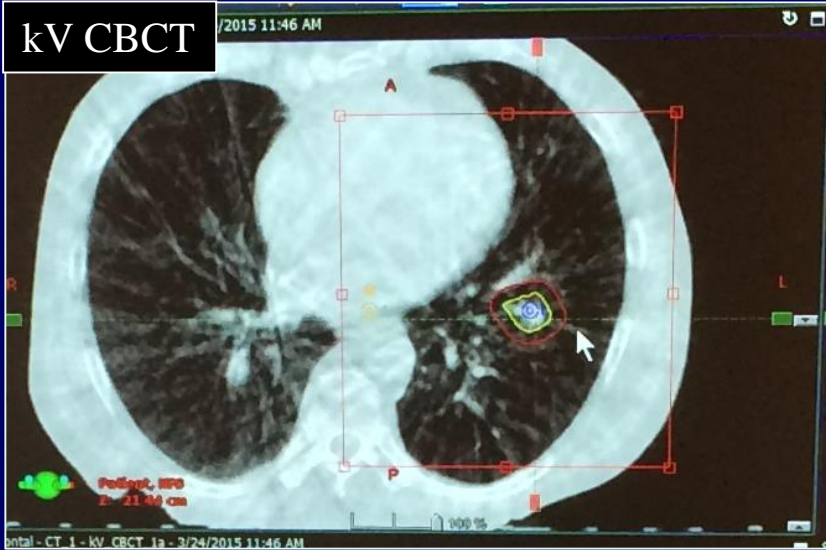
RT delivery with 180° table rotation



# IGRT using kilovoltage cone-beam CT (kV-CBCT)

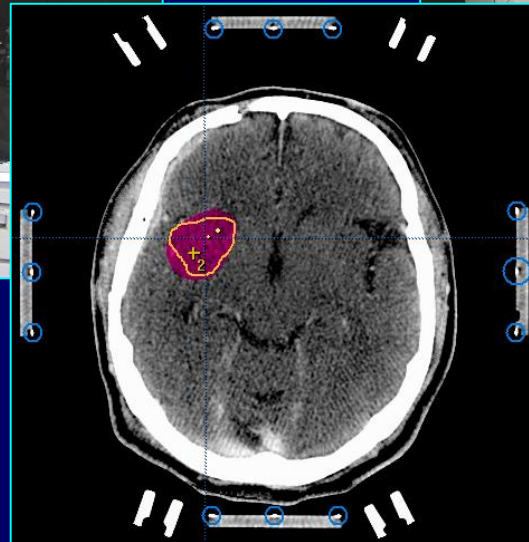
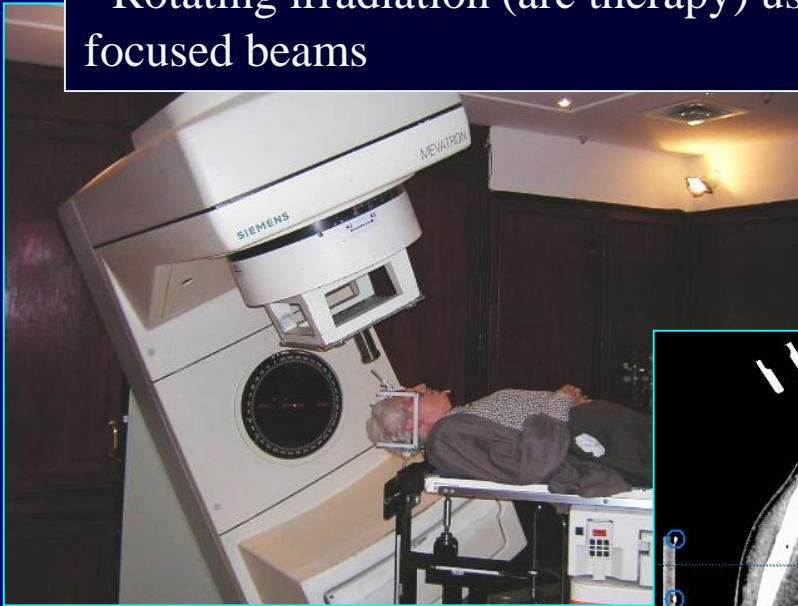
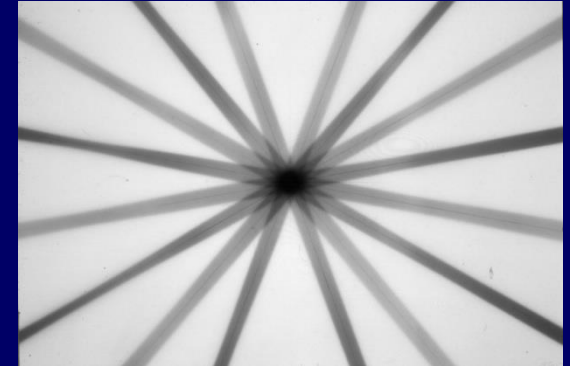


Couch Shift [cm]	
Vrt	+0.30
Lng	+0.42
Lat	-0.10
Couch Shift [°]	
Include	
Rtn	-0.1 <input checked="" type="checkbox"/>
Pitch	-0.1 <input checked="" type="checkbox"/>
Roll	+0.1 <input checked="" type="checkbox"/>



# Stereotactic radiosurgery (SRS)

- Single-fraction high-dose irradiation for limited volume neurological malformations
- Fixation and 3D localization with stereotactic head-frame
- High-precision CT/MRI-based 3D imaging and treatment planning
- Rotating irradiation (arc therapy) using small and highly focused beams



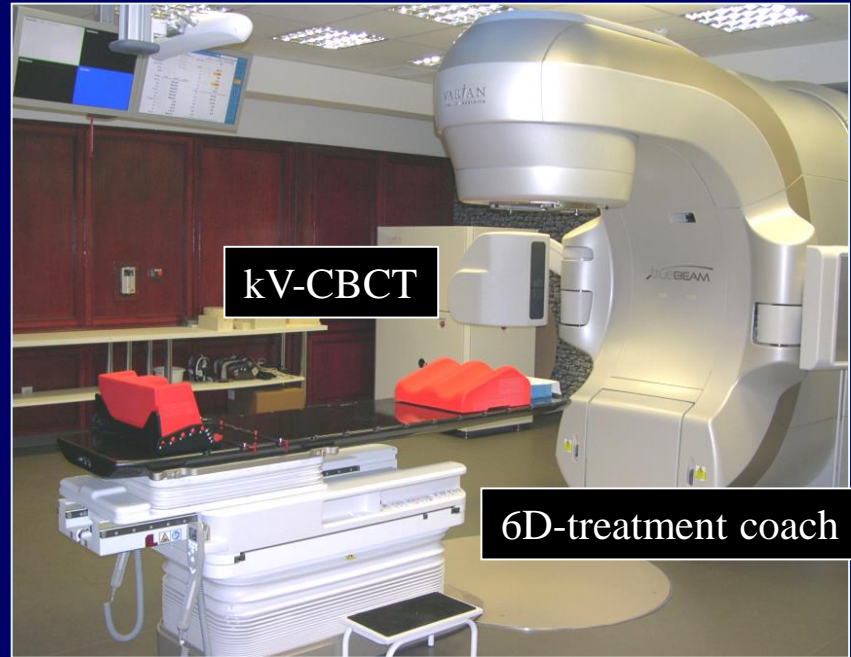
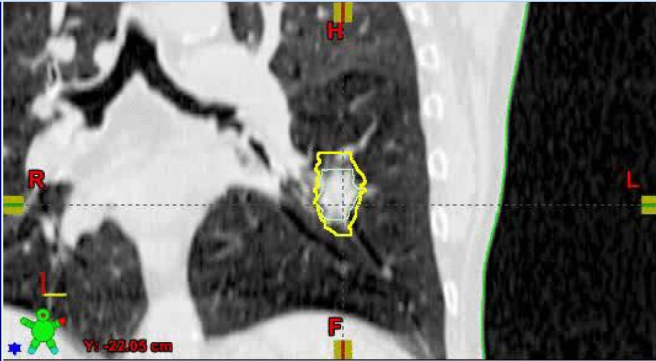
**Dose prescription:  
16 Gy to the 50% isodose**

# Stereotactic Ablative Body Radiotherapy = SABRT



## Technical needs:

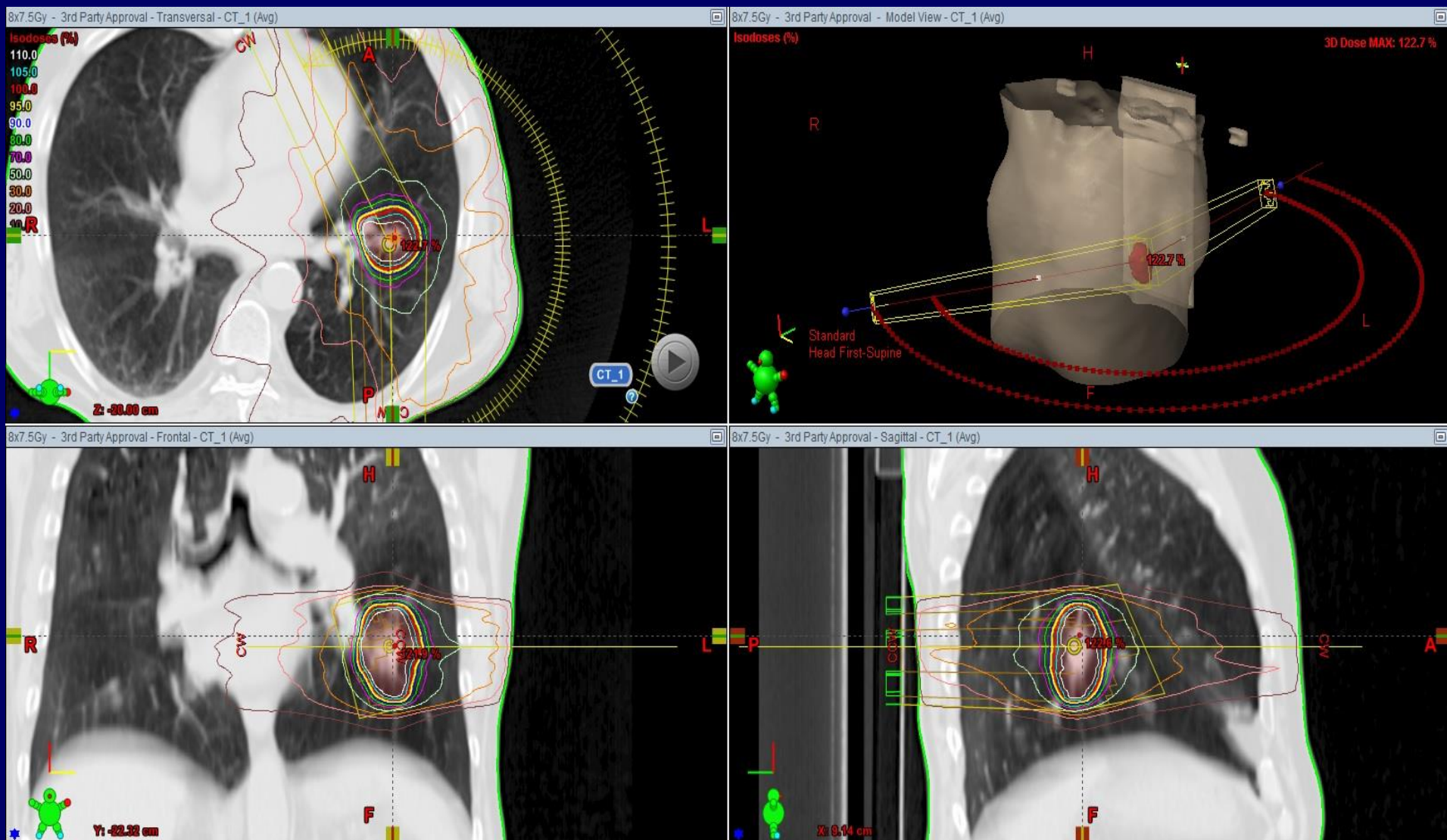
- 4D-CT
- 6-degree of freedom treatment coach
- kV-CBCT



kV-CBCT

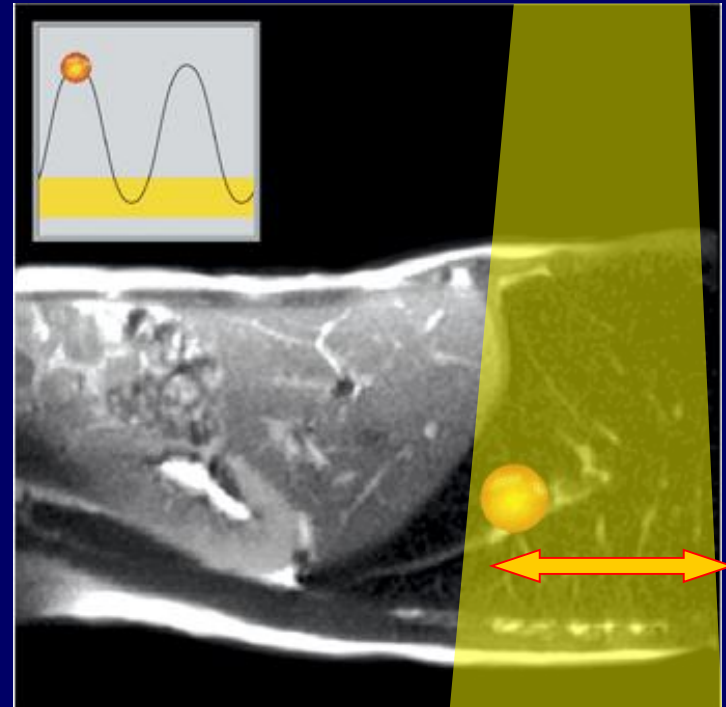
6D-treatment coach

# Stereotactic Ablative Body RadioTherapy = SABRT



# Irradiation of moving targets – Conventional technique

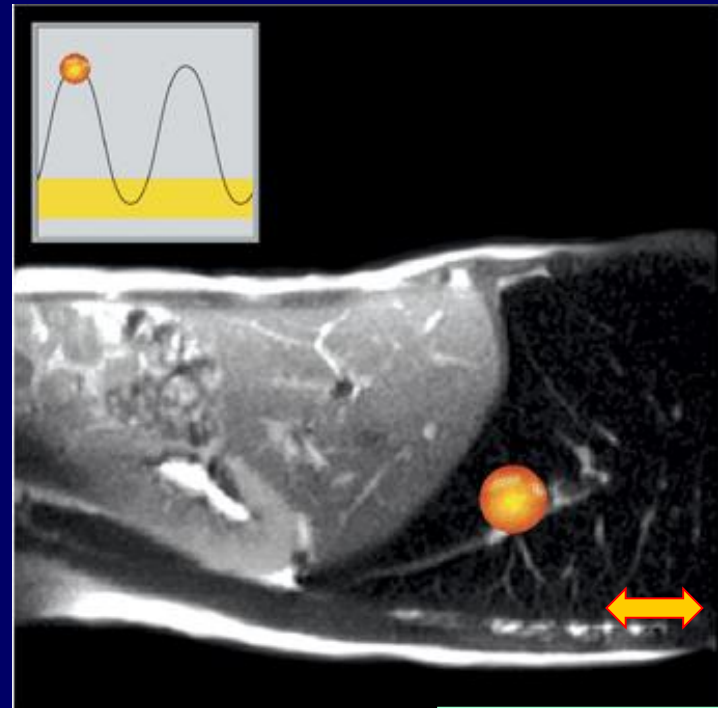
Breathing cycle



Wide radiation  
safety margin

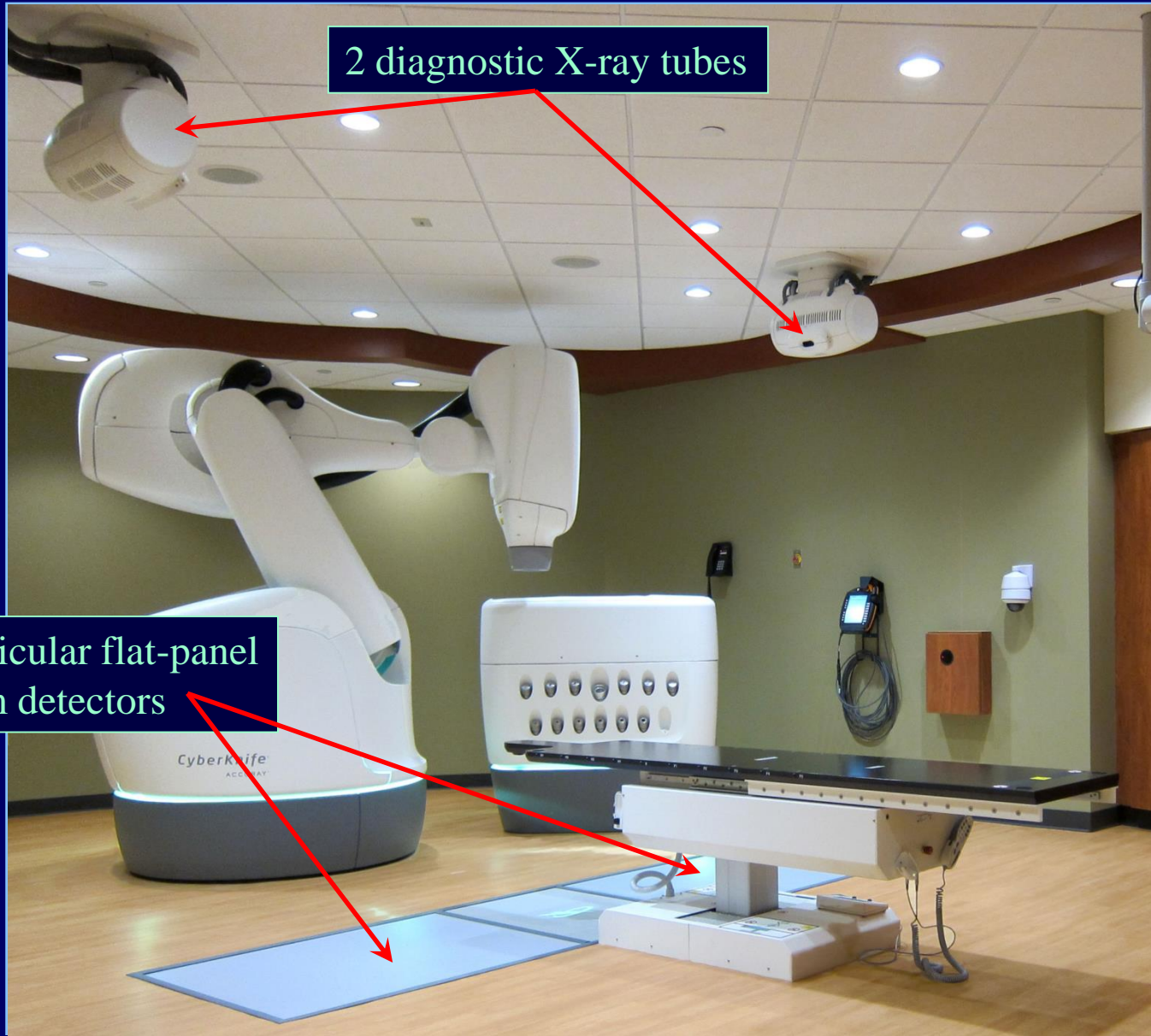
# Irradiation of moving targets – Gated radiotherapy

Narrow safety margin ->  
Less side-effect  
and/or  
Dose escalation



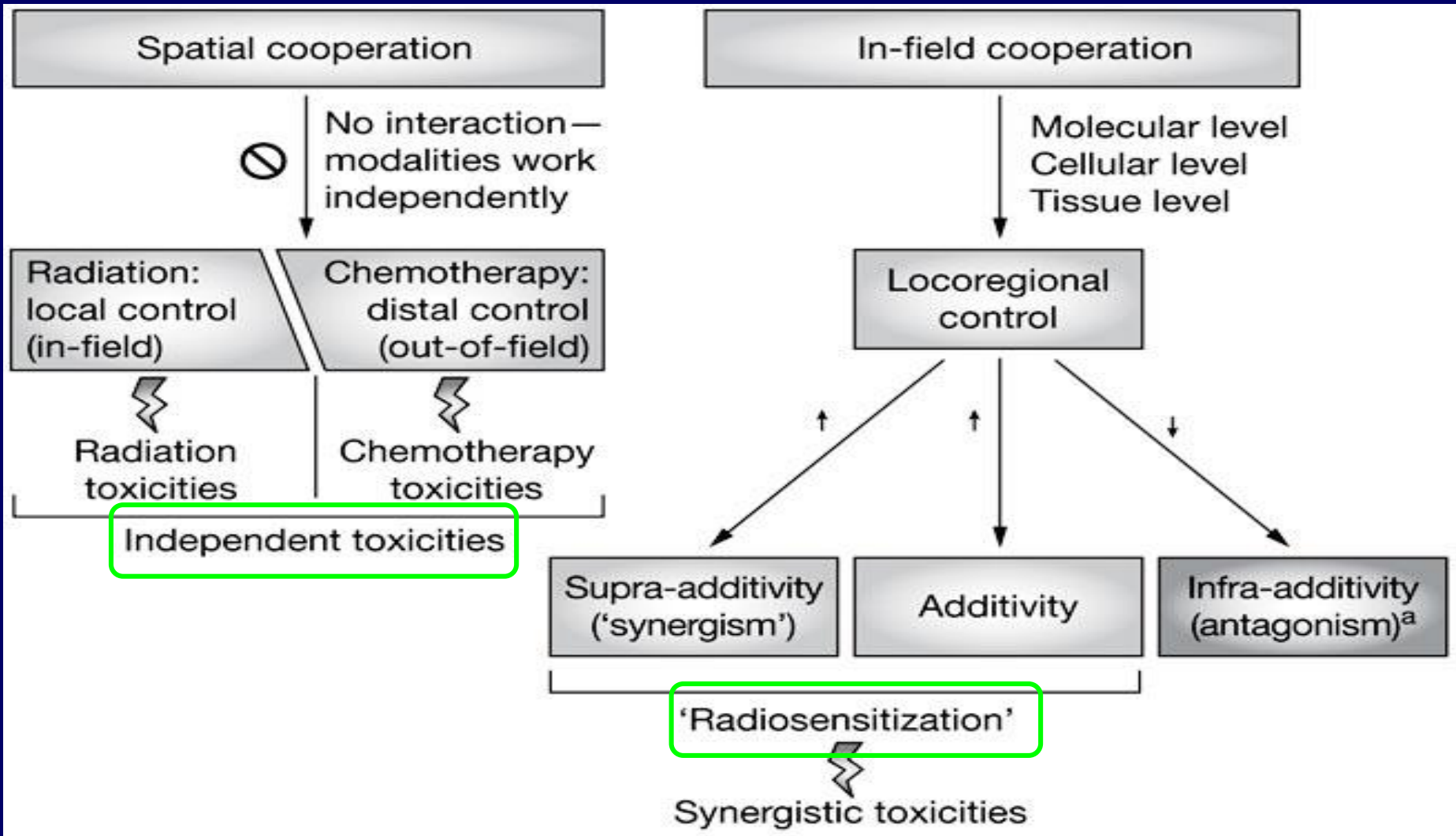
Narrow radiation  
safety margin

# Cyberknife = Robotic arm + LINAC






# Rationale for adding chemotherapy to radiation



## Interactions of RT and CT

- Additive: The overall effect of  $RT + CT =$  the sum of the separate effect of each modality.
- Subadditive: The overall effect of  $RT + CT <$  the sum of the separate effects of the two modalities.
- Synergistic: The overall effect of  $RT + CT >$  the sum of the separate effects of the two modalities.
- Antagonistic: The overall effect of  $RT + CT <$  the effect of RT alone  
 radioprotective effect.

## Possible interactions of RT and CT in tumours and normal tissues

	Tumour	Normal tissue
Optimal	sinergistic	antagonistic
Reality	additive	subadditive

# Evidence based indications of RCT according to disease entities

**Table 1** Overview of disease entities and indications in which concurrent chemoradiotherapy is used.<sup>a</sup>

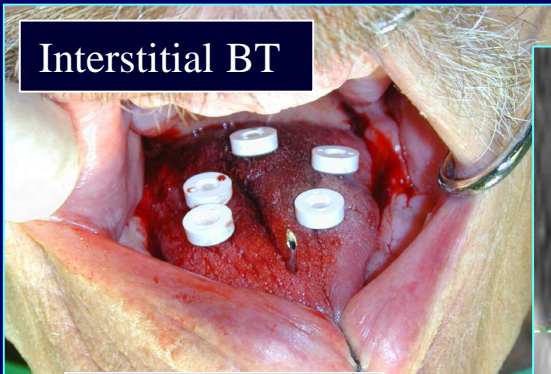
Disease entity	Indication and treatment	Commonly used agents	Benefit
<b>Upper aerodigestive tract cancers</b>			
Head and neck cancer	Locally advanced HNC—primary or adjuvant treatment	Cisplatin, 5-FU, FHX, cetuximab	Improved organ preservation and survival compared with radiation alone
Non-small-cell lung cancer	Stage IIIB, nonoperable nonmetastatic disease	Cisplatin, carboplatin/paclitaxel, cisplatin/etoposide	Curative approach in poor surgical candidates or IIIB disease
Small-cell lung cancer	Limited stage disease	Cisplatin/etoposide	Curative in ~20% of patients
Esophageal cancer	Locally advanced disease	Cisplatin/5-FU	Survival benefit, increased cure rates, organ preservation
<b>Gastrointestinal malignancies</b>			
Rectal cancer	Neoadjuvant	5-FU	Improved sphincter preservation, decrease in local and distal failures
Anal cancer	Mainstay of curative treatment	5-FU, MMC	Improved organ preservation
Gastric cancer	Adjuvant	Cisplatin, 5-FU	Some data indicate a survival benefit
Pancreatic cancer	Adjuvant, unresectable locoregionally advanced tumors	5-FU	Improved locoregional control, possibly a survival benefit
Cholangiocarcinoma	Adjuvant, unresectable locoregionally advanced tumors	5-FU	Some data indicate a survival benefit
<b>Gynecological and genitourinary cancers</b>			
Cervical cancer	Primary modality	Cisplatin, 5-FU, hydroxyurea	Improved local and distal control, organ preservation
Bladder cancer	Primary modality	Cisplatin	Improved local control
<b>Other cancers</b>			
Glioblastoma	Adjuvant	Temozolomide	Survival benefit
Sarcoma	Neoadjuvant	Doxorubicin	Downstaging, improved organ preservation

<sup>a</sup>This is a limited overview, and concurrent chemoradiotherapy is used in most solid tumors either as a standard treatment or investigationally. For further details please refer to the organ-specific literature. Abbreviations: 5-FU, 5-fluorouracil; FHX, 5-FU, hydroxyurea and radiation; HNC, head and neck cancer; MMC, mitomycin C.

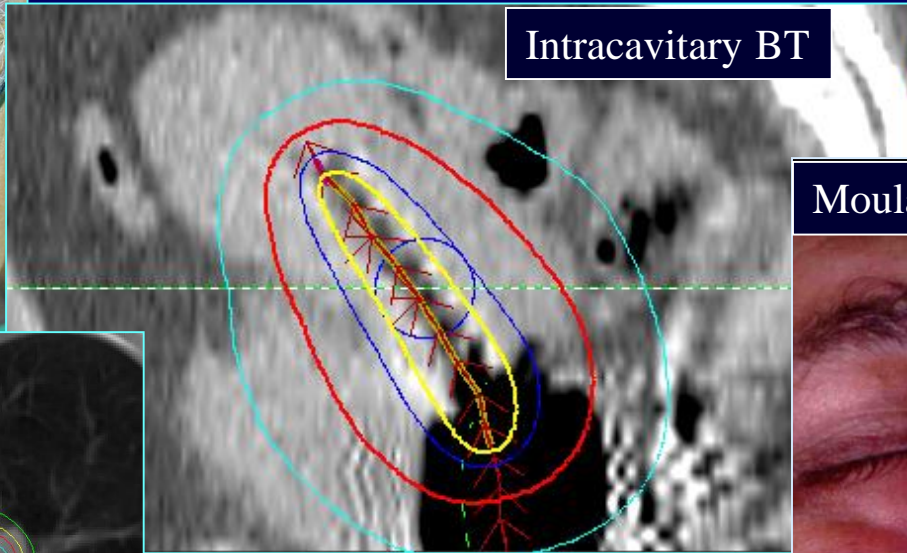
# Clinical forms of brachytherapy (BT) I

- interstitial BT (prostate, breast, oral cavity, base of tongue)
- intracavitary BT (GYN, nasopharyngeal cc.)
- intraluminal BT (lung, esophagus)
- superficial "moulage" BT (skin, hard palate, tonsillar fossa)

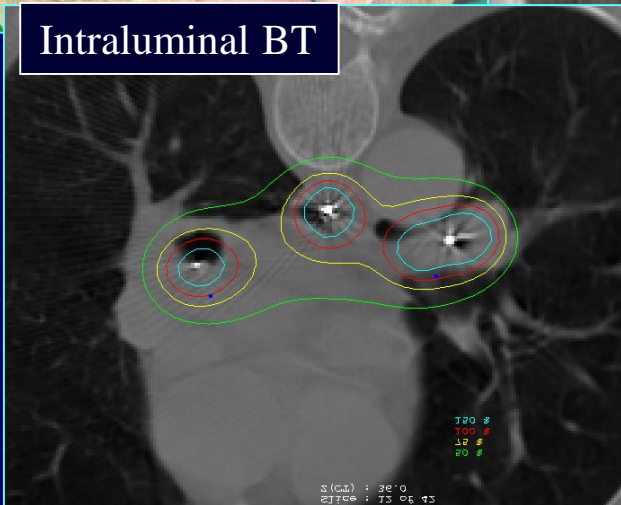
Interstitial BT



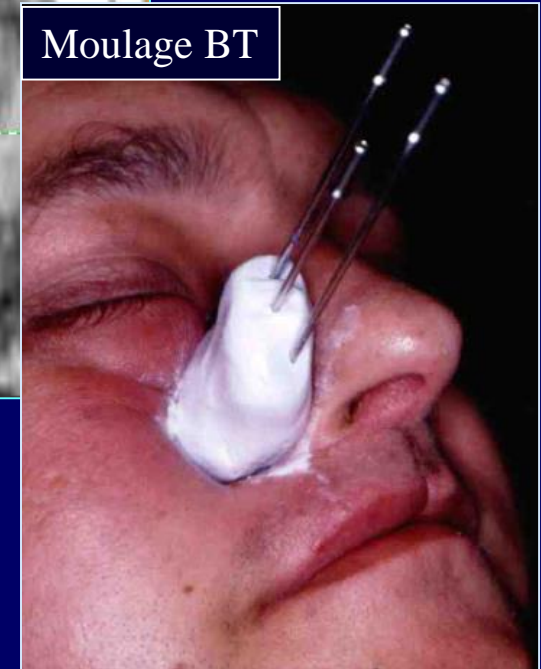
Intracavitary BT



Intraluminal BT



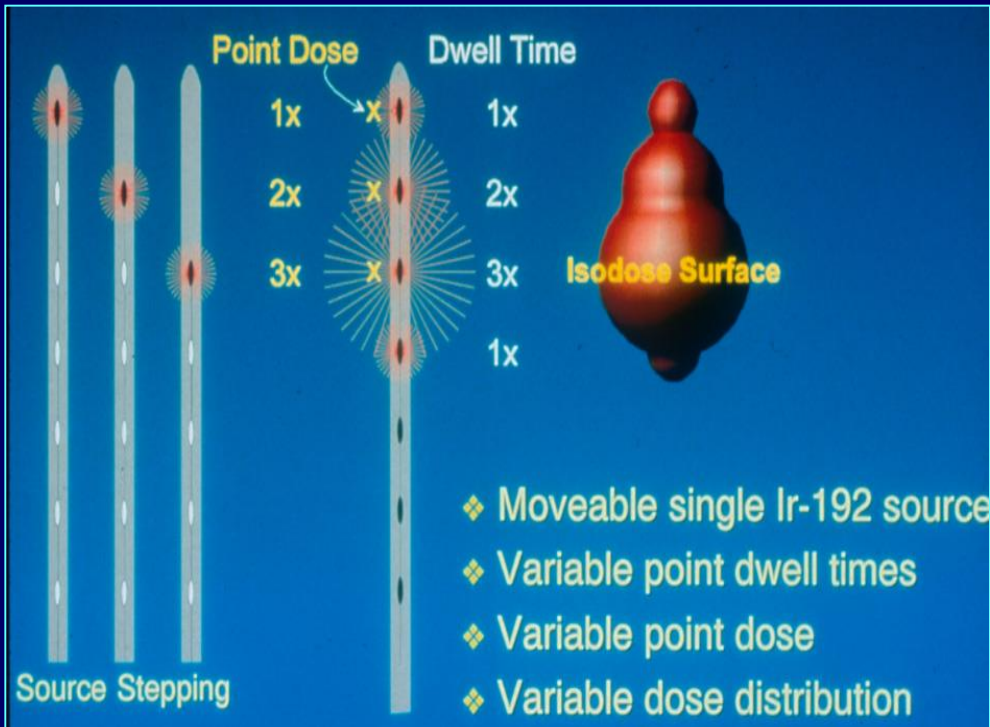
Moulage BT



# Clinical forms of BT II

- Low-dose-rate: 0-2 Gy/h
- Medium-dose-rate: 2-12 Gy/h
- High-dose rate: > 12 Gy/h
- Pulsed-dose-rate: ultra-fractionated HDR
- After-loading technique:
  - remote after-loading of the radiation source

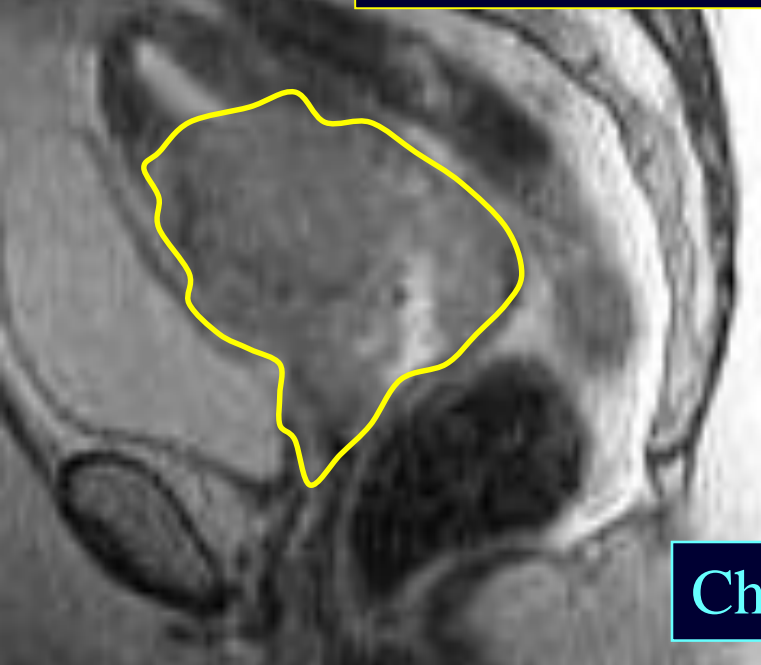
HDR afterloader



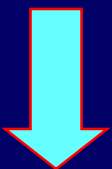
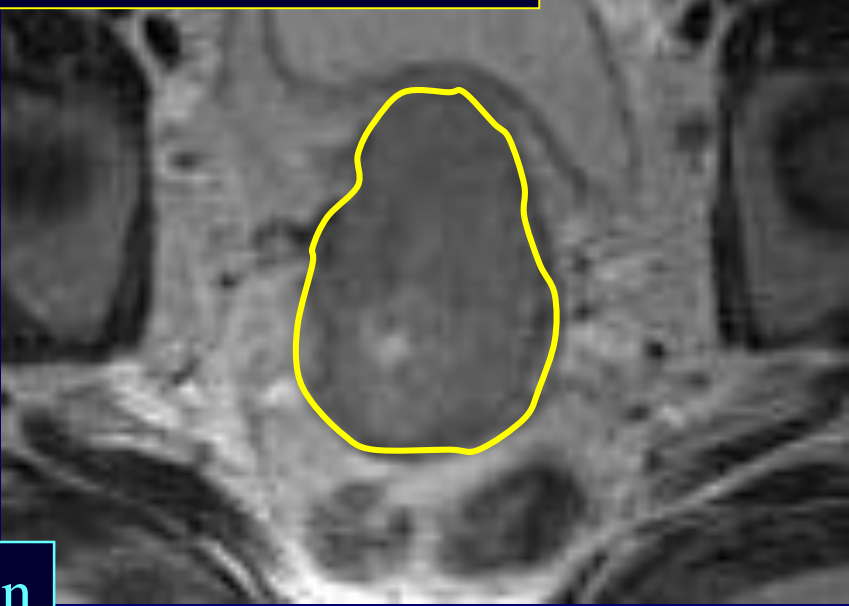
# Standard BT applicators for the treatment of cervical cancer



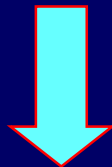
# Role of RCT followed by brachytherapy boost



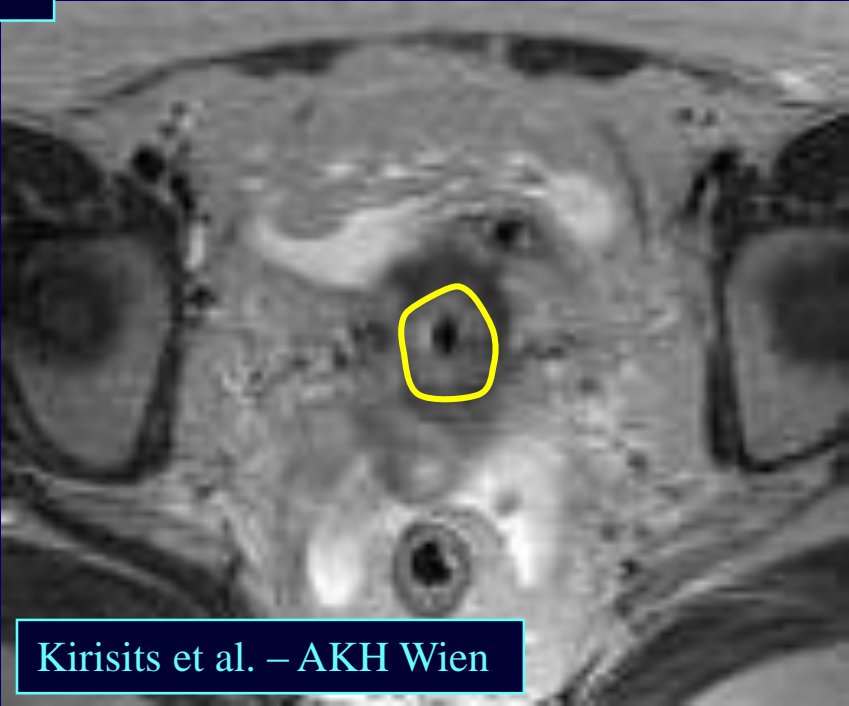
Before  
RCT



Chemoradiation



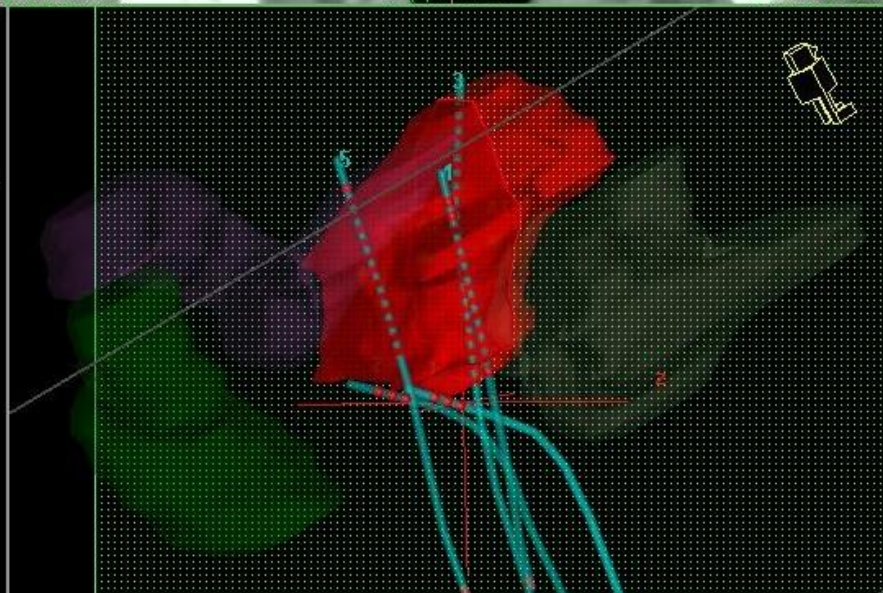
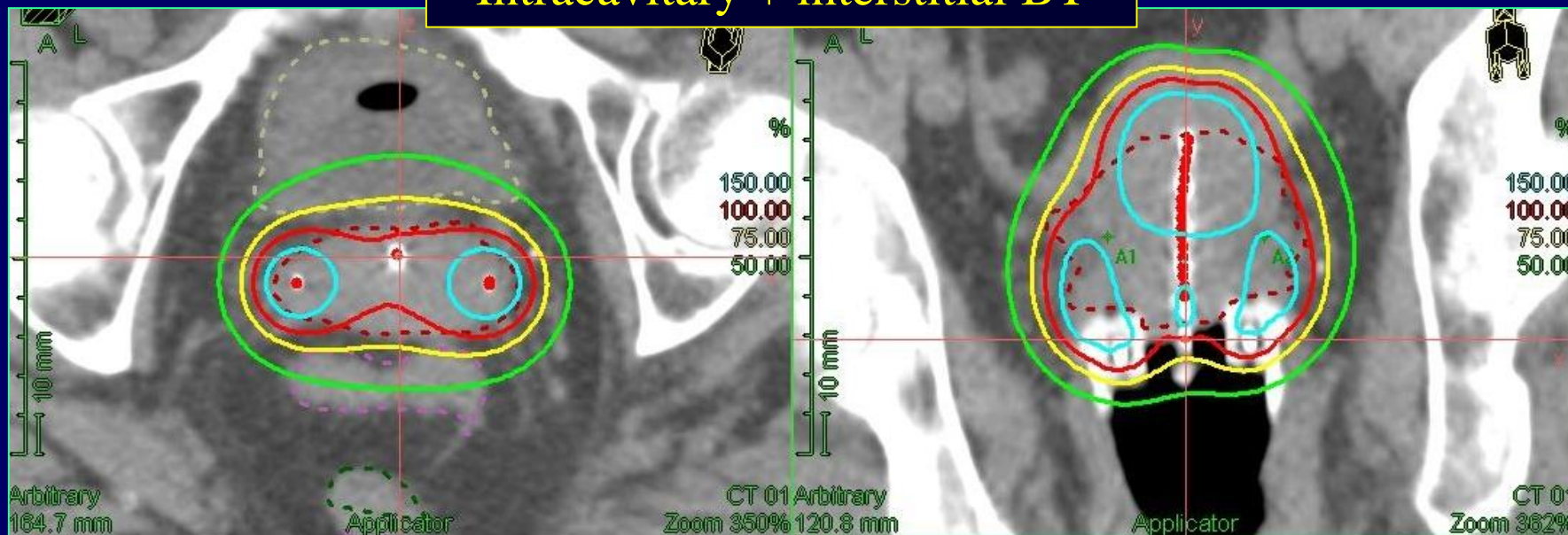
HDR-BT  
boost





# CT-based brachytherapy of cervical cancer

## Intracavitary + interstitial BT

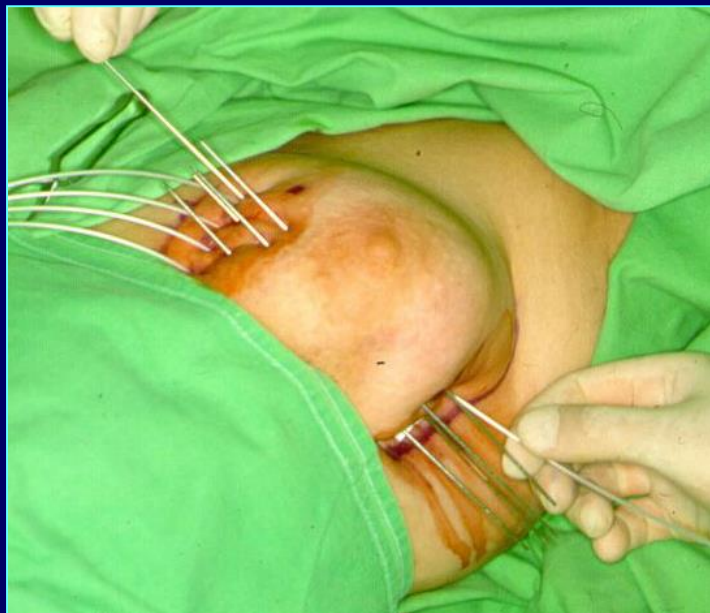
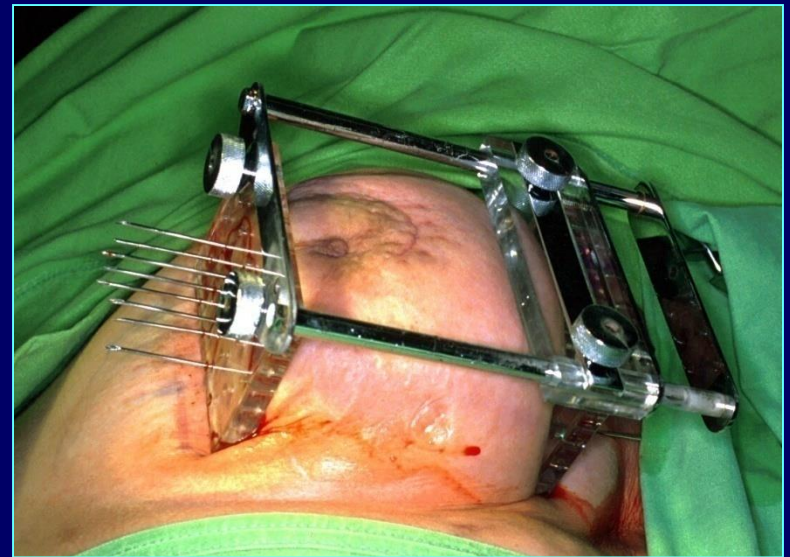
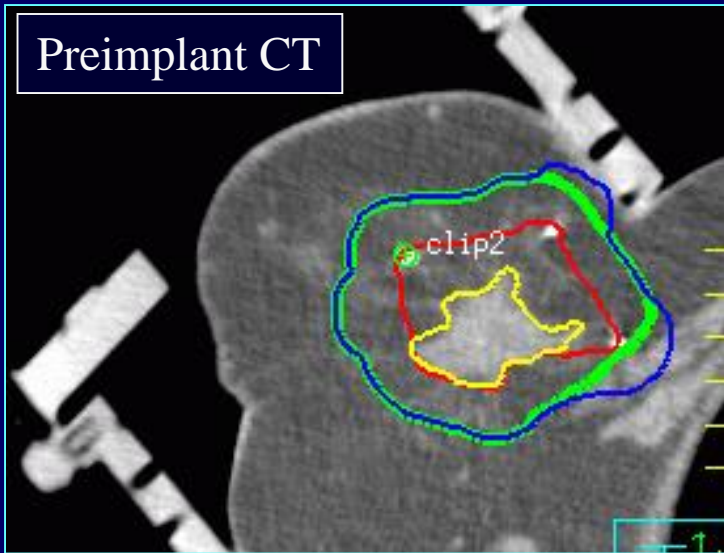


# Interstitial brachytherapy of vulvar cc.

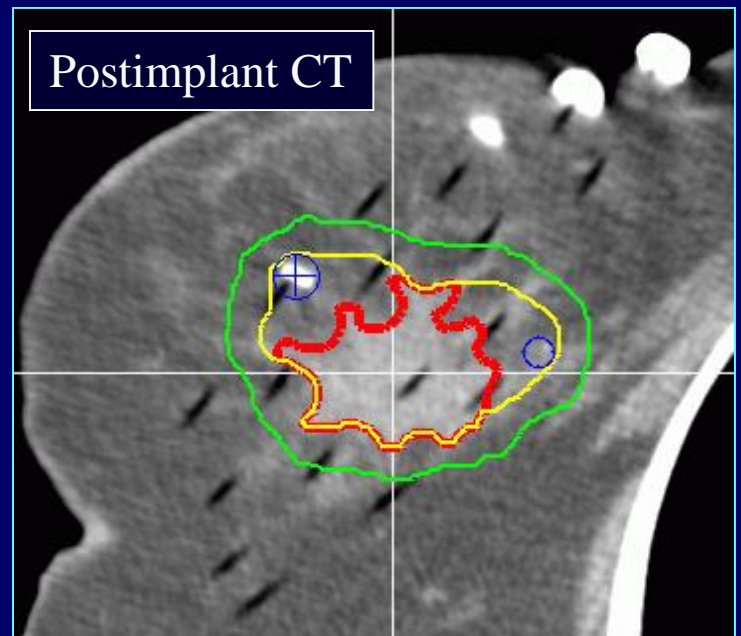


# CT-based interstitial breast brachytherapy

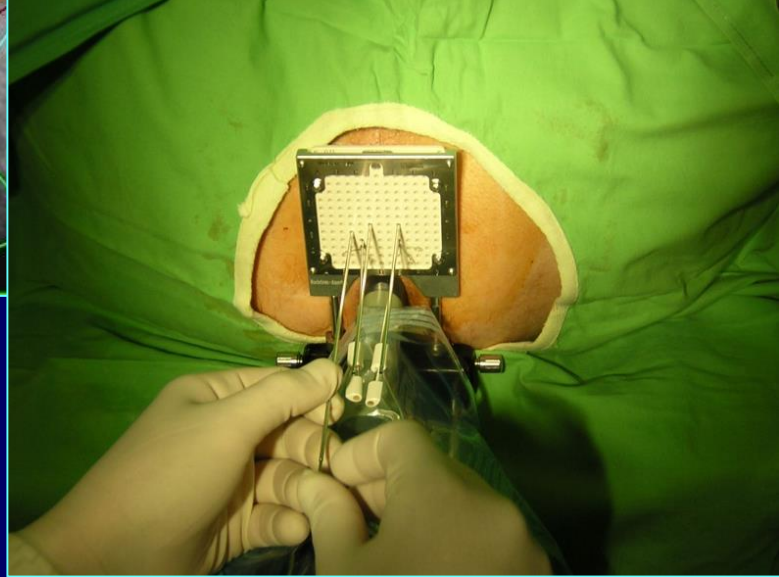
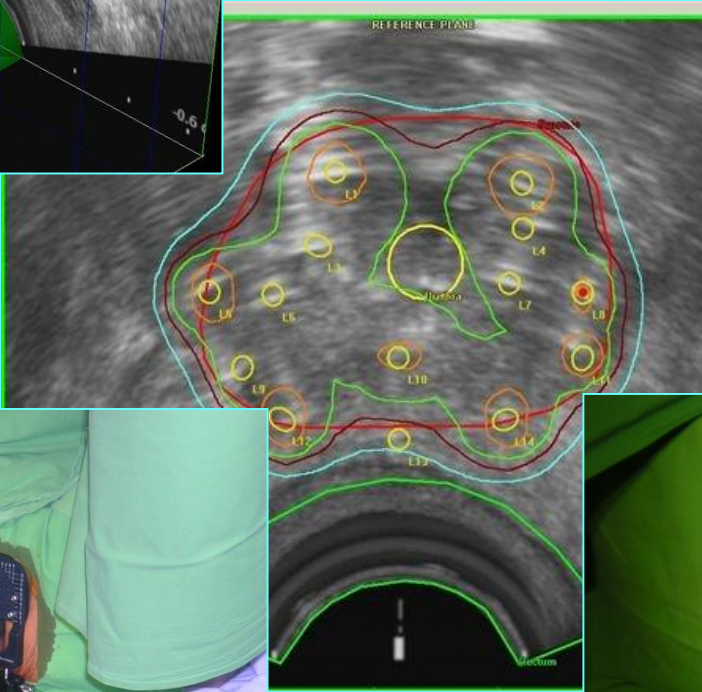
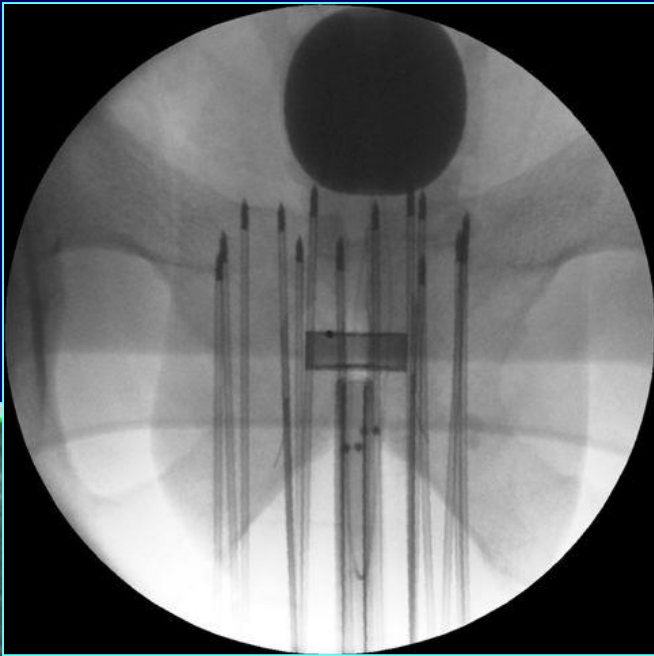
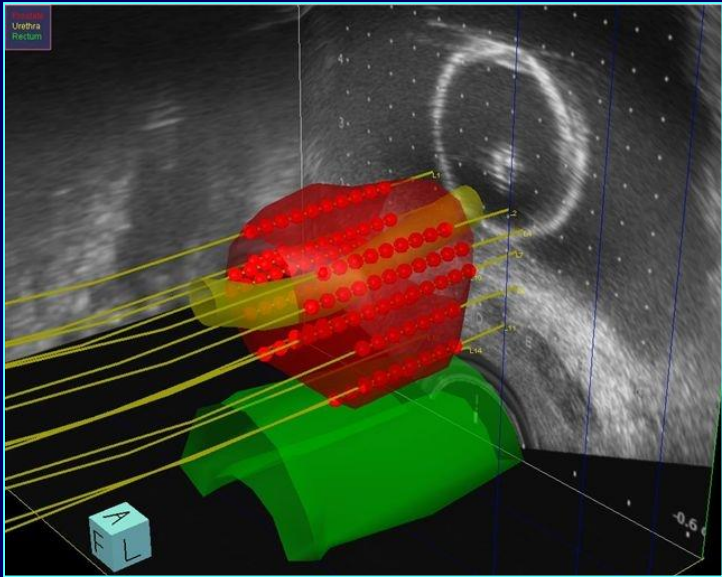
Preimplant CT



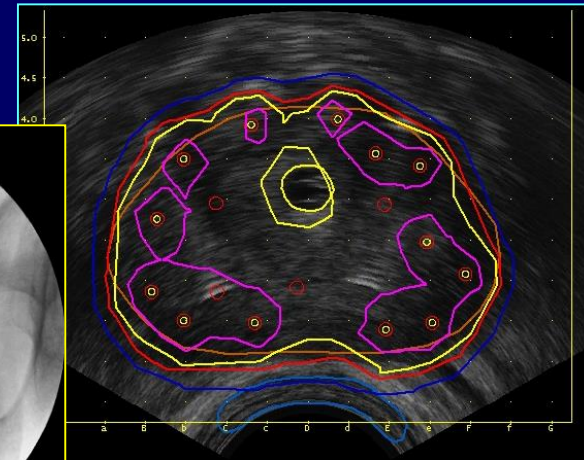
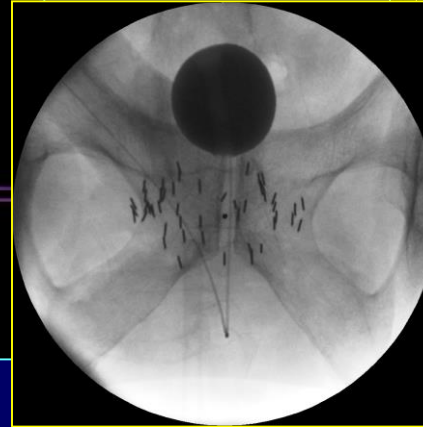
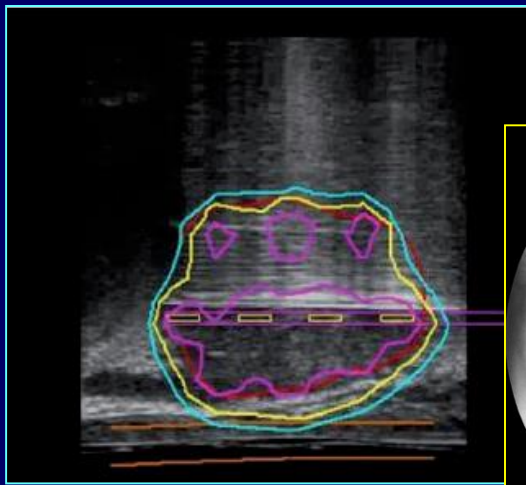
Postimplant CT



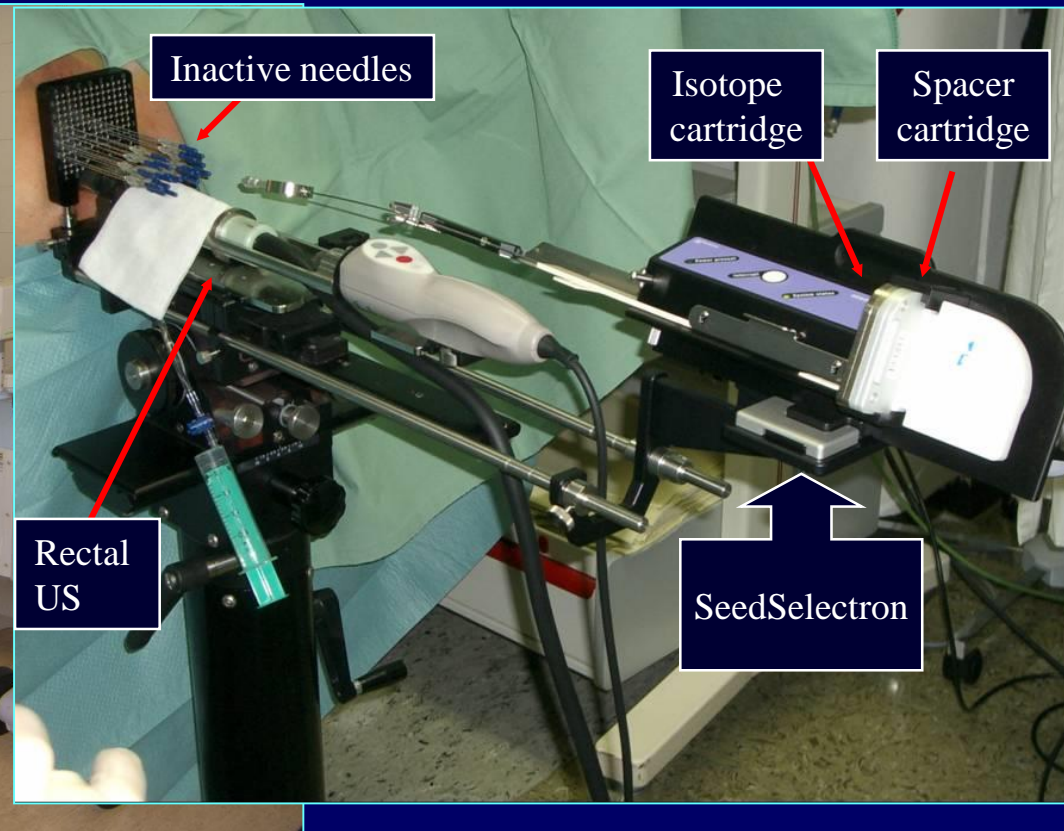
# US-based prostate HDR brachytherapy



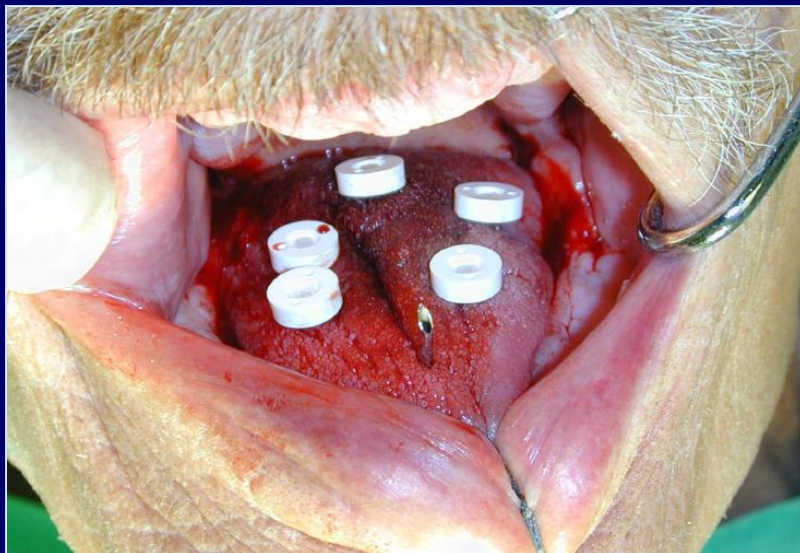
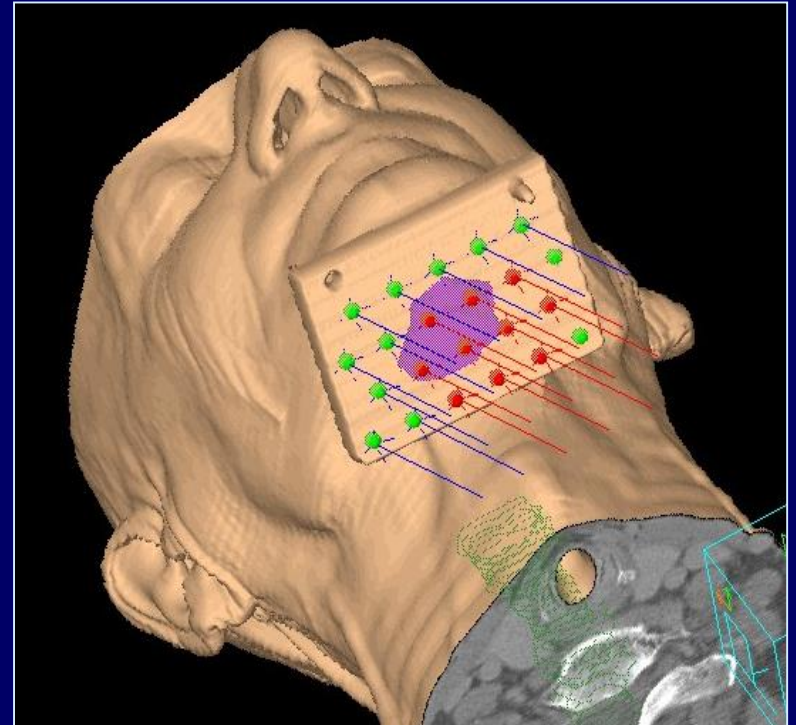
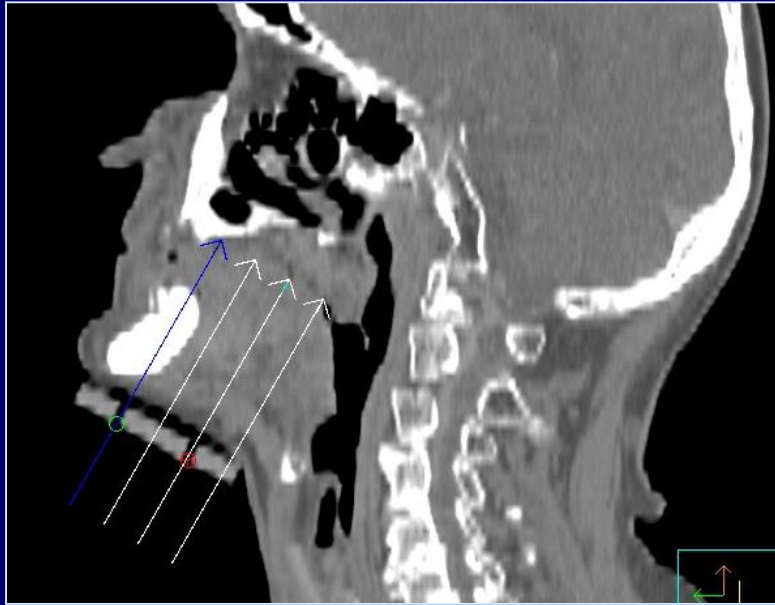
US-based  
permanent  
implantation  
prostate  
brachytherapy  
(PIPB)



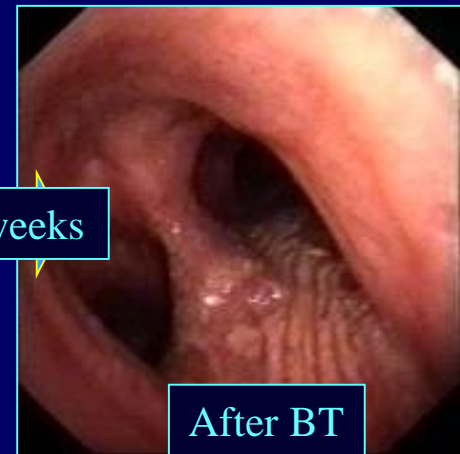
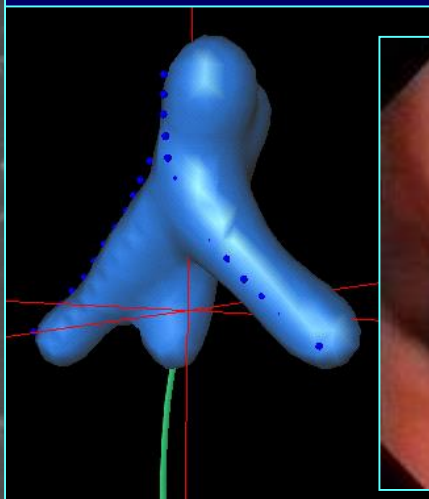
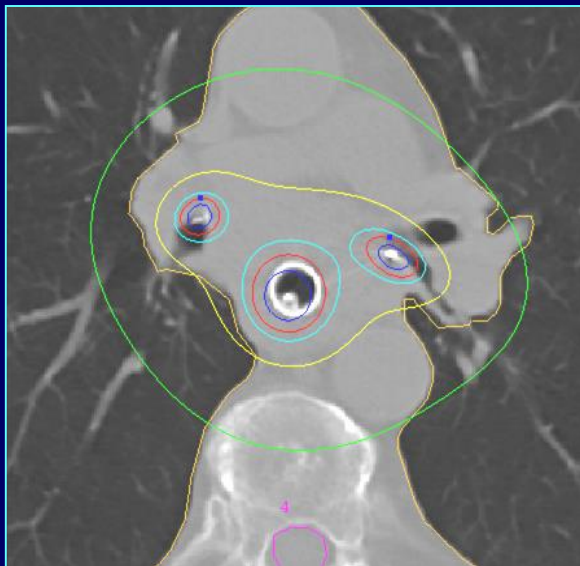
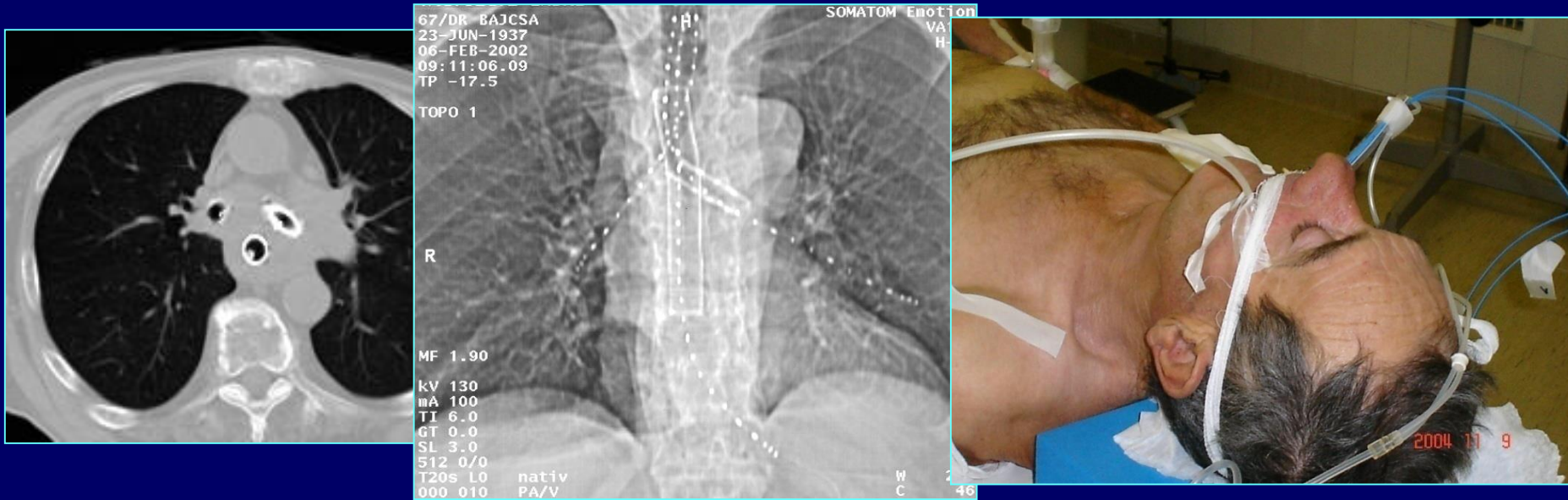
Brachytherapy OR



# Carcinoma of the floor of mouth – CT-based interstitial BT



# Intraluminal lung + esophageal brachytherapy



Thanks for your kind attention!

