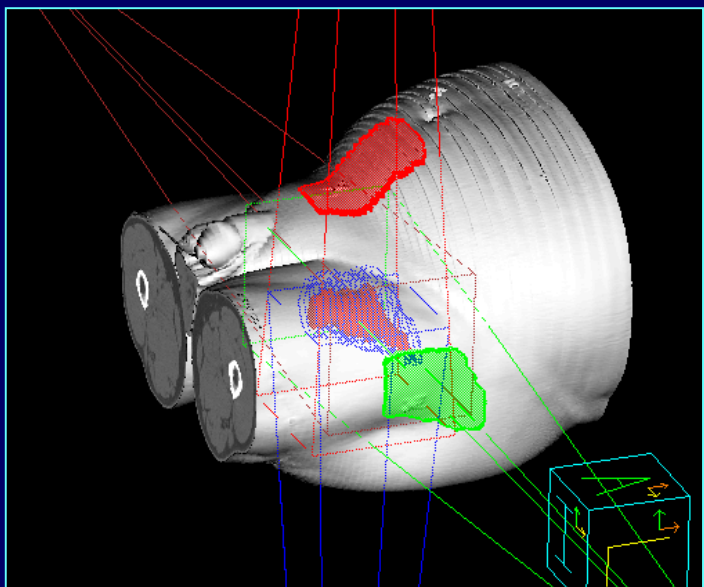
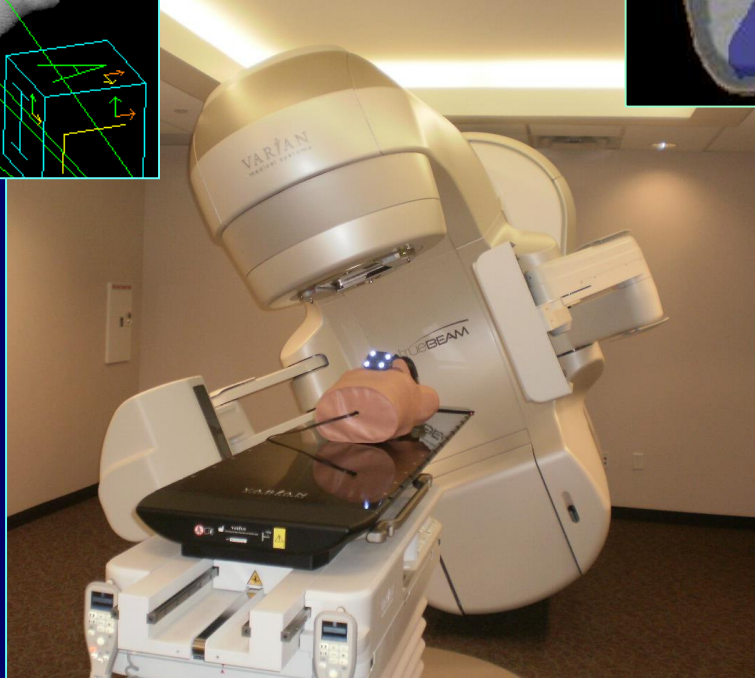


Principles of radiotherapy and radio-chemotherapy of malignant tumours



Polgár Cs.^{1,2} –
National Institute of
Oncology¹,
Chair of Oncology,
Semmelweis
University²



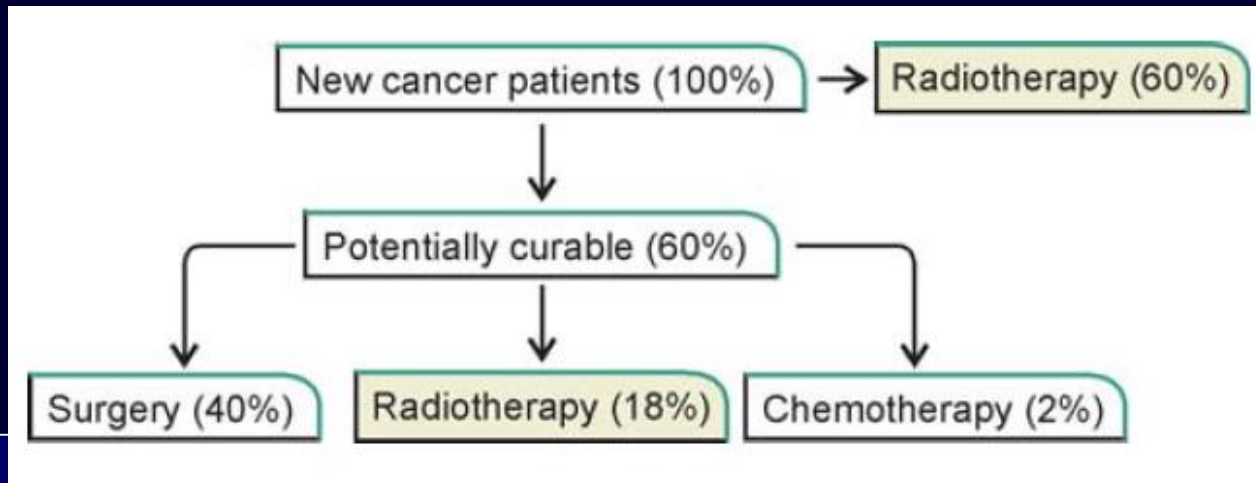
Multidisciplinary treatment of malignant tumours

- 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 2nd. 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: concomittant 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")

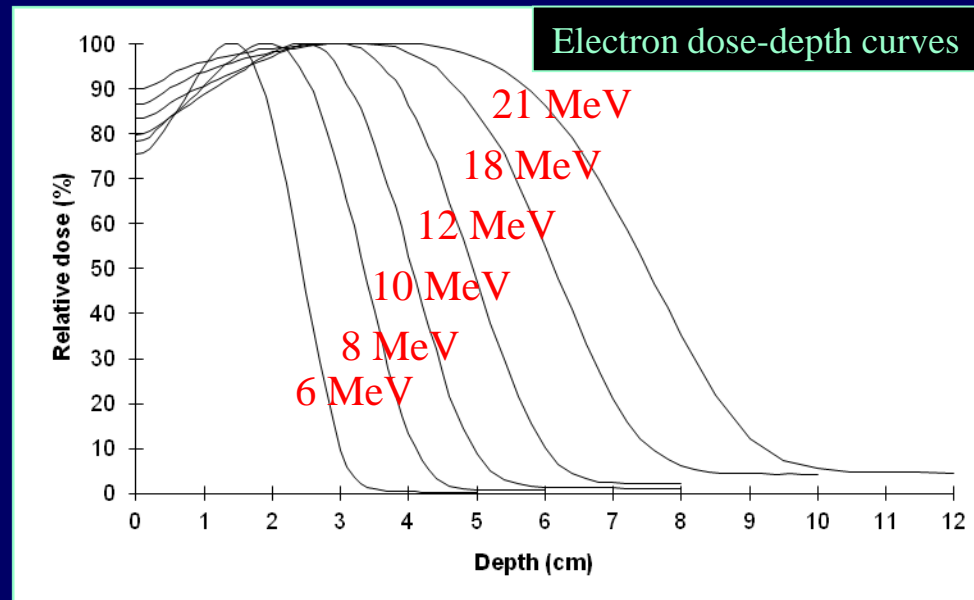
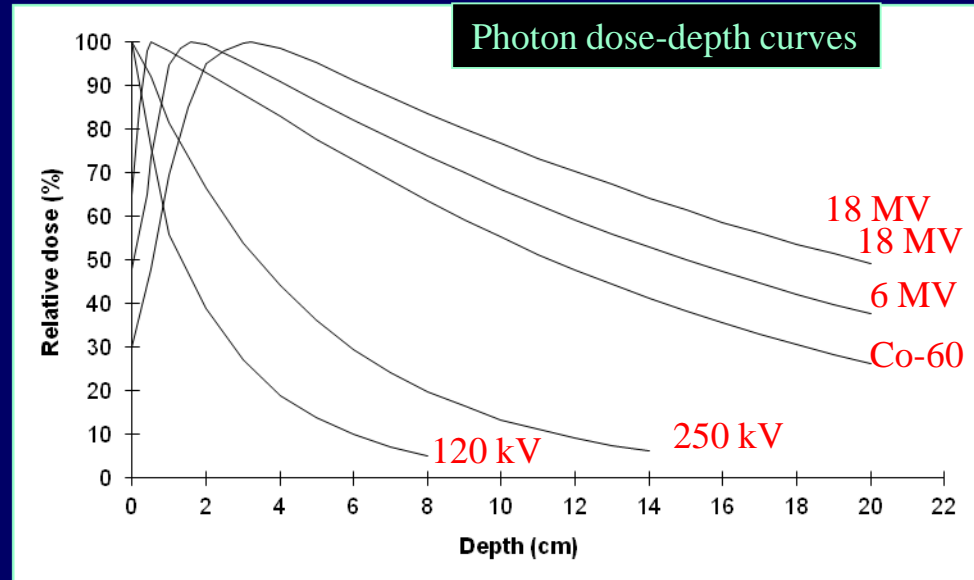
Absorbed dose: absorbed energy by a unit of tissue mass.
SI unit: Gray (Gy)

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

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 O₂, 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
 - LINear ACcelerators (LINAC): 4-29 MV photons OR electrons

Telecobalt



LINAC



LINAC + CT „on rail”

Gantry

CT

LINear ACcelerator = LINAC

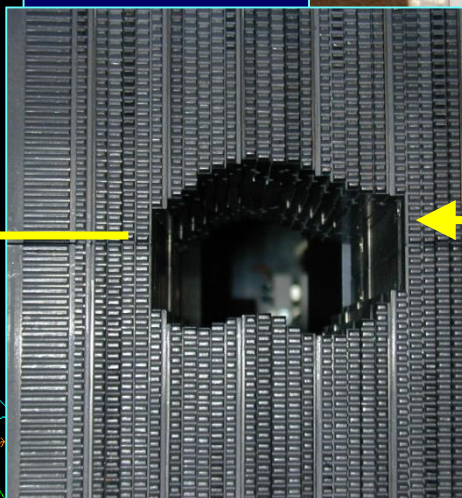
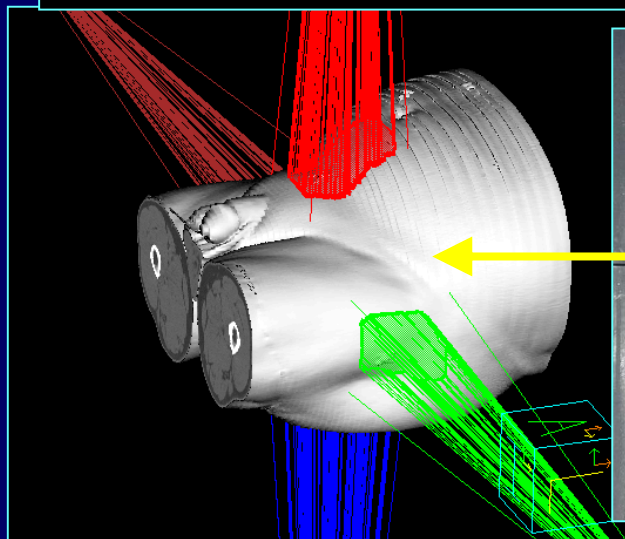
LINAC + kV cone-beam CT

Gantry

Flat-panel
detector

CB-CT

3D conformal radiotherapy = 3D-CRT



Multi-leaf collimator = MLC

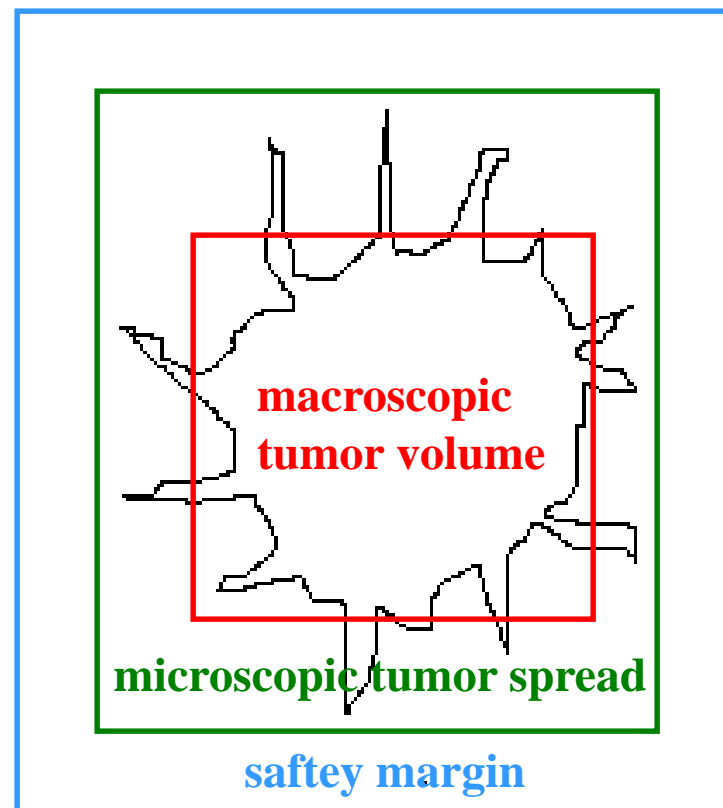


Definition of target volumes for radiotherapy treatment planning

GTV = Gross Tumor Volume ← CT, MRI, US

CTV = Clinical Target Volume

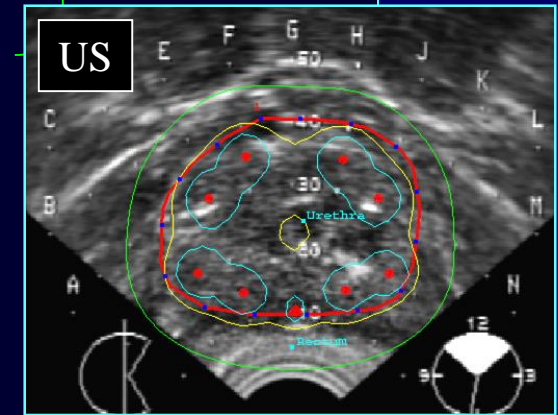
PTV = Planning Target Volume



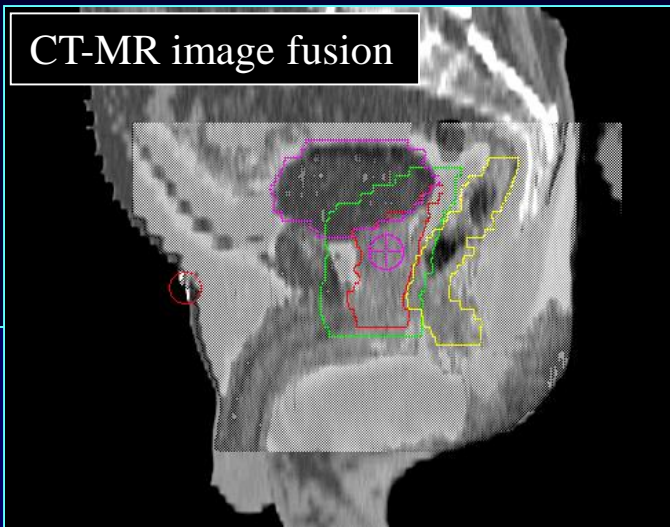
Informations needed for radiotherapy treatment planning

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

PET/CT

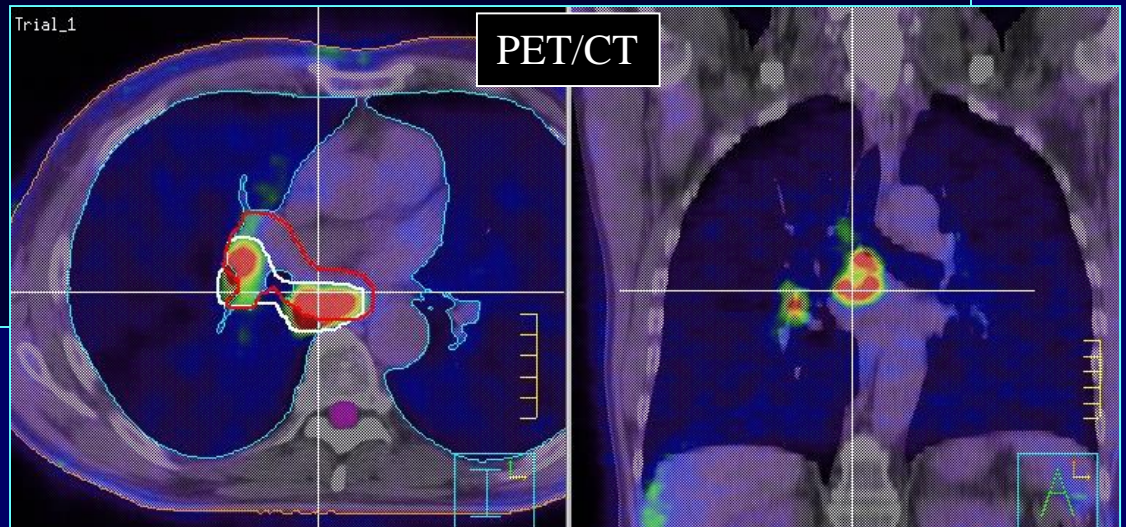


CT-MR image fusion



Trial_1

PET/CT

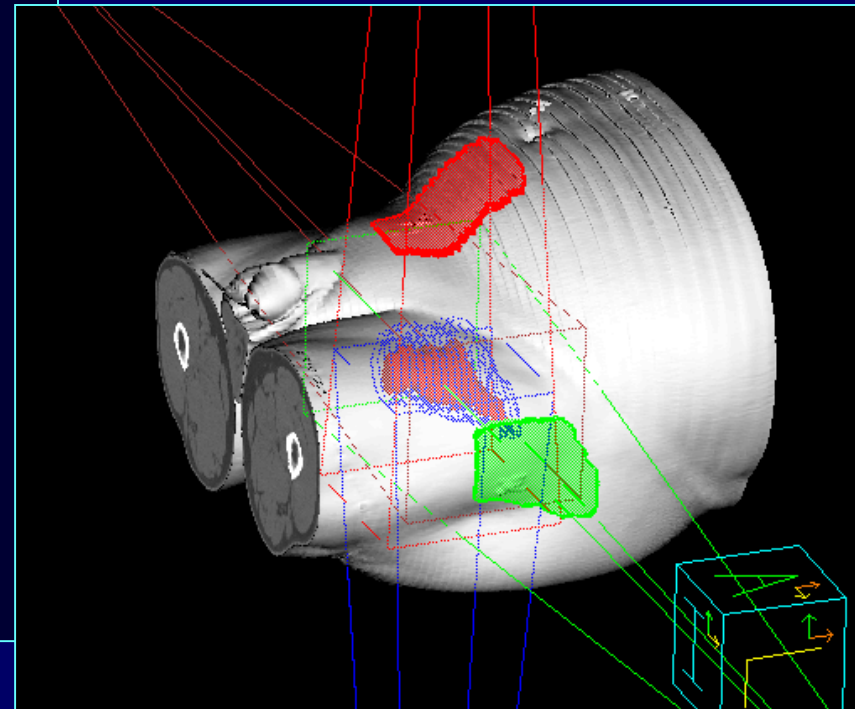
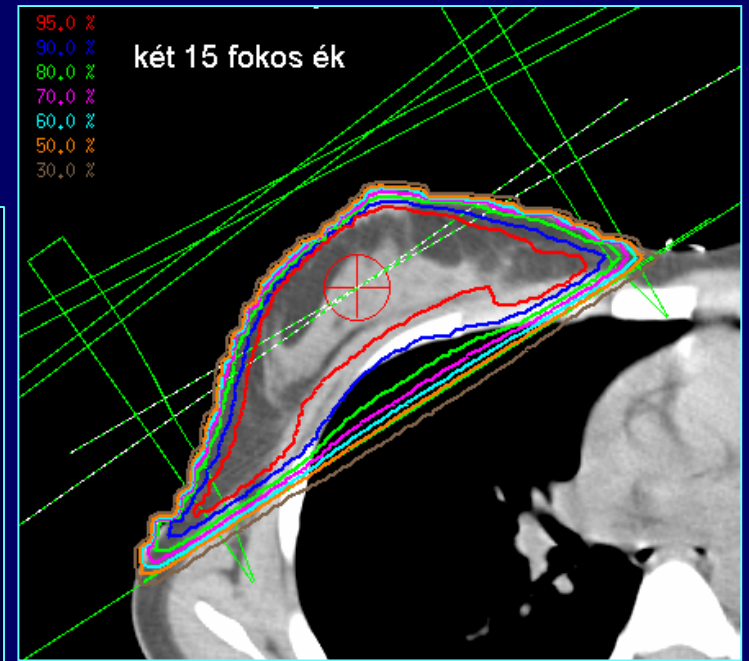


Treatment planning

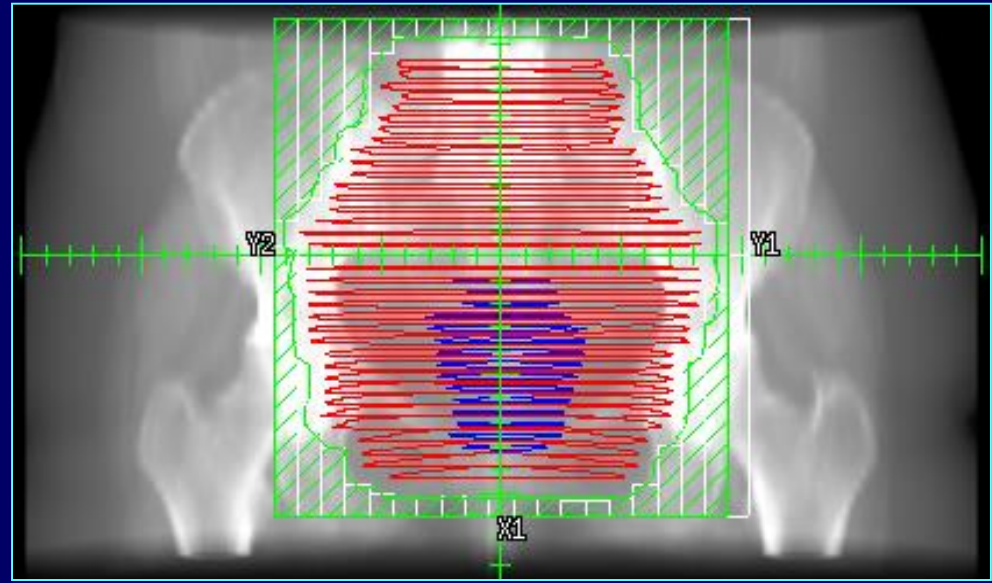
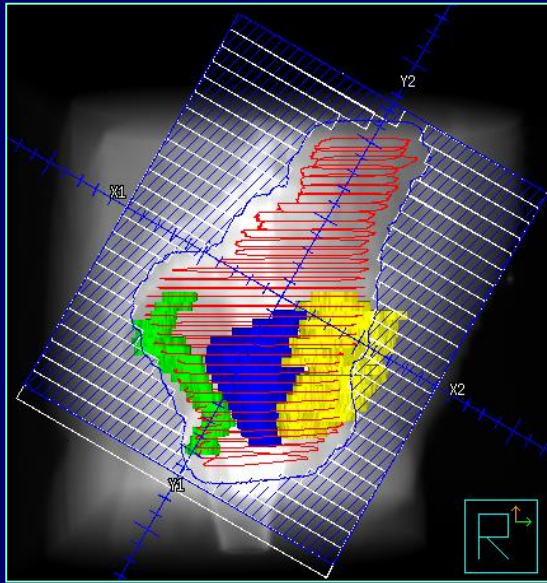
- Reproducible patient positioning + CT-based treatment planning



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

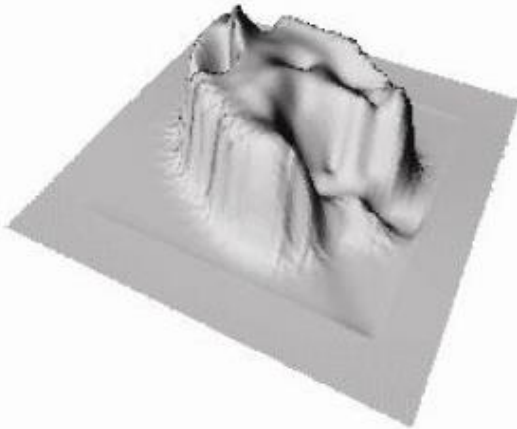


3D-CRT = individual, irregular fields conforming to the 3D shape of the target volume

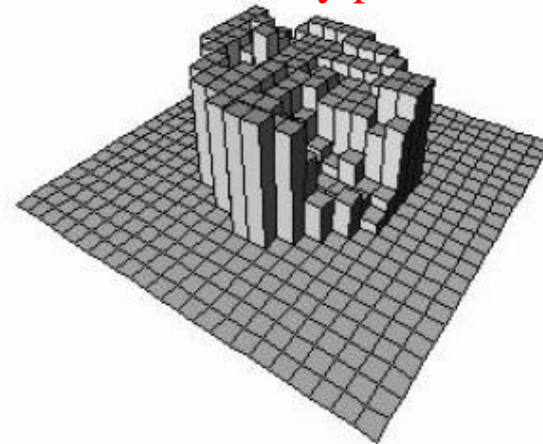


Intensity modulated RT (IMRT) = modulation of intensity within the radiation field

Ideal intensity profile

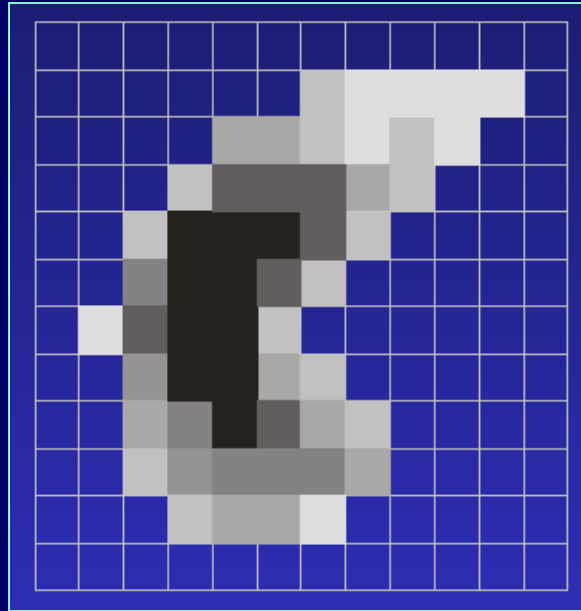


Achievable intensity profile using MLC

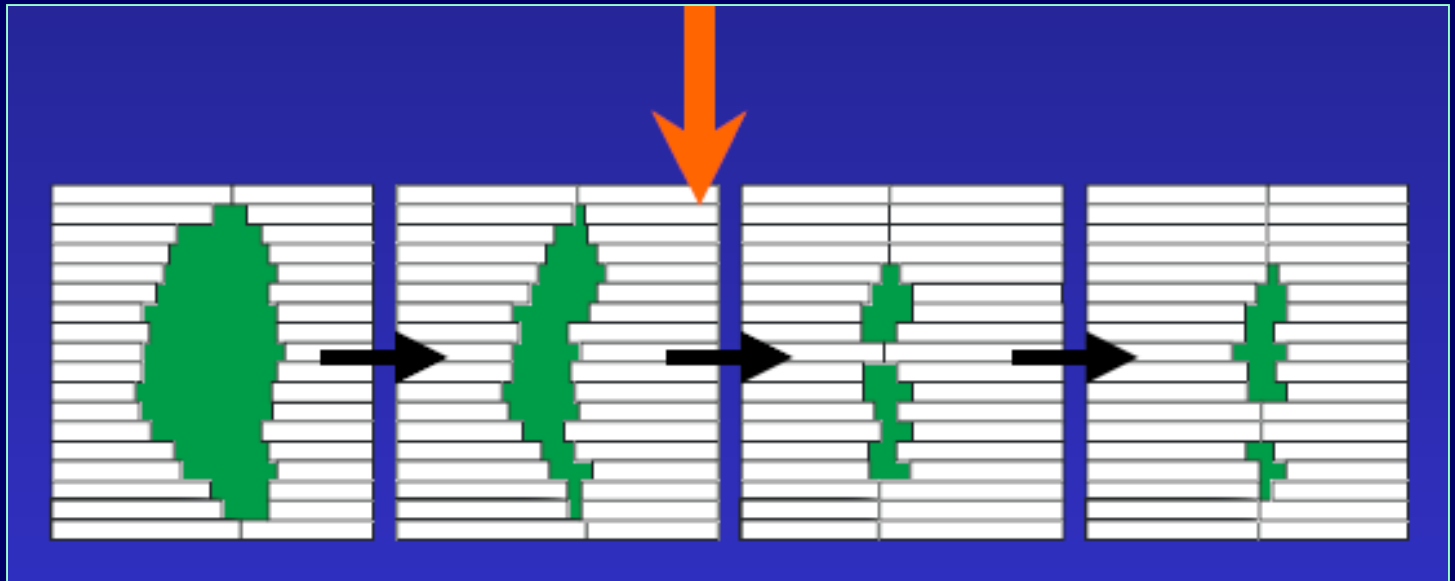


Intensity modulated radiotherapy (IMRT)

- 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)

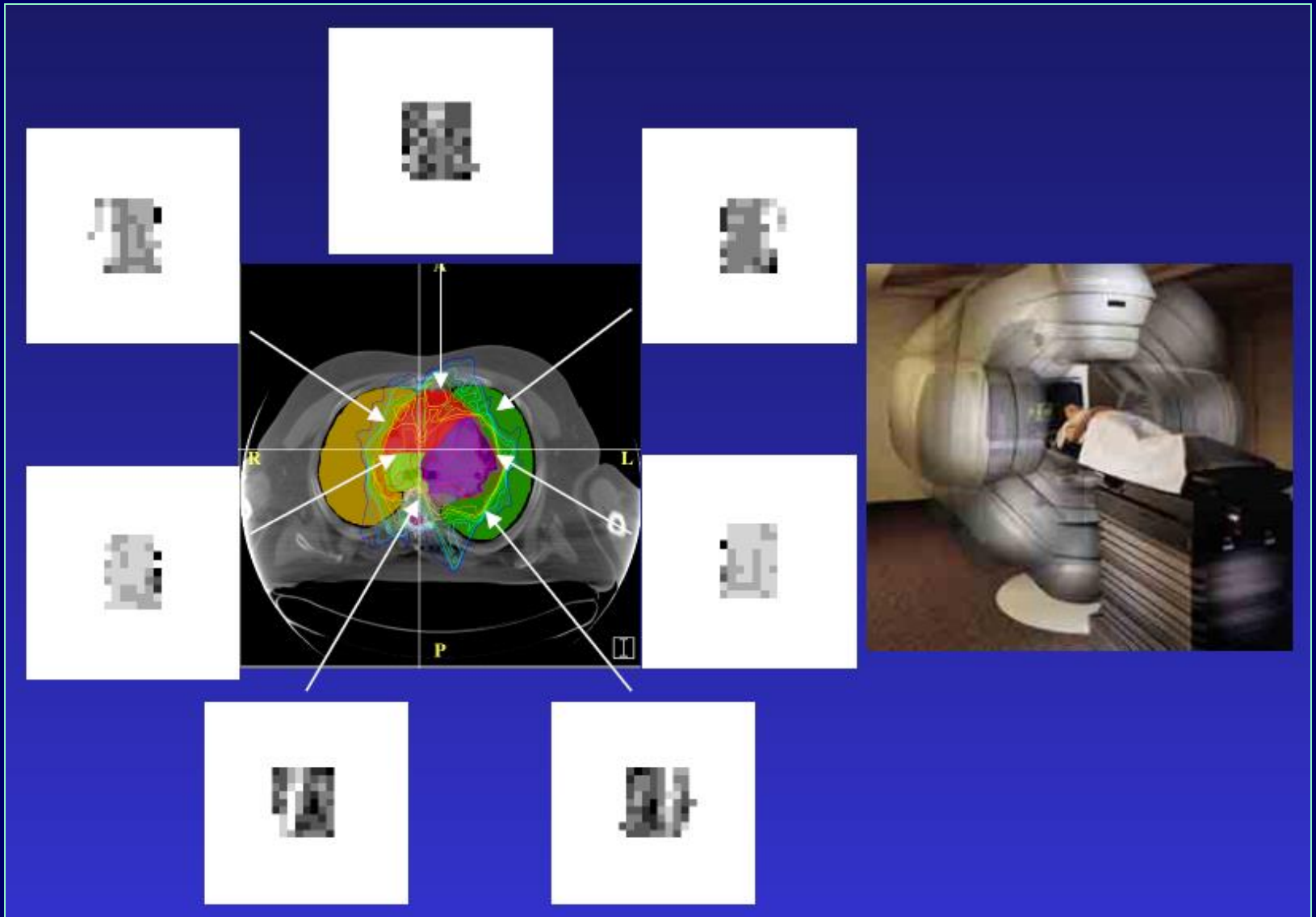


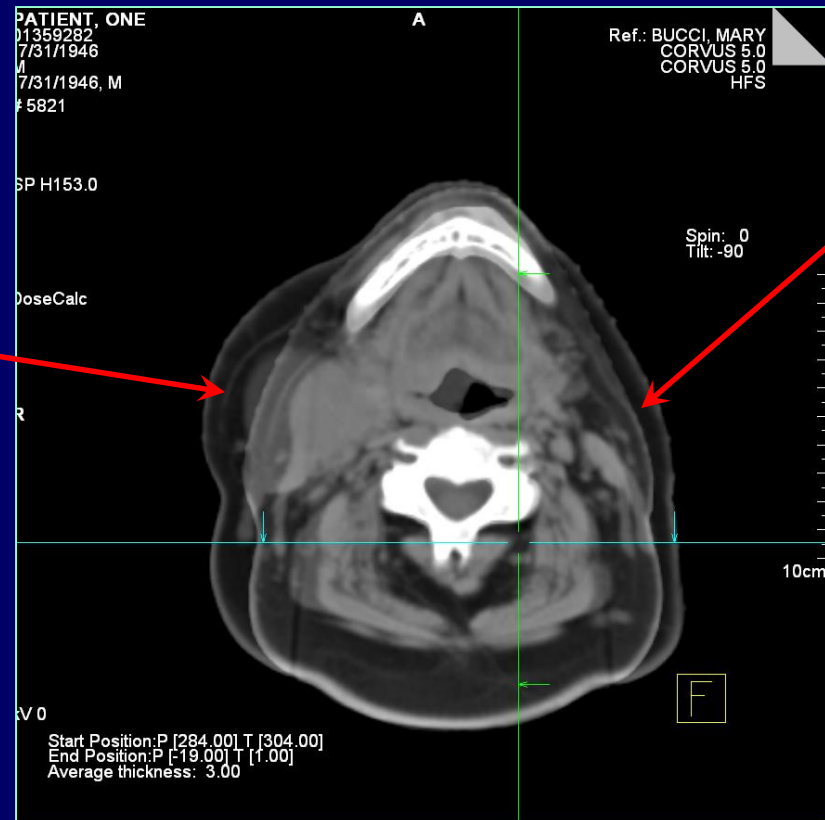
Image-guided radiotherapy = IGRT

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

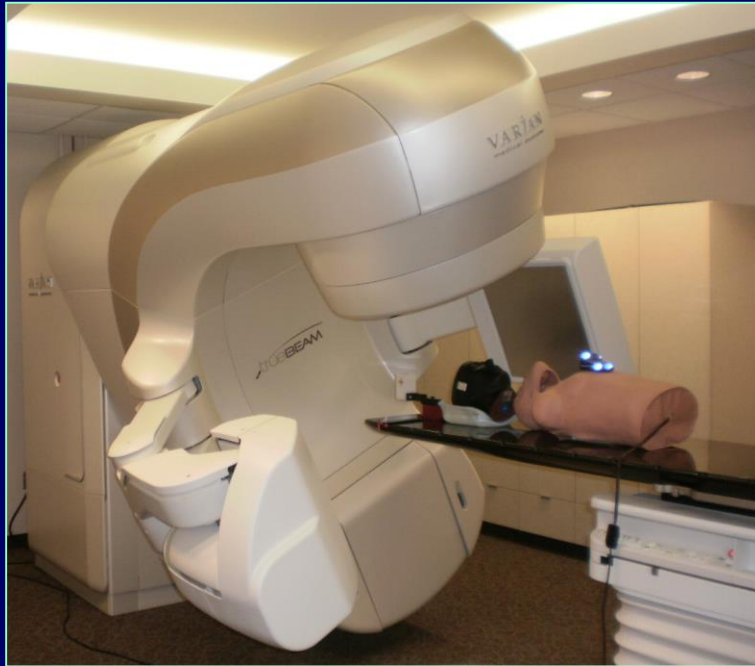


IGRT using LINAC + integrated CT on-rail

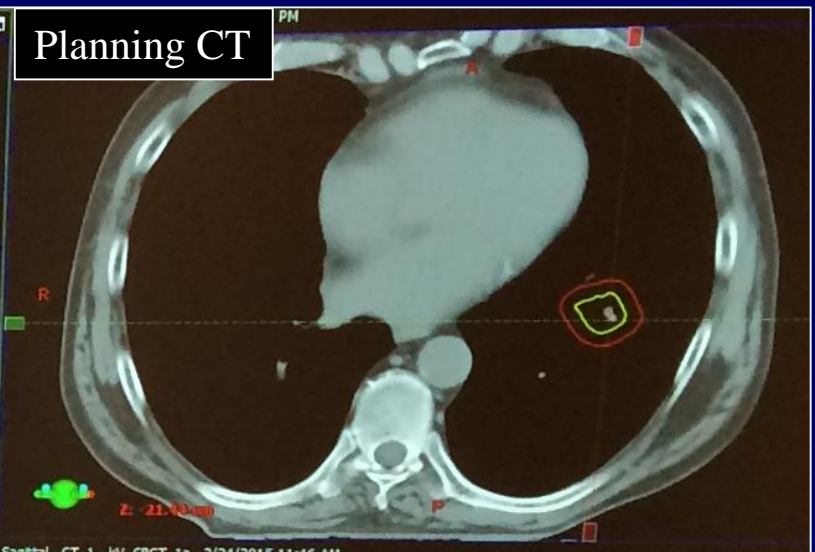
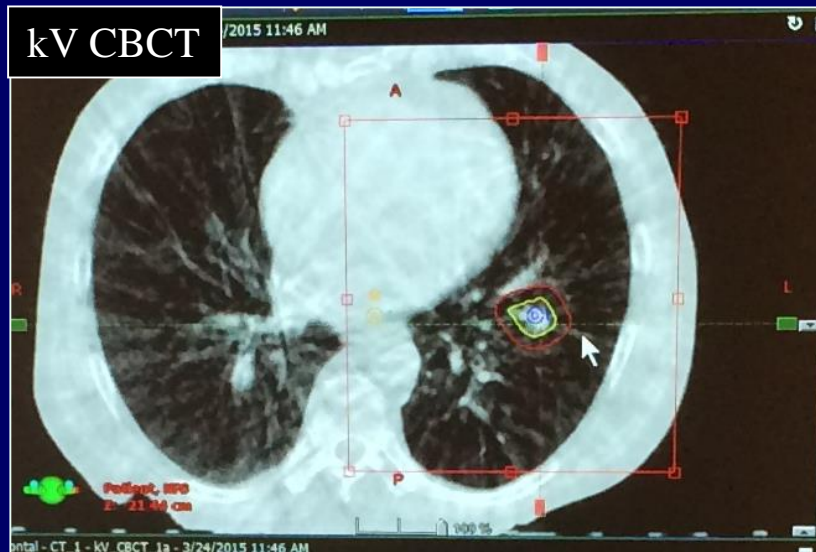
RT delivery with 180° table rotation



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

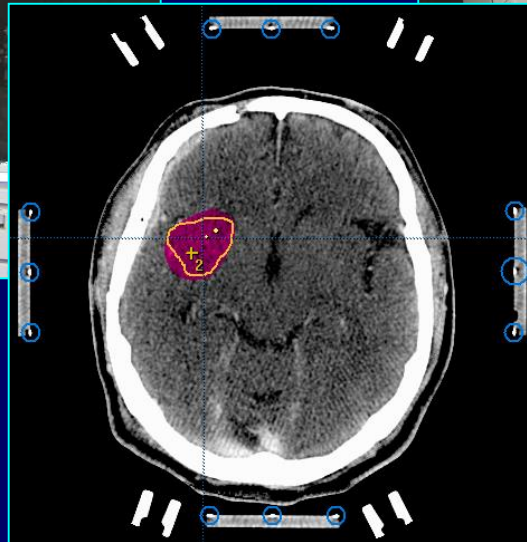
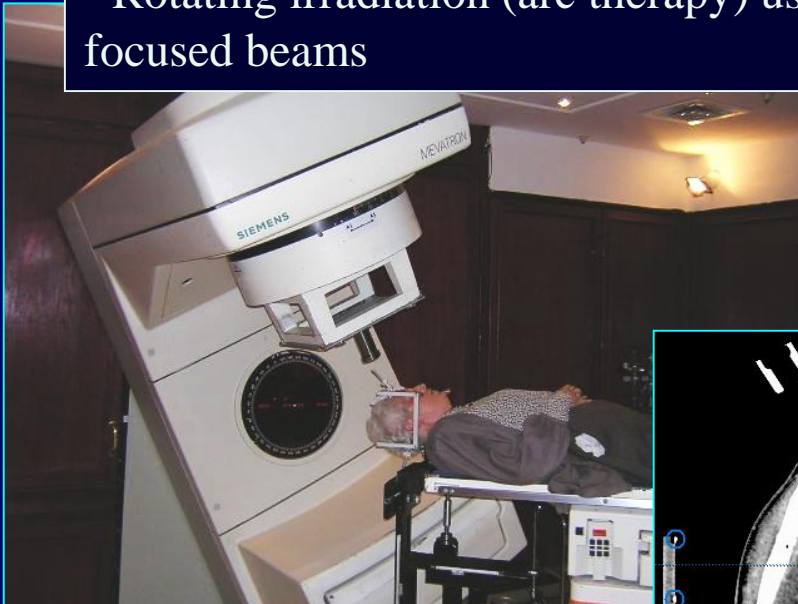
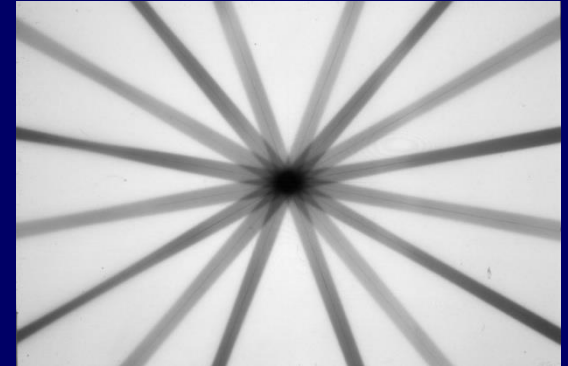


Couch Shift [cm]	
Vrt	+0.30
Lng	+0.42
Lat	-0.10
Couch Shift [°]	
Rtn	-0.1 <input checked="" type="checkbox"/>
Pitch	-0.1 <input checked="" type="checkbox"/>
Roll	+0.1 <input checked="" type="checkbox"/>



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



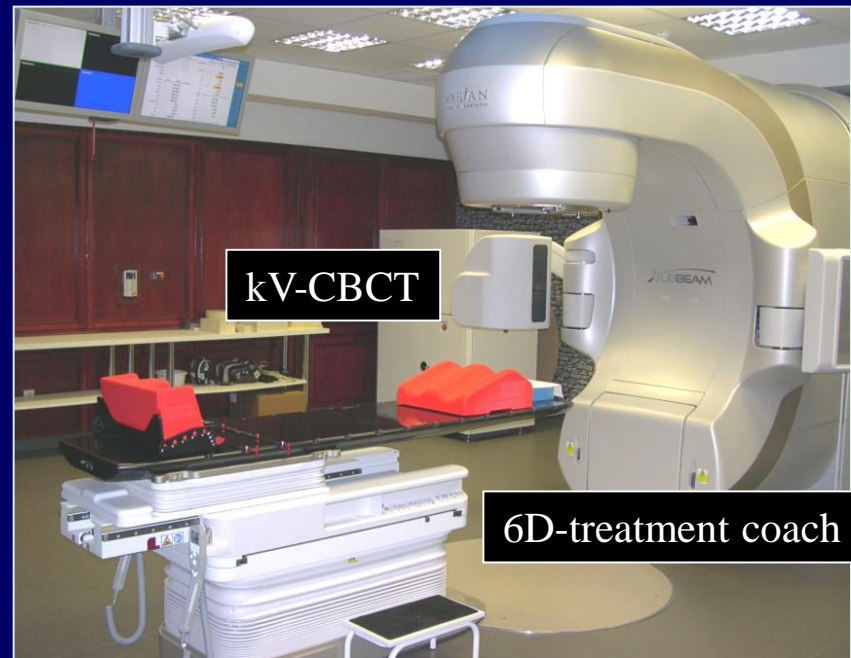
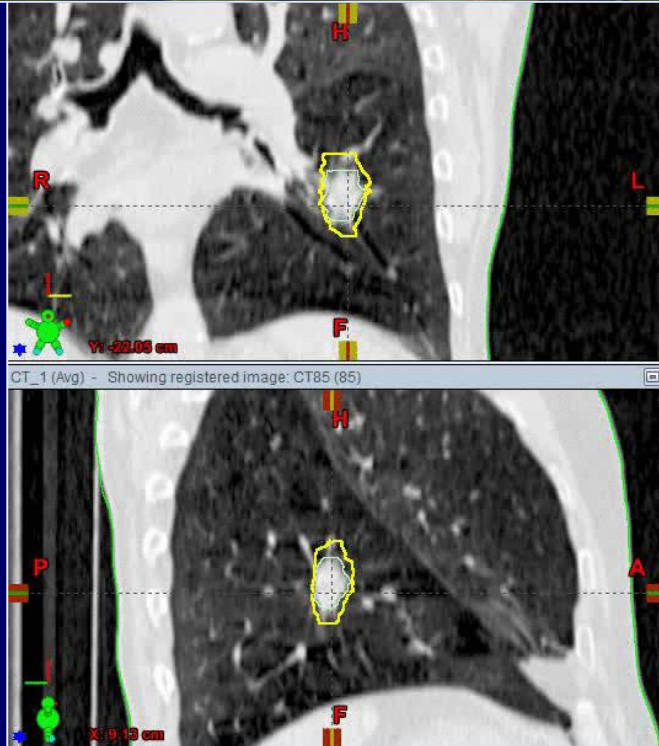
**Dose prescription:
16 Gy to the 50% isodose**

Stereotactic Ablative Body RadioTherapy = SABRT

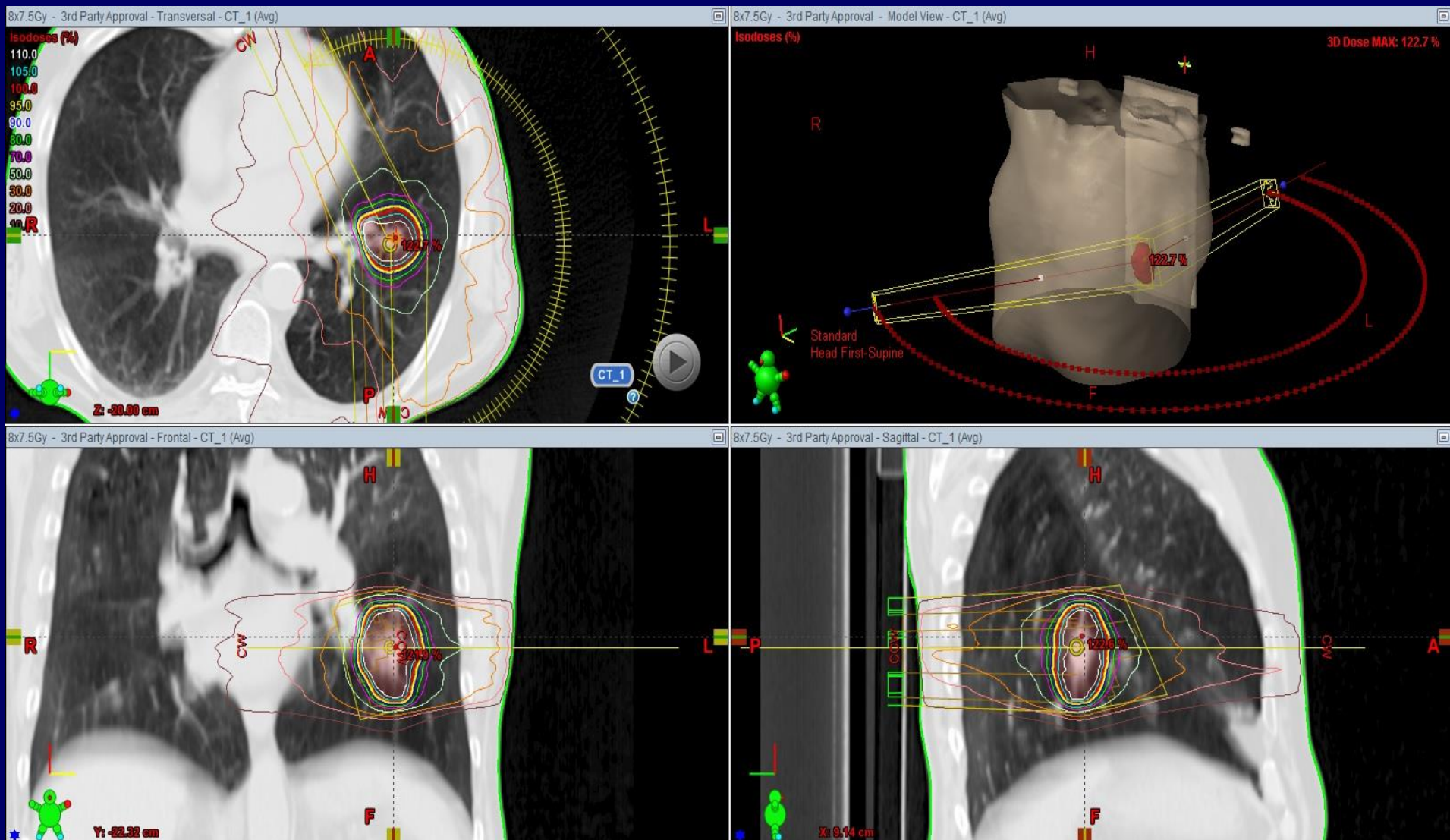


Technical needs:

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

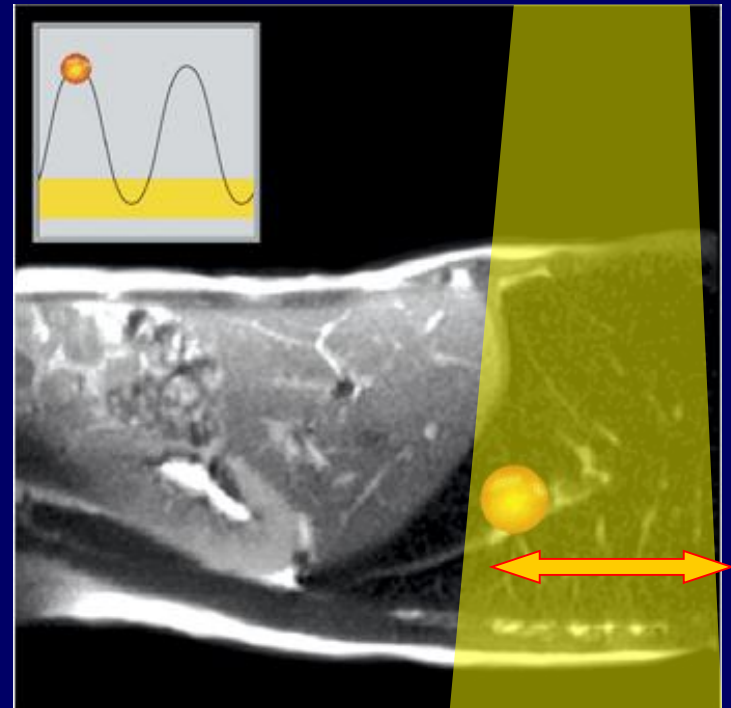


Stereotactic Ablative Body RadioTherapy = SABRT



Irradiation of moving targets – Conventional technique

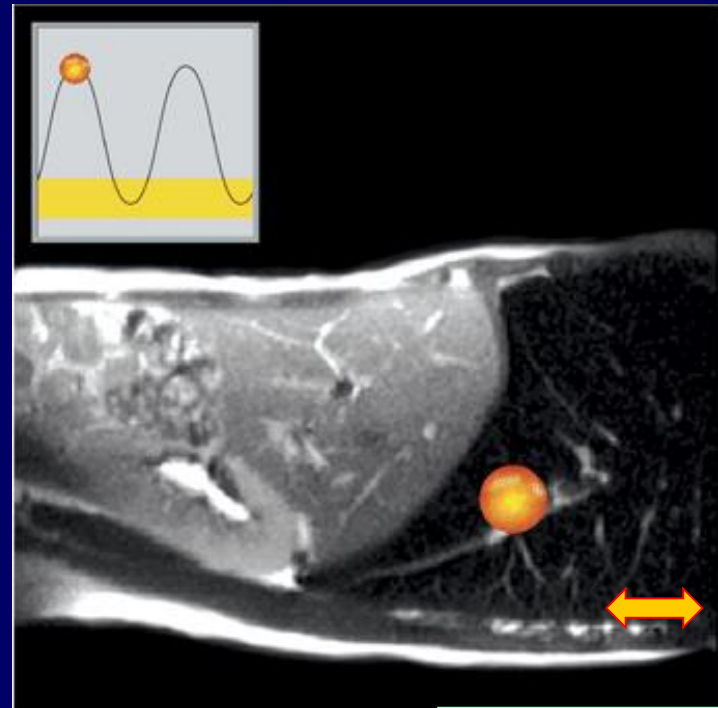
Breathing cycle



Wide radiation
safety margin

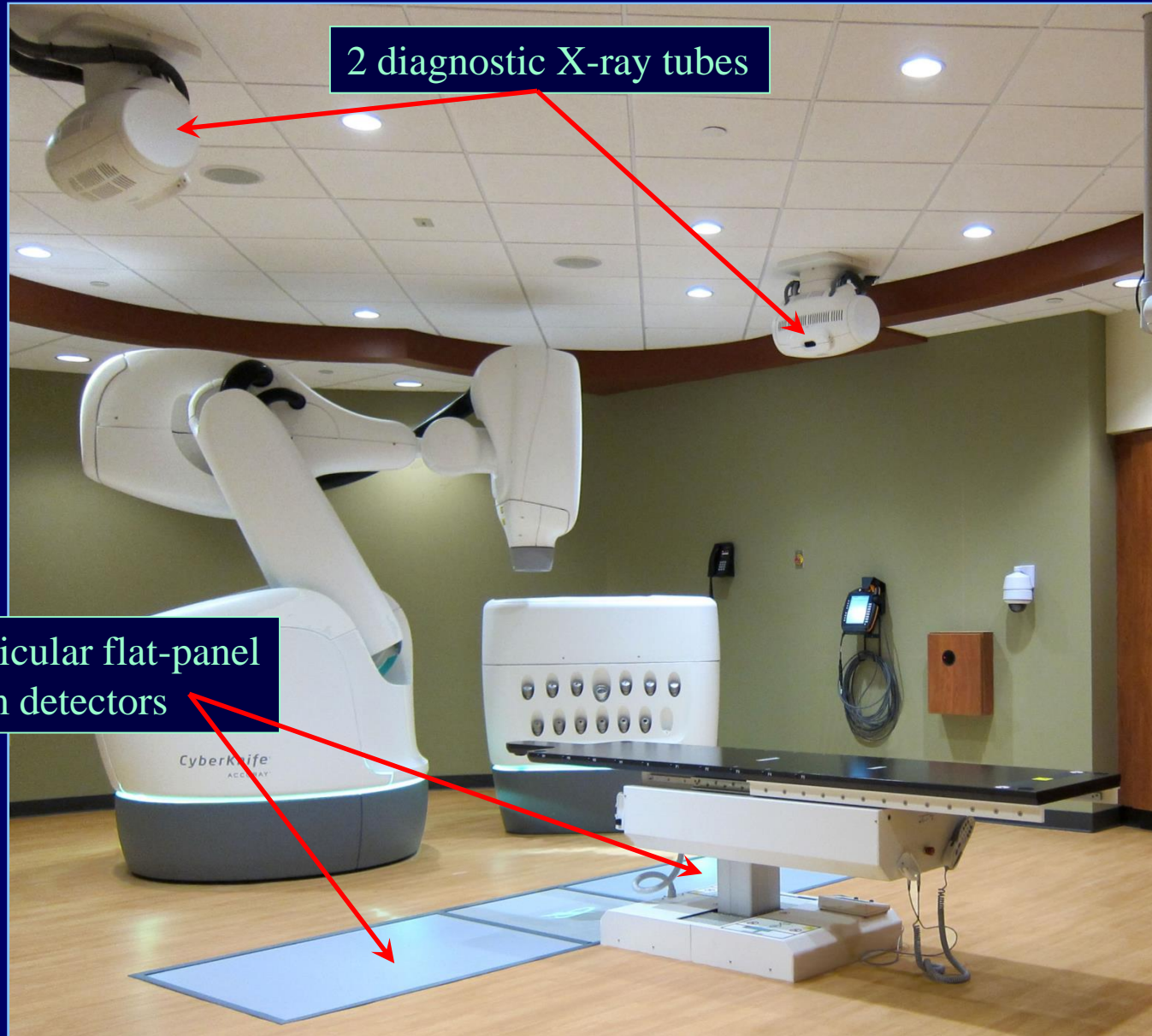
Irradiation of moving targets – Gated radiotherapy

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

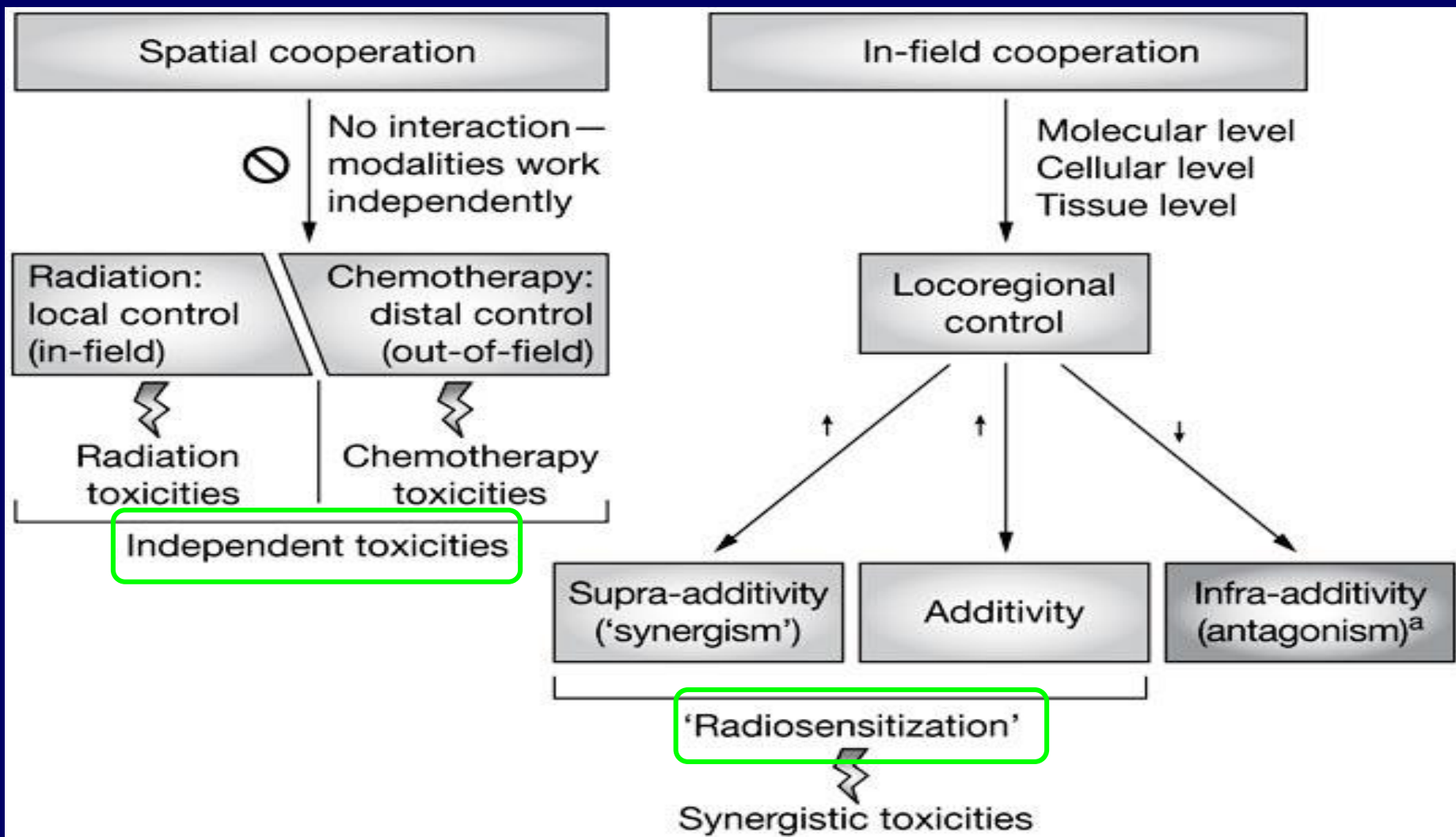


Narrow radiation
safety margin


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.^a

Disease entity	Indication and treatment	Commonly used agents	Benefit
Upper aerodigestive tract cancers			
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
Gastrointestinal malignancies			
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
Gynecological and genitourinary cancers			
Cervical cancer	Primary modality	Cisplatin, 5-FU, hydroxyurea	Improved local and distal control, organ preservation
Bladder cancer	Primary modality	Cisplatin	Improved local control
Other cancers			
Glioblastoma	Adjuvant	Temozolomide	Survival benefit
Sarcoma	Neoadjuvant	Doxorubicin	Downstaging, improved organ preservation

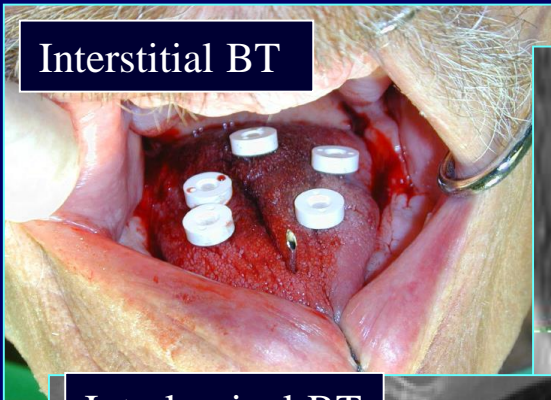
^aThis is a limited overview, and concurrent chemoradiotherapy is used in most solid tumors either as a standard treatment or investigationally. For further details please refer to the organ-specific literature. Abbreviations: 5-FU, 5-fluorouracil; FHX, 5-FU, hydroxyurea and radiation; HNC, head and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

Seiwert TY *et al.* The concurrent chemoradiation paradigm—general principles *Nat Clin Pract Oncol* 2007;4:86–100

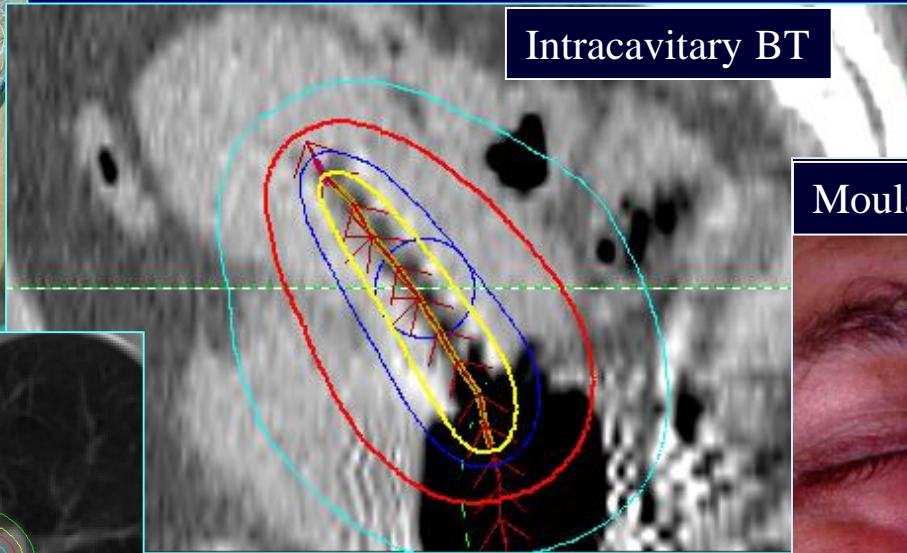
Clinical forms of brachytherapy (BT) I

- 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)

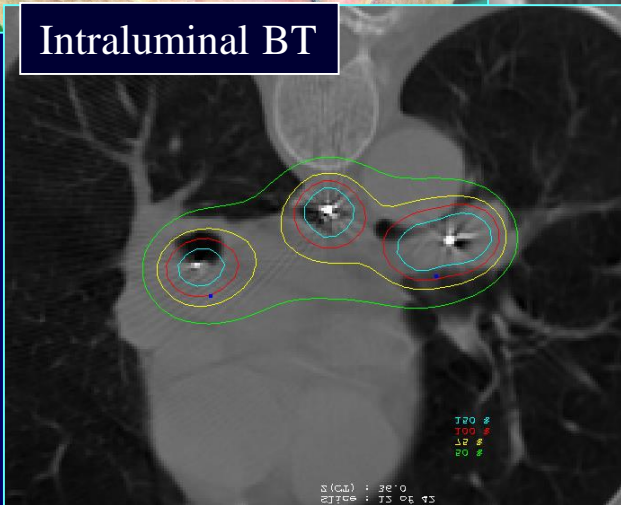
Interstitial BT



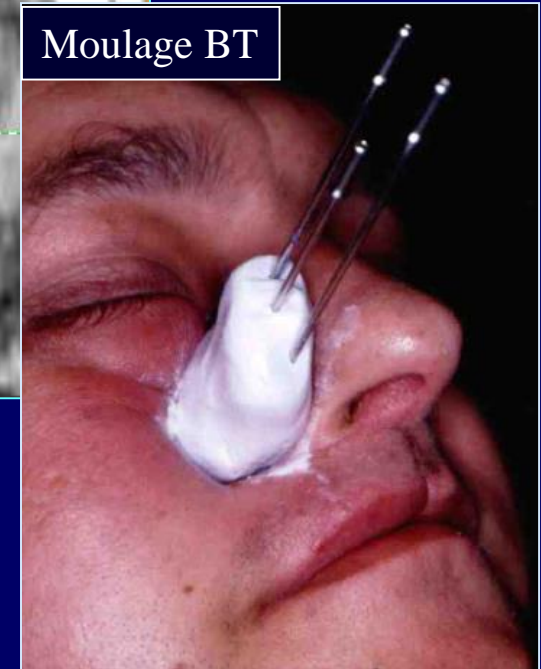
Intracavitary BT



Intraluminal BT

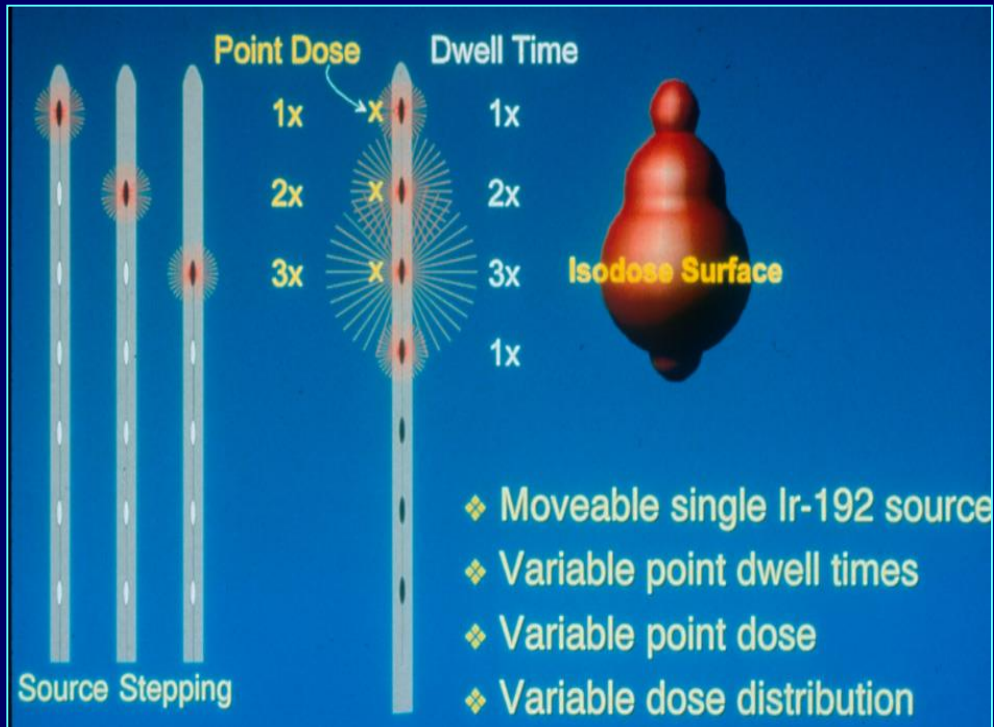


Moulage BT



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

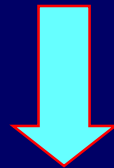


Standard BT applicators for the treatment of cervical cancer

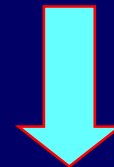


Role of RCT followed by brachytherapy boost

Before
RCT



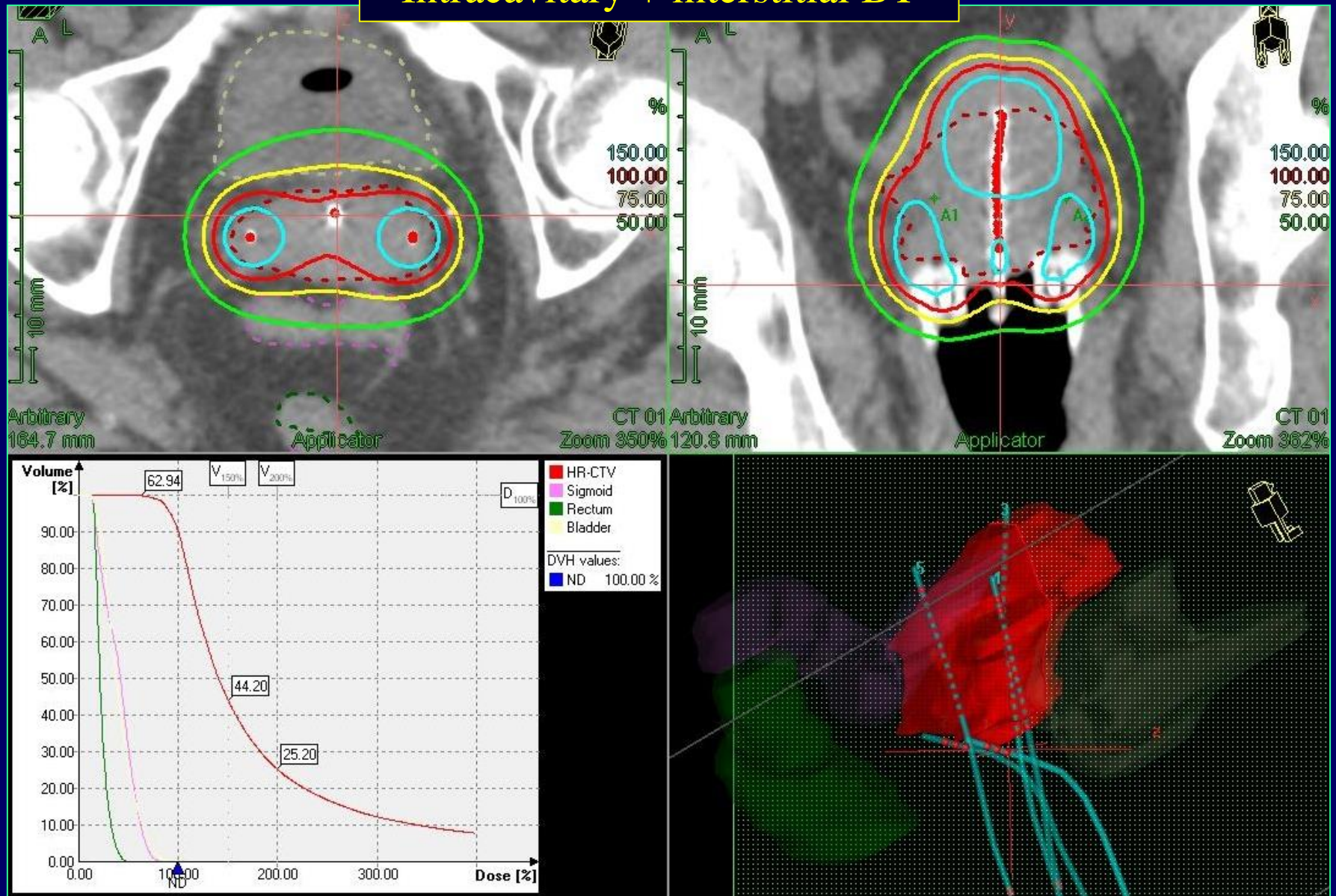
Chemoradiation



HDR-BT
boost

CT-based brachytherapy of cervical cancer

Intracavitary + interstitial BT

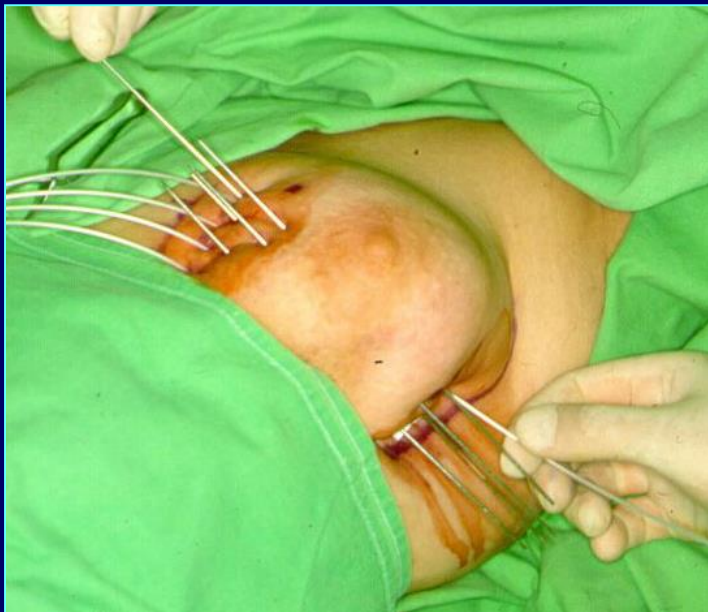
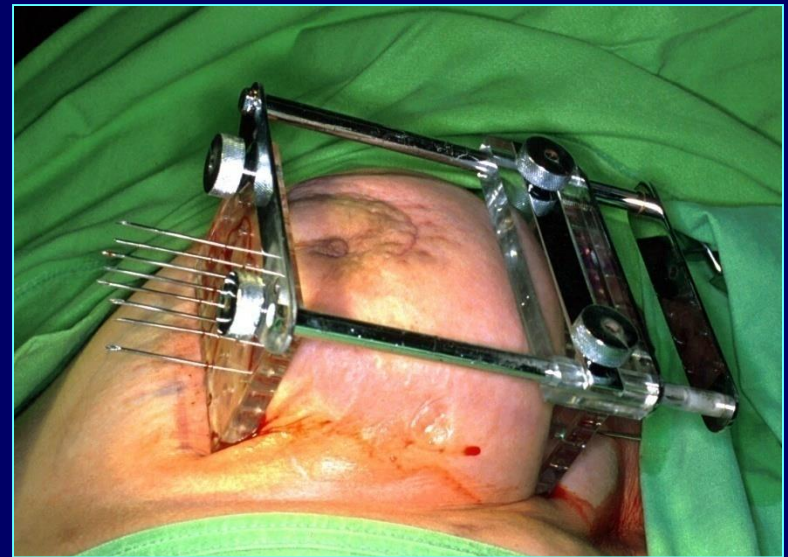
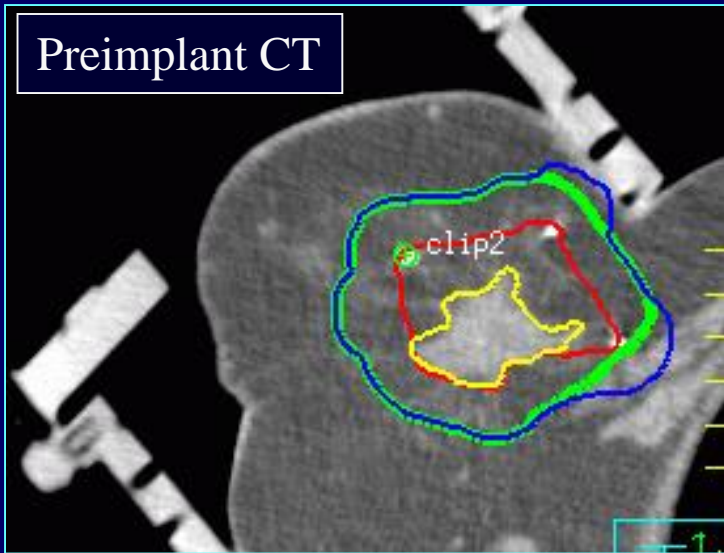


Interstitial brachytherapy of vulvar cc.

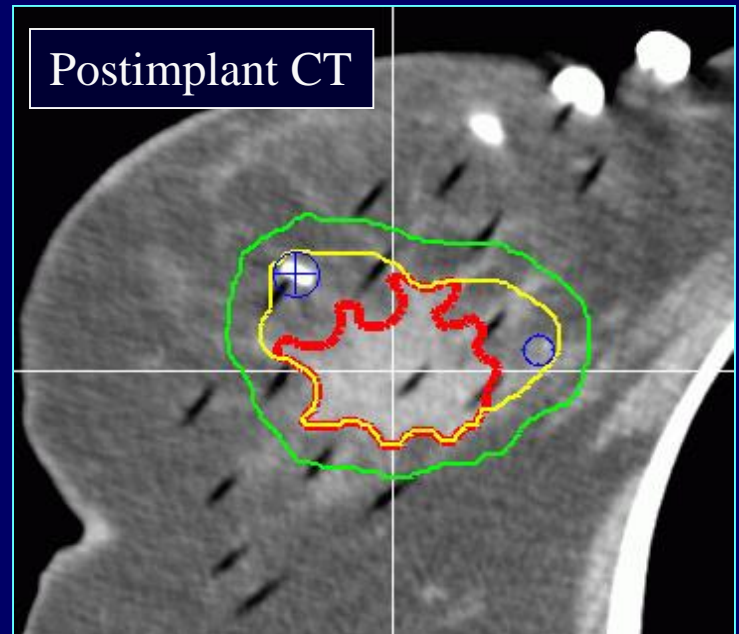


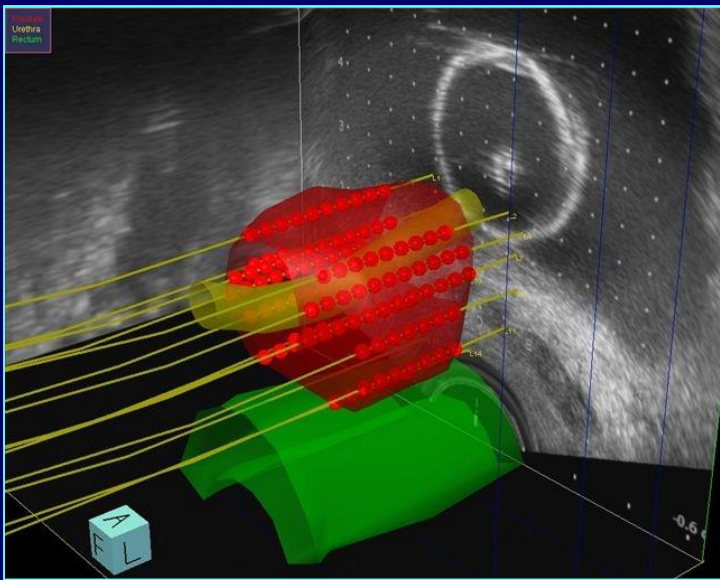
CT-based interstitial breast brachytherapy

Preimplant CT

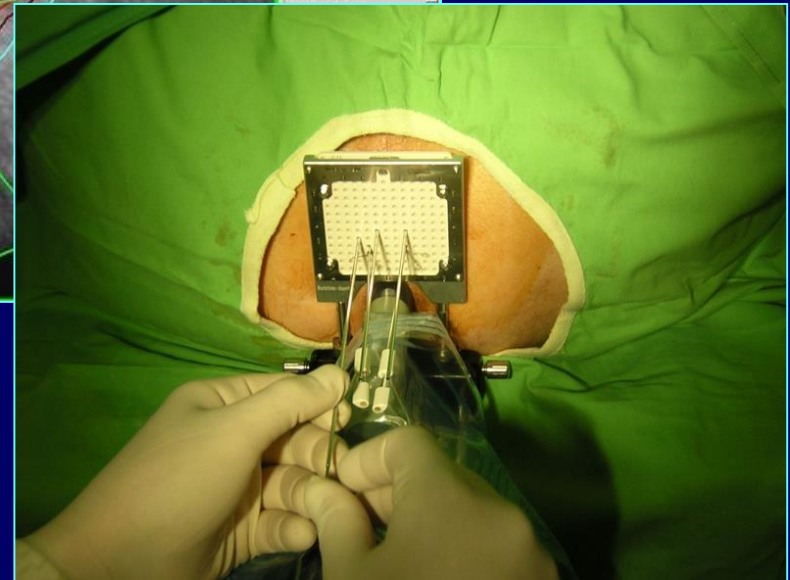
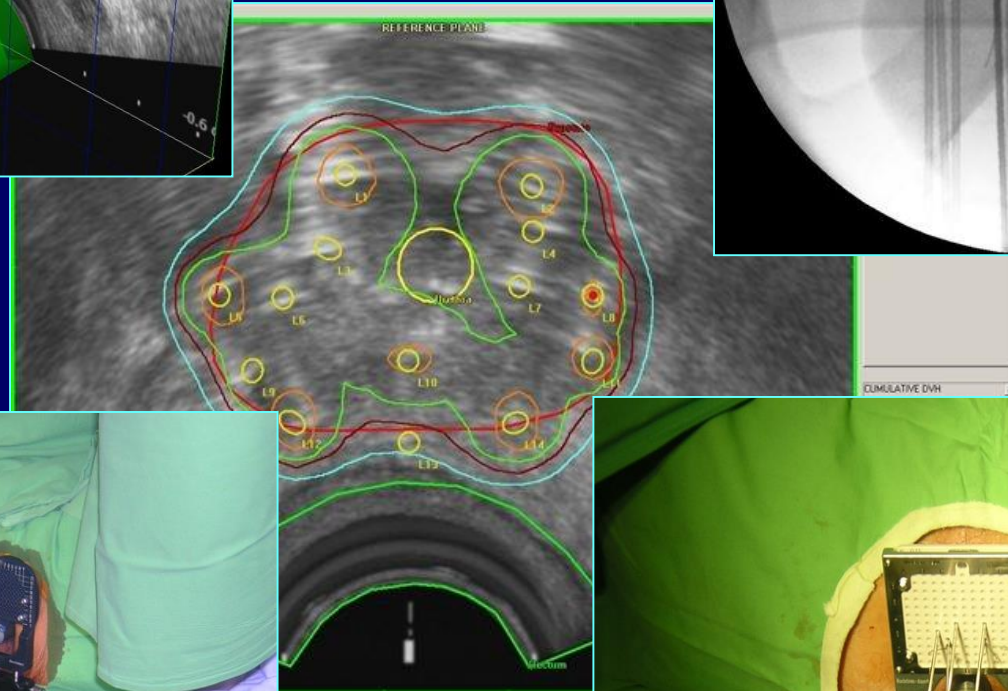
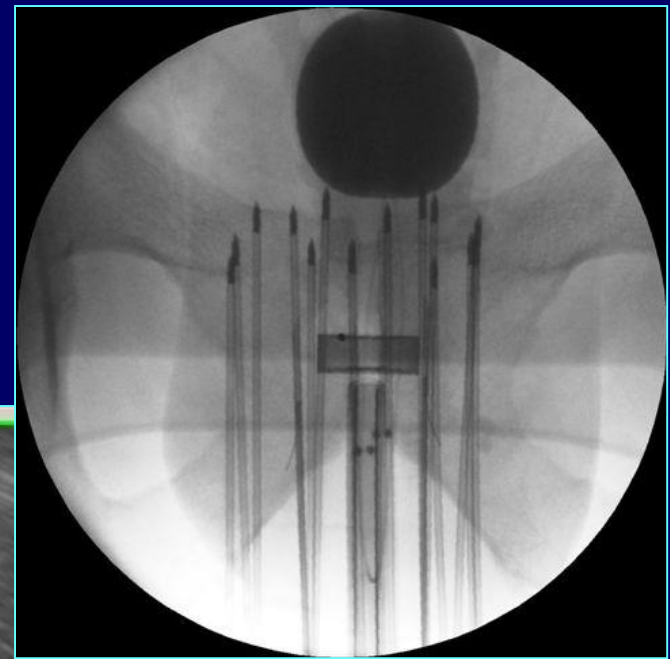


Postimplant CT

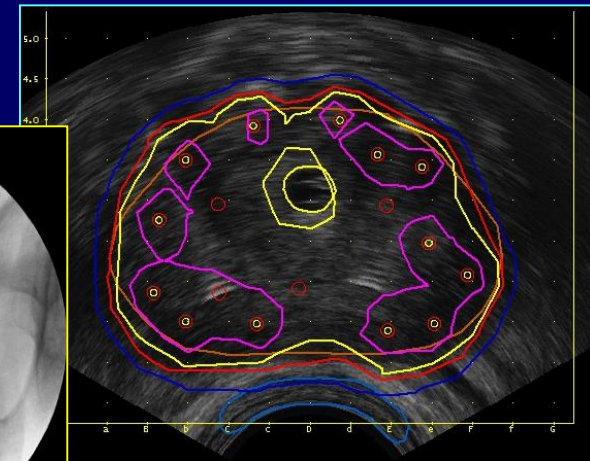
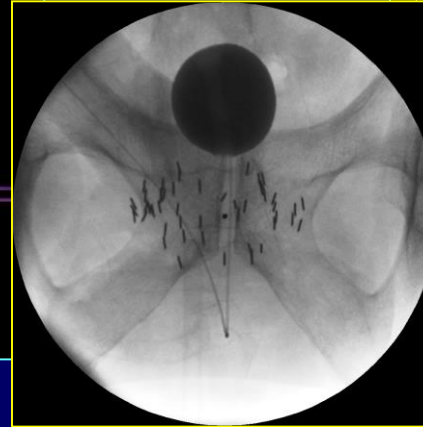
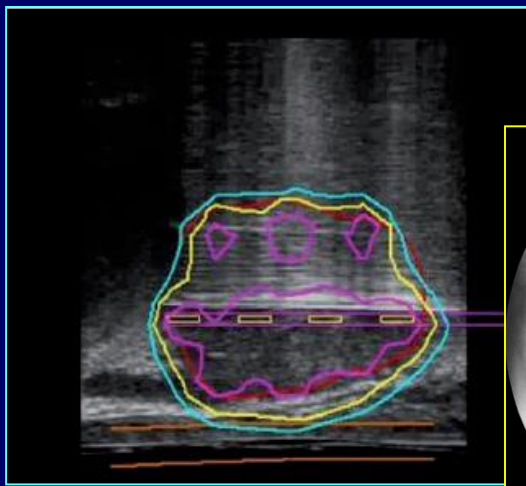




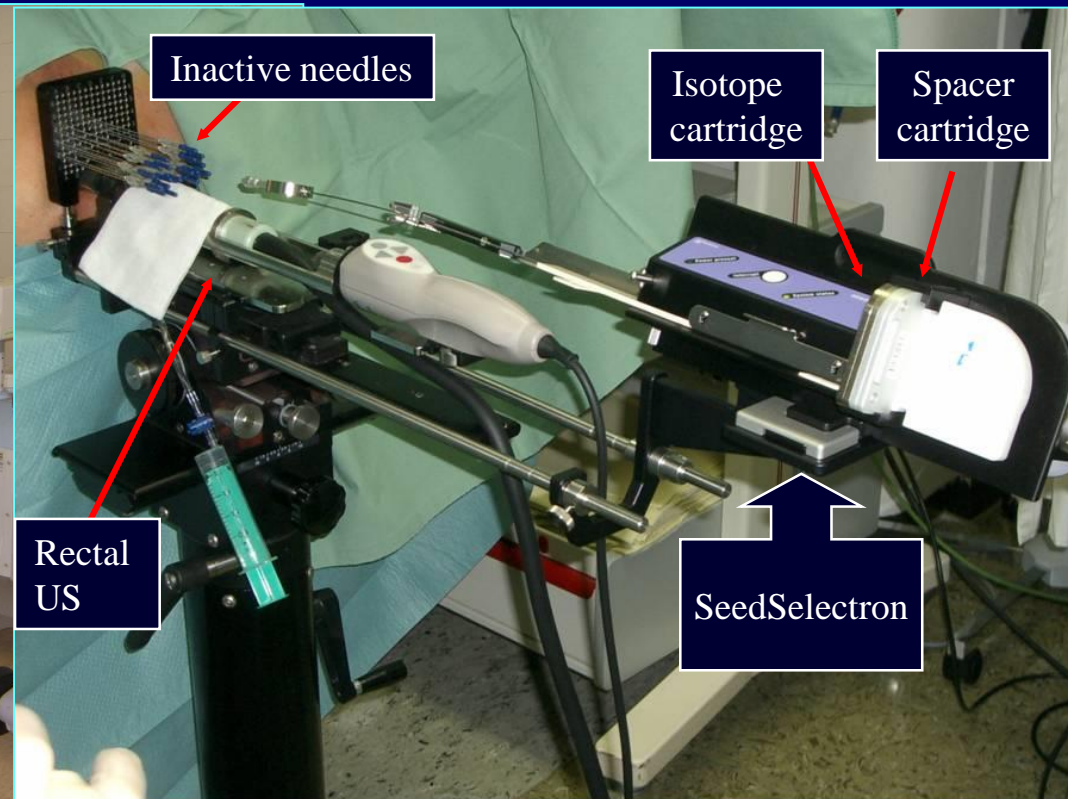
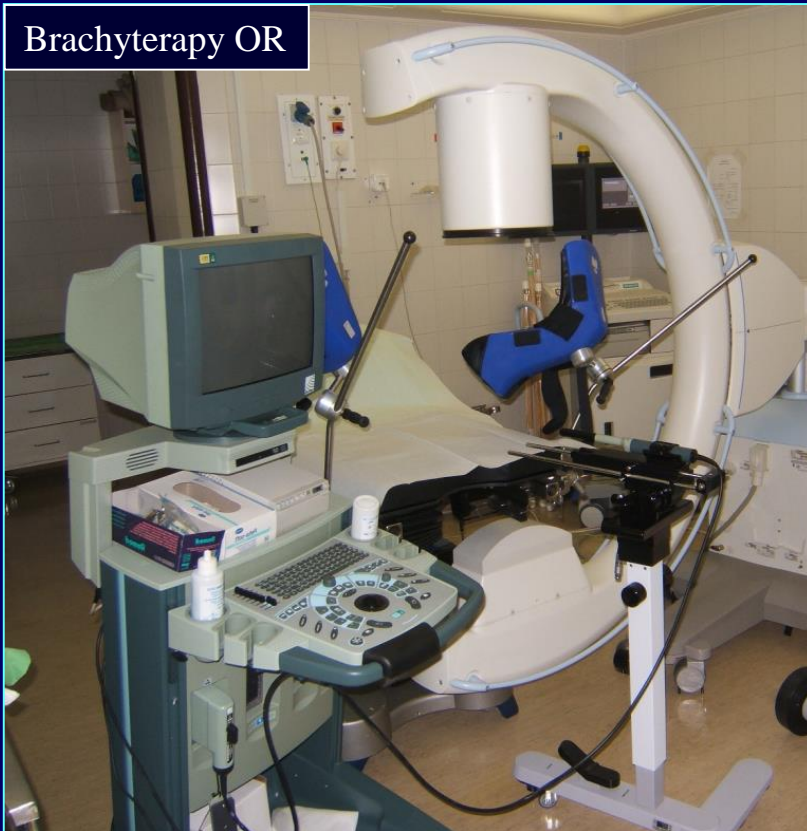
US-based prostate HDR brachytherapy



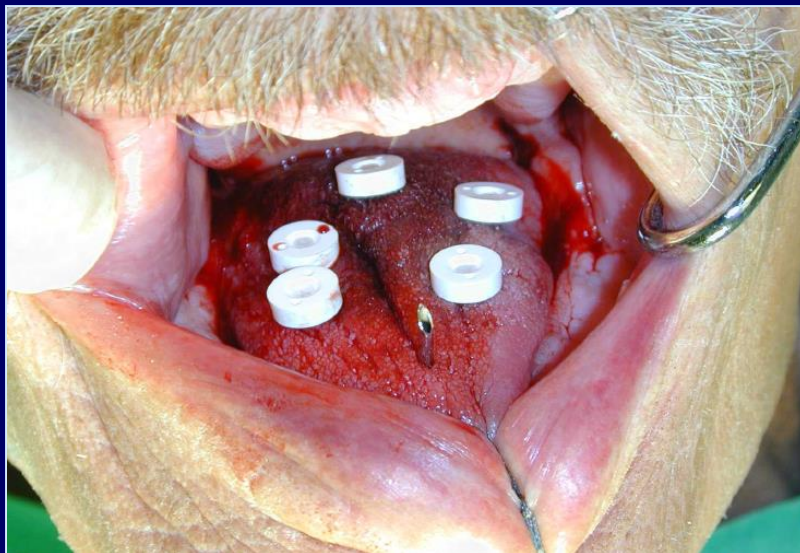
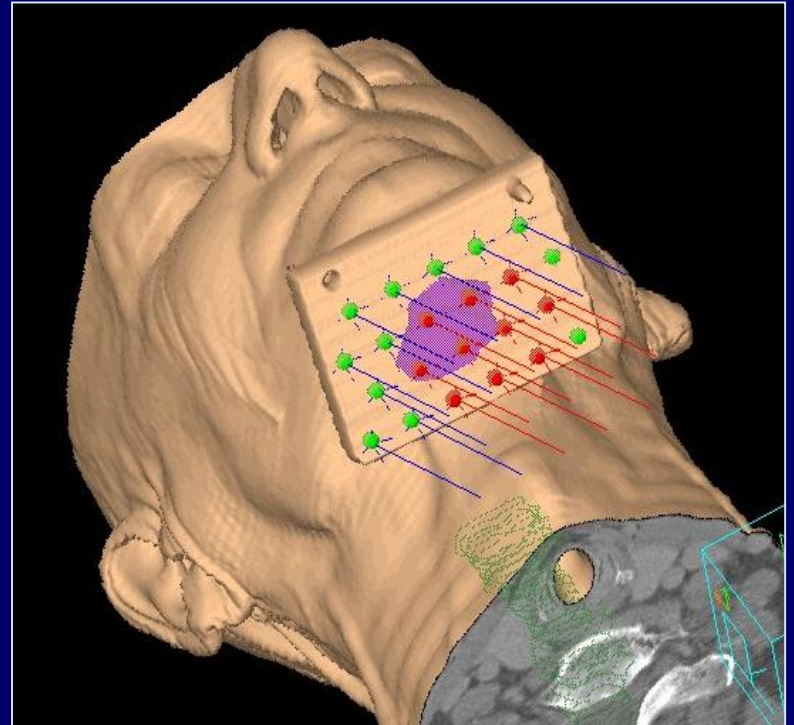
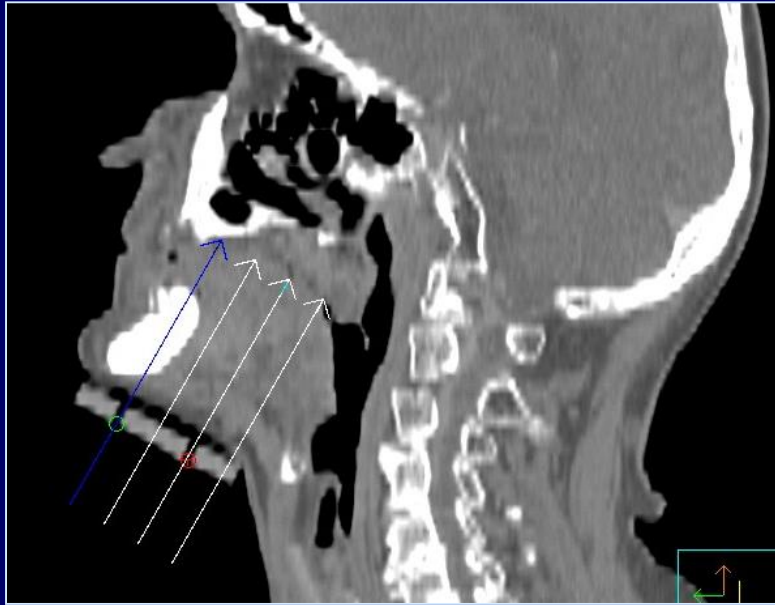
US-based permanent implantation prostate brachytherapy (PIPB)



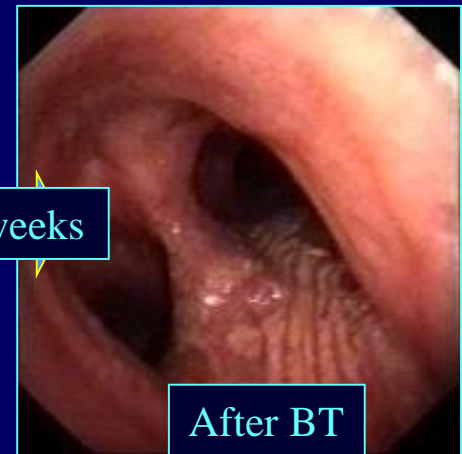
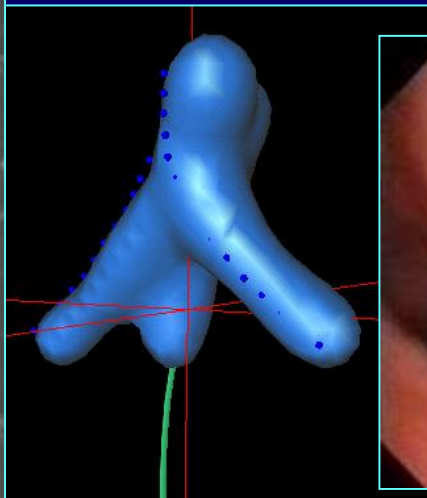
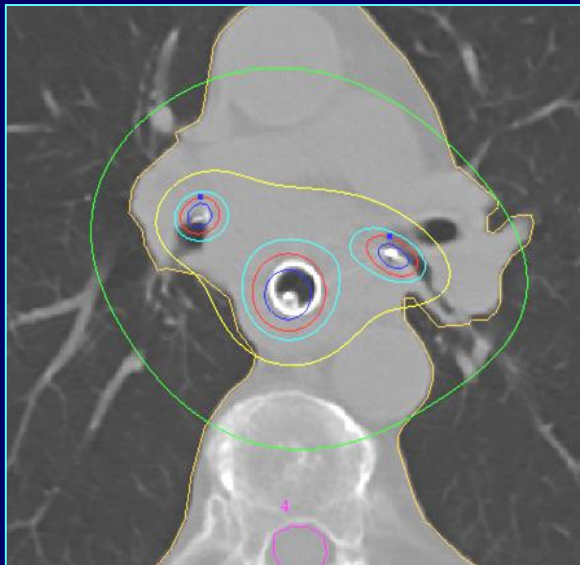
Brachytherapy OR



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



Intraluminal lung + esophageal brachytherapy



3 weeks

Thanks for your kind attention!

