Ipofrazionamento in Radioterapia:

esperienza con un sistema dedicato

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AIRO 2013

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IEO
Arc Advanced Radiotherapy Center

IEO
Arc

fondazioneCNAO

Radiation Therapy

Empiric Art, not Exact Science

& Fractionation

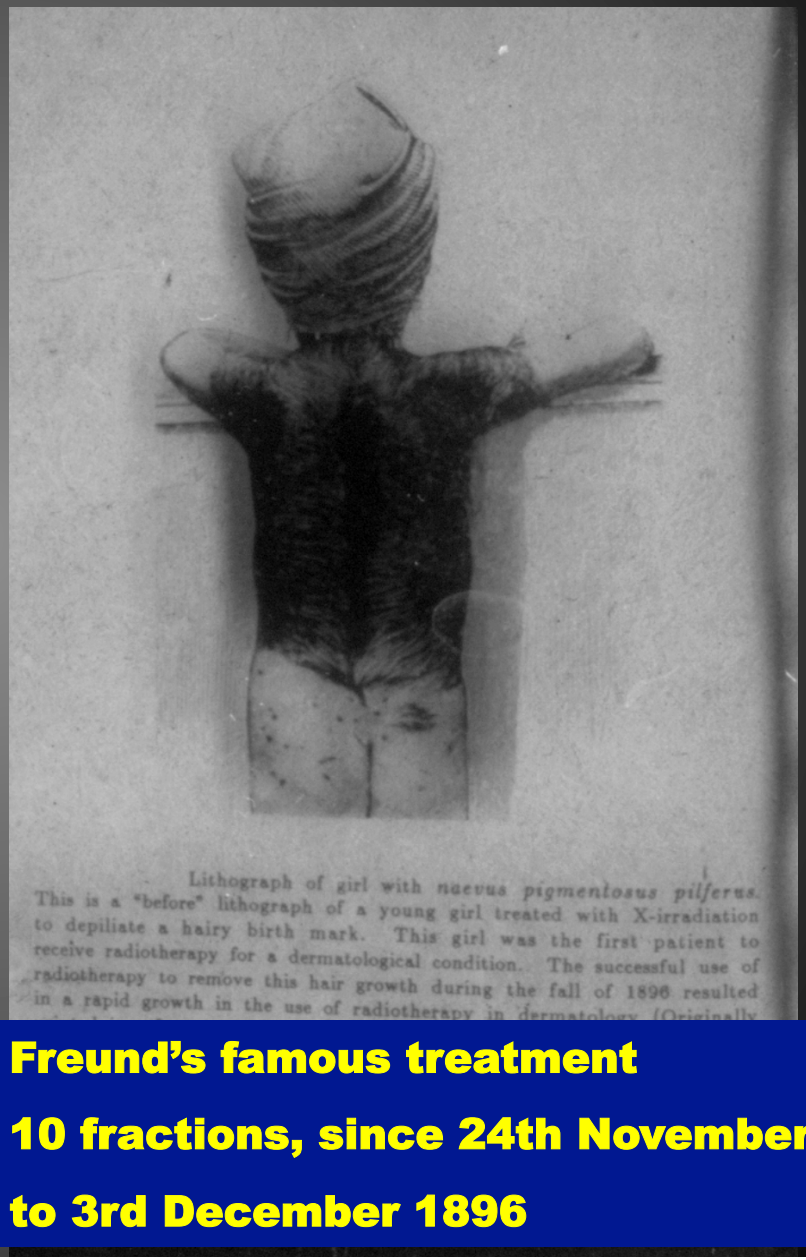
Radiobiology

Technology

“Terapia Magna Sterilans”

In Germany massive single dose

in France fractionated therapy



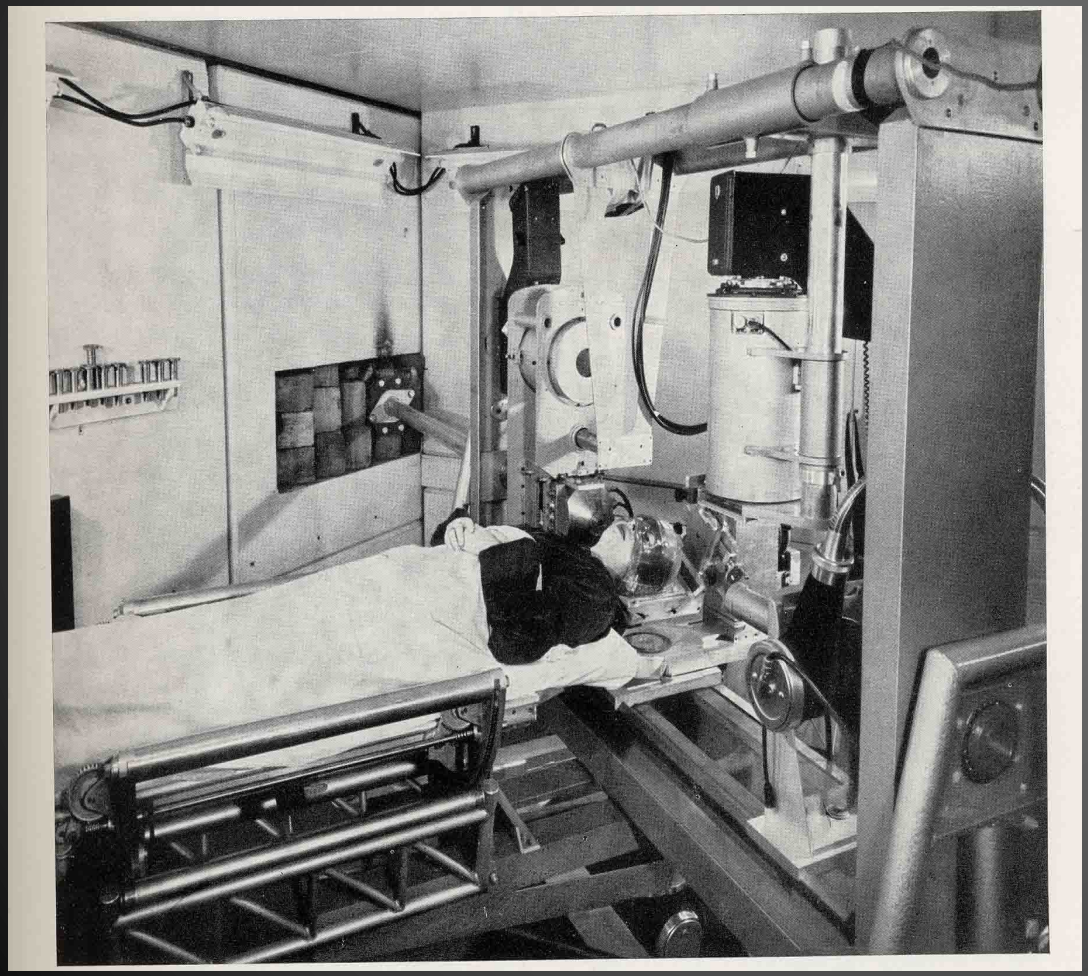
Lithograph of girl with *naevus pigmentosus pilferus*. This is a "before" lithograph of a young girl treated with X-irradiation to depiliate a hairy birth mark. This girl was the first patient to receive radiotherapy for a dermatological condition. The successful use of radiotherapy to remove this hair growth during the fall of 1896 resulted in a rapid growth in the use of radiotherapy in dermatology. (Originally

Freund’s famous treatment

10 fractions, since 24th November to 3rd December 1896

The Early 1920s

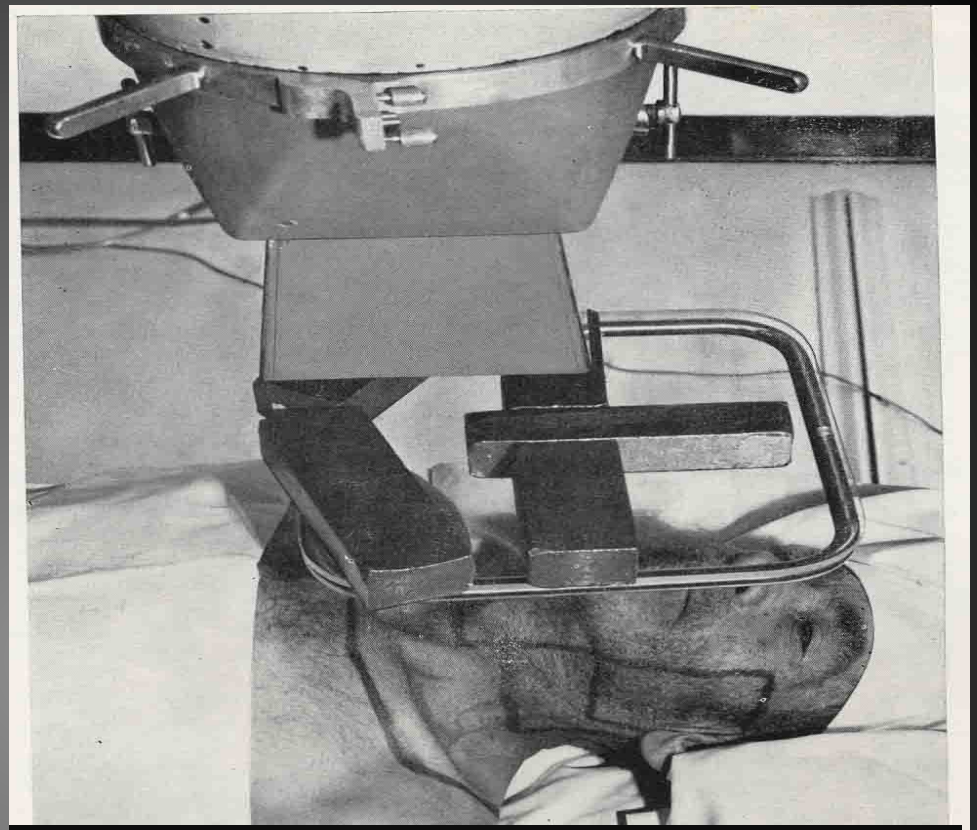
Coutard: daily fractions lasting 2-3 hours on regimen lasting 4-6 weeks



Baclesse: daily doses of 200R (1.8 Gy) given over 10 minutes using regimens of up to 4 months

G Fletcher since1948

As a results of his influence and teaching there is a belief amongst radiation oncologists in the USA that to treat using fewer than 30 fractions is inherently dangerous



Coincidentally, owing to reimbursement practices in the USA, regimen using fewer than 30 fractions are also less lucrative

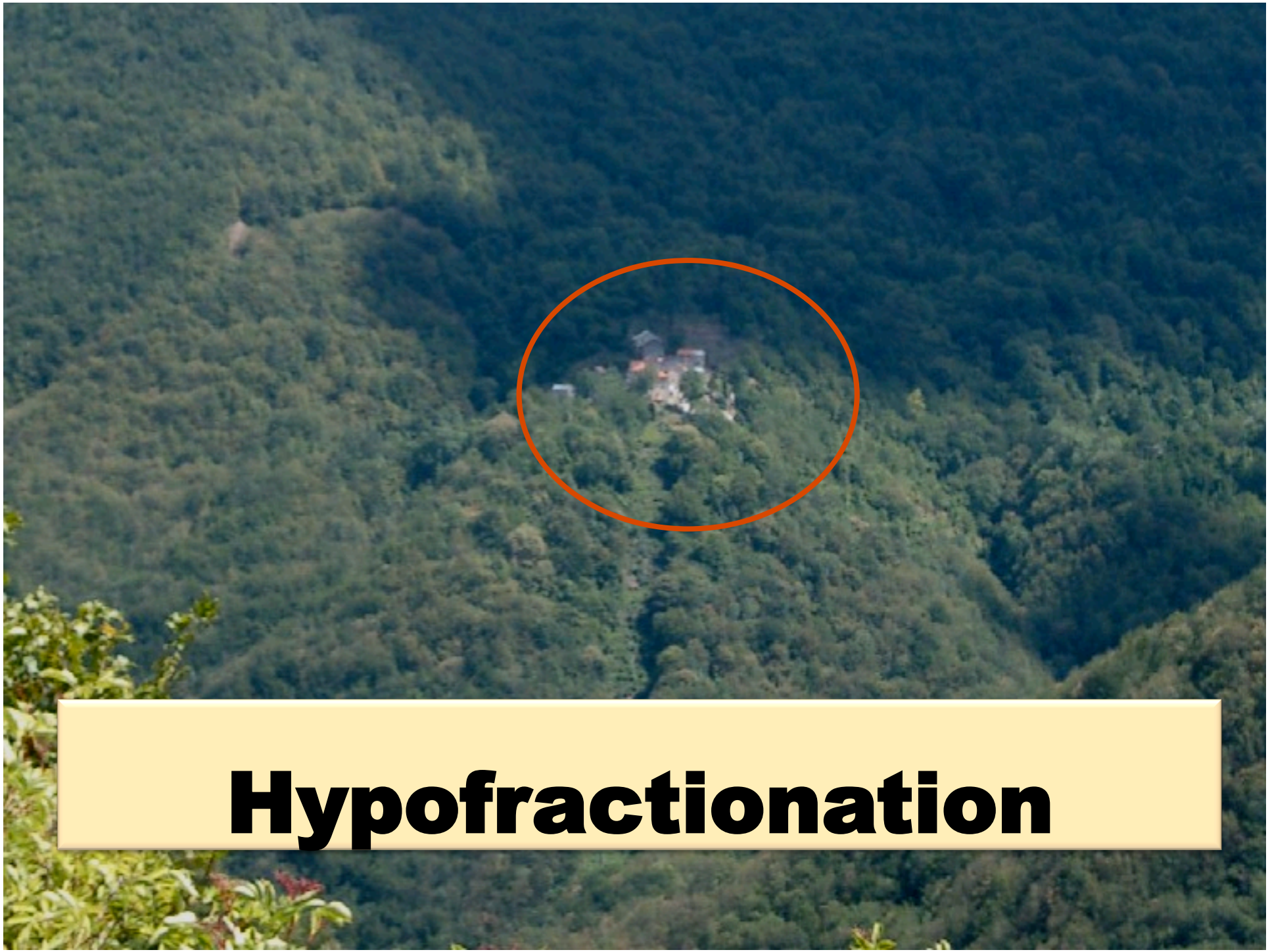
→ Standard Fractionaction

5 daily treatments, with a total treatment time of several weeks (from 5 to 8)

But in UK, School of Manchester

This regimen reflects:

- Practical aspects of dose delivery to a patients
- Successful outcome of patient's treaments
- Convenience to staff delivering the treatment


Hypofractionation

The Future of RT in the US ……, JCO 2010

Patients expected between 2010 to 2020
(+ 22%)

Prostate + 35%

Stomach + 27%

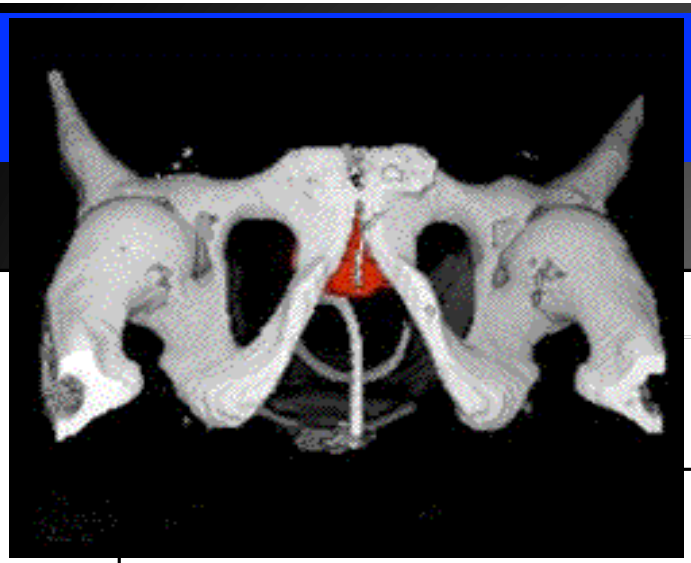
Liver + 26%

Pancreas + 25%

Lung + 25%

Breast + 15%

Prostate Cancer at IEO



- 6 linacs for EBRT (6 IGRT systems)
- 2 linacs for IORT
- 4 systems for BRT
- 2 systems for permanent implants
- 2 CT scans (one 4D-CT)
- Last generation TPSs
- Link to MRI and PET scan

	Linac	Tumor sites
1.	**Vero**	**Stereotactic body RT, prostate cancer IMRT,**
2.	**CyberKnife**	**Brain and spine stereotactic RT**
3.	**Tomotherapy**	**Breast cancer IMRT, glioblastoma, mesothelioma**
4.	**Trilogy**	**Head and neck IMRT, pelvic IMRT**
5.	**Clinac 600**	**Breast cancer 3D-CRT, palliative 3D-CRT**
6.	**Clinac 2100**	**Various 3D-CRT (lung tumors, lymphoma, seminoma etc.)**

- 3287 new patients in 2012
- > 3500 in 2013

Numbers:

Breast cancer	46%
Metastatic patients	22%
Prostate cancer	8%
Head and neck cancer	6%
Thorax	4%
Gastrointestinal	4%
Gynecological cancer	3%
Other	7%

Evolution of SBRT at IEO

- 3D CT
- BrainLab m3 (mMLC)
- Positioning with Exactrac
- Set-up evaluation with PI
- 3D correction

- 3D CT
- BrainLab m3 (mMLC)
- Positioning with Exactrac
- Set-up evaluation with stereoscopic X-ray
- 6D automatic correction with robotic couch

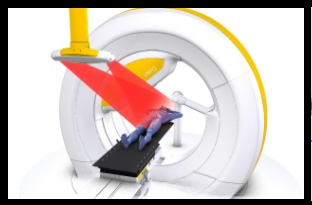
- 4D CT
- VERO
- Positioning with Exactrac
- Tumor localization with CBCT
- 6D automatic correction with robotic couch +ring

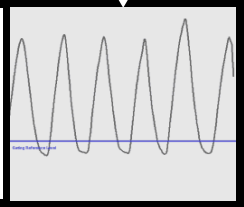
Current implementation: Tumor tracking

VERO system (BrainLab/MHI)

Dynamic Tumor Tracking

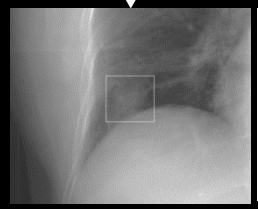
Patient set-up

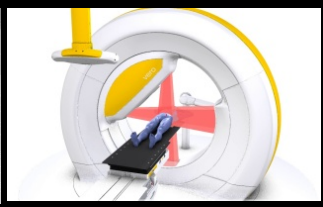




synchronize

correlate



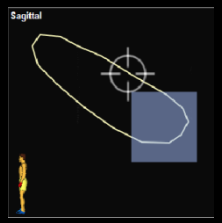


Acquisition of breating signal

IR markers on patient chest

Acquisition of fluoro sequences

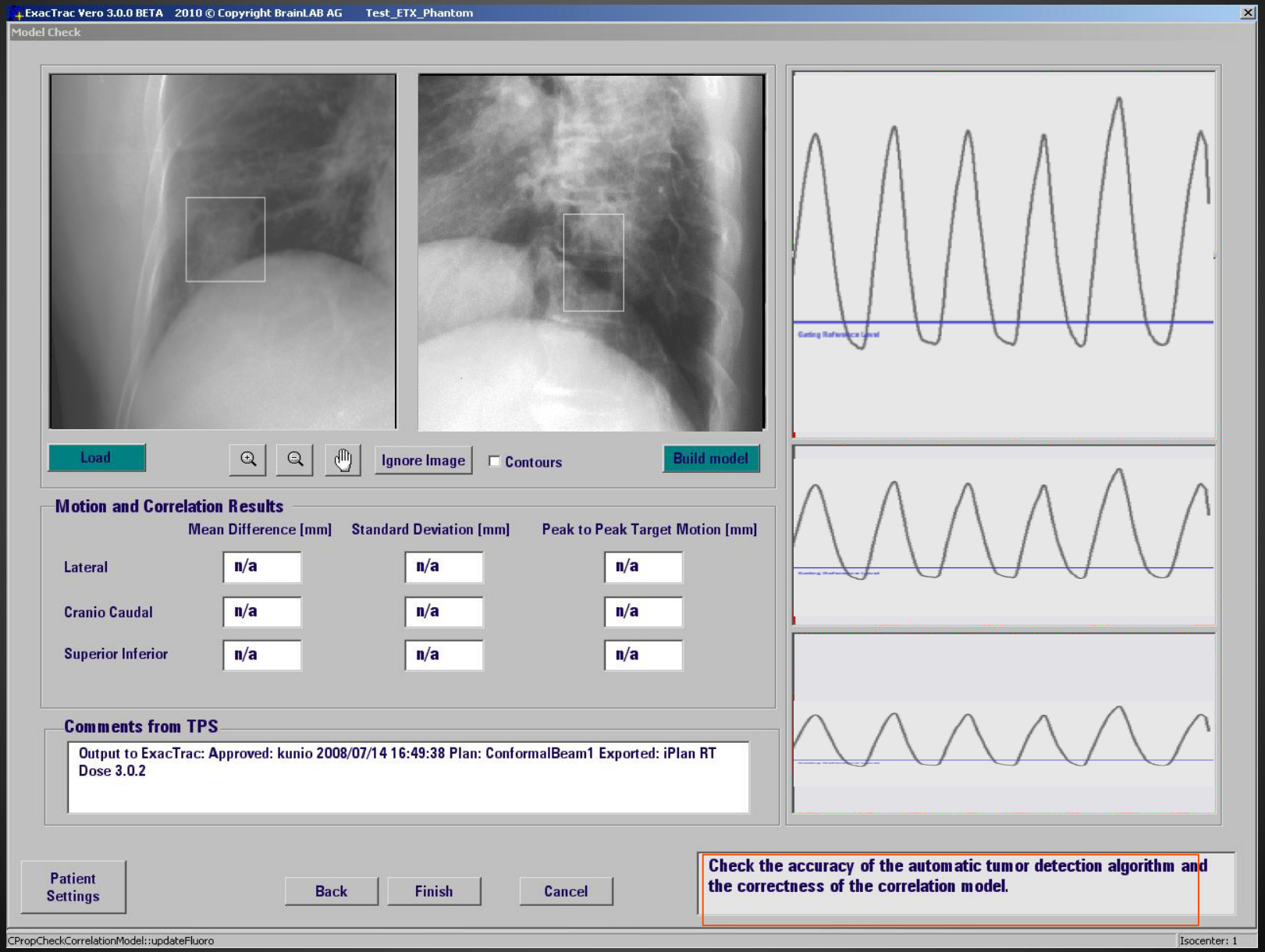
Two sources, simultaneous or interlaced



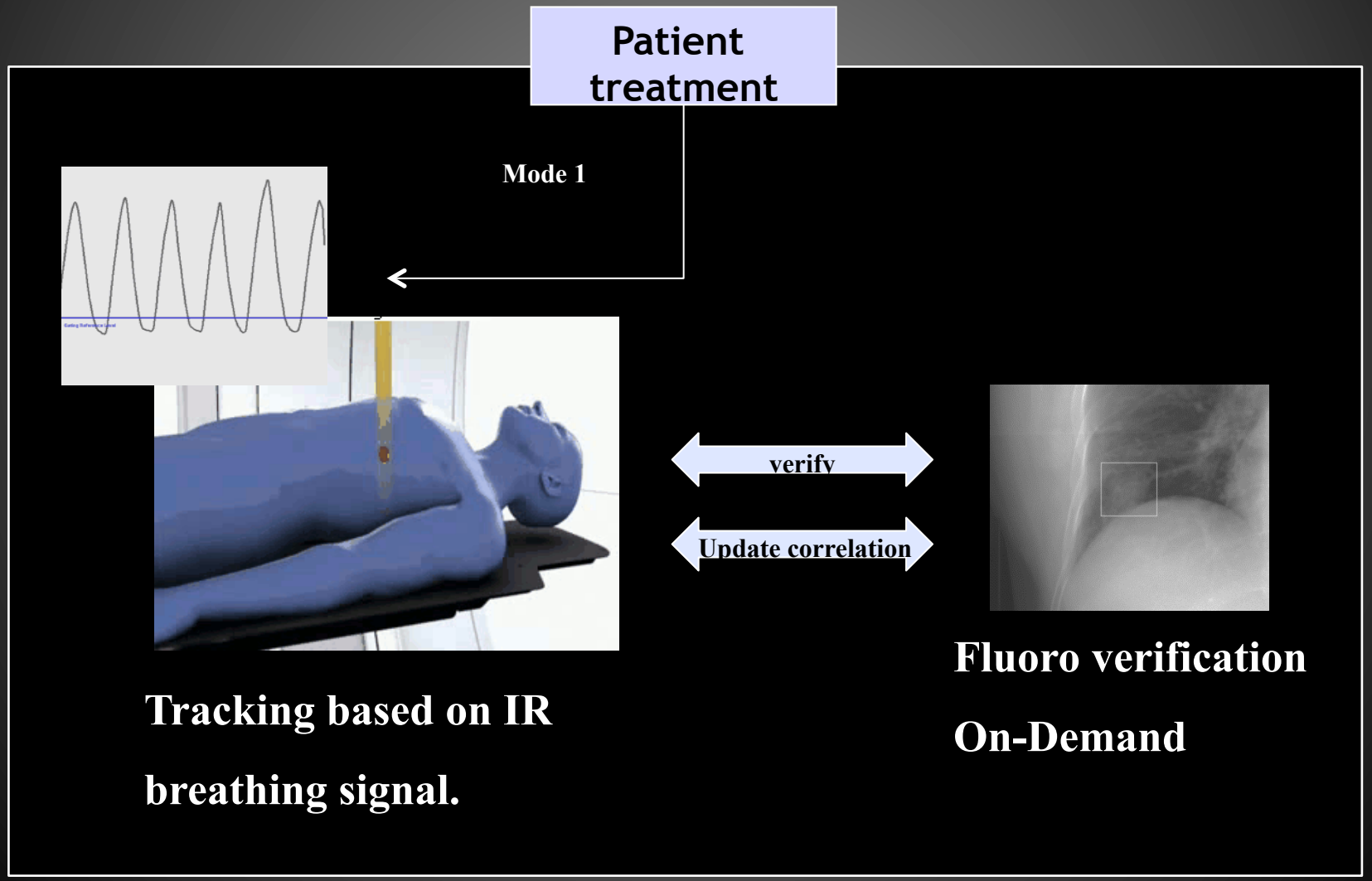
Determine tumor motion trajectory

Define best patient treatment position

Dynamic Tumor Tracking



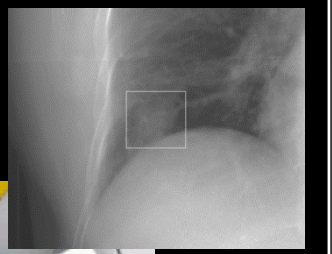
Dynamic Tumor Tracking

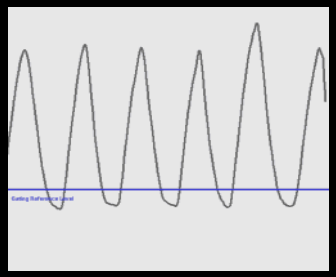


Dynamic Tumor Tracking

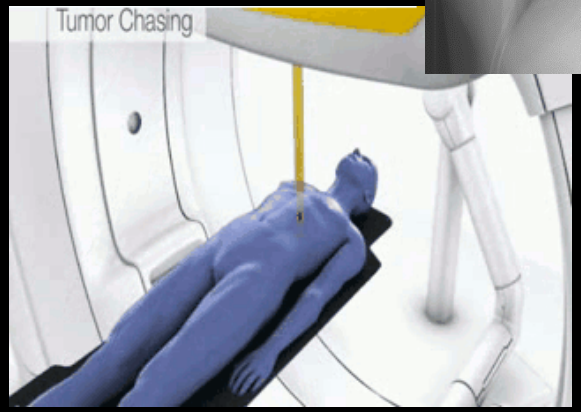
Patient treatment

Mode 2





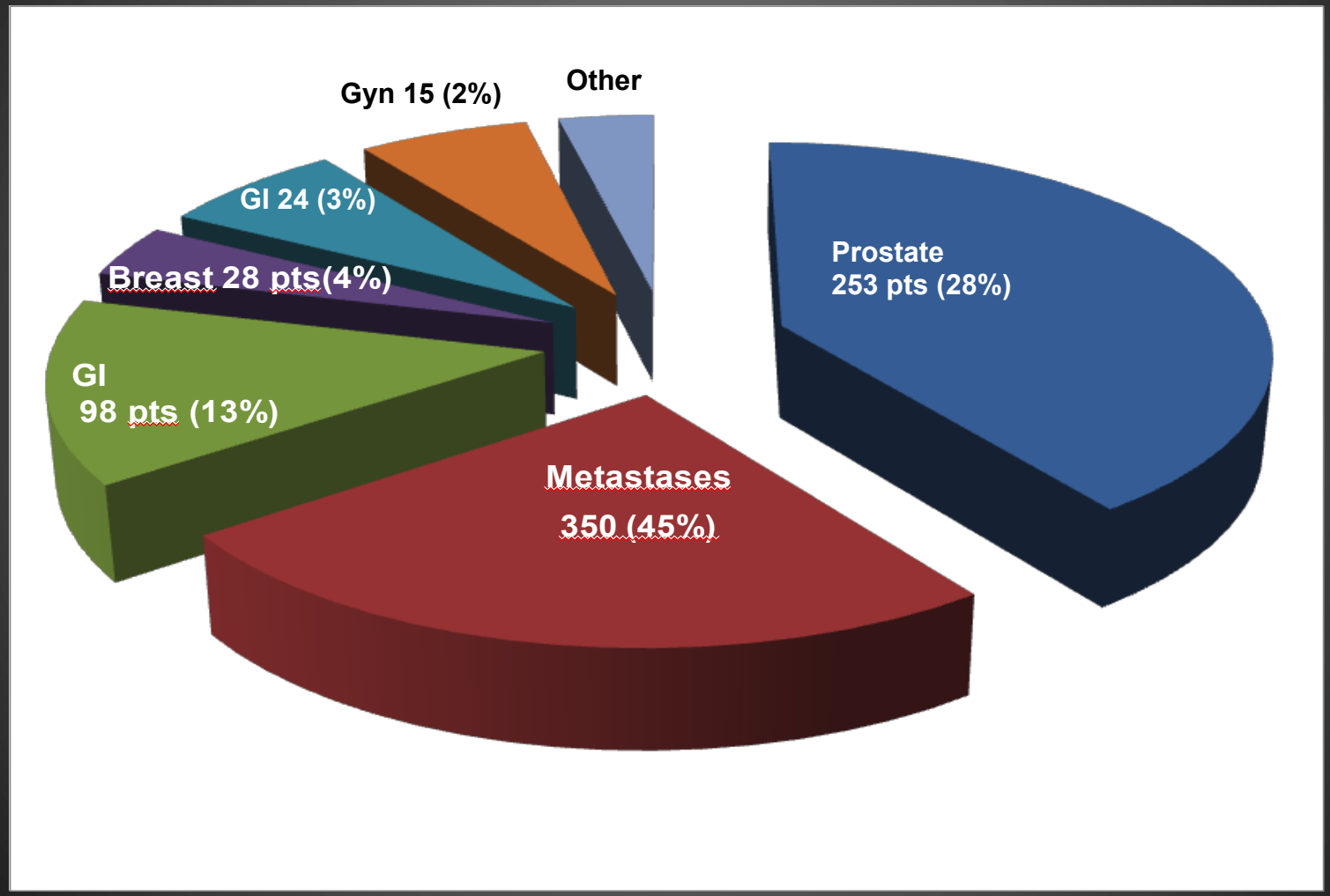
verify



IR breathing signal for target pos. verification and back-up

Real-time tumor tracking

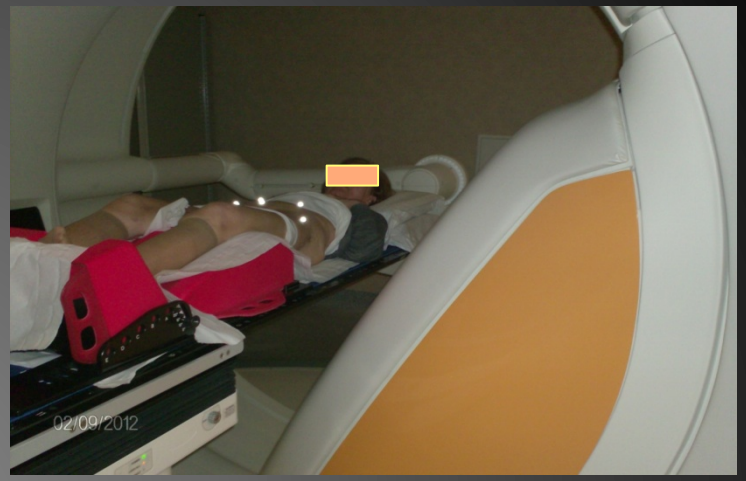
799 patients treated between April 2012 - October 2013

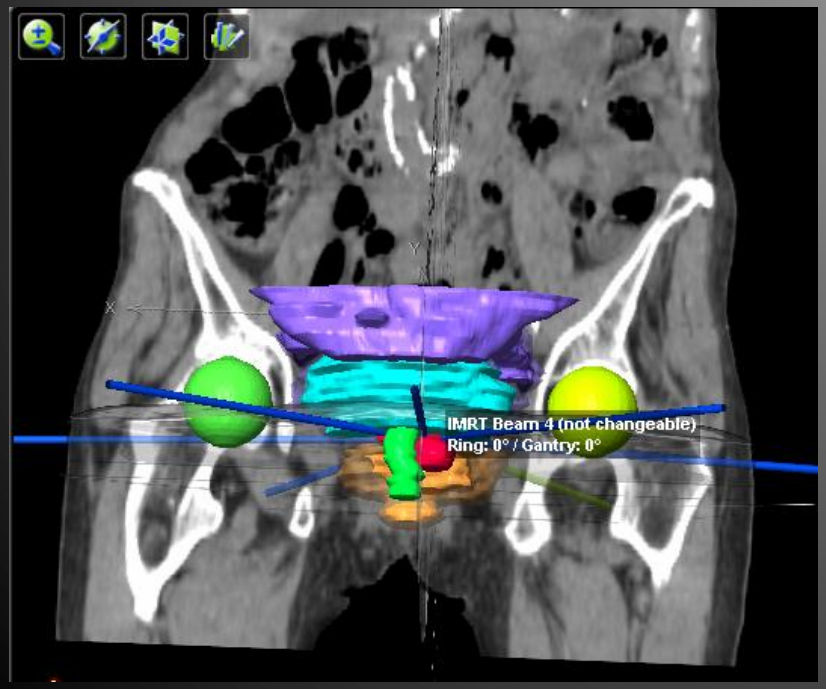


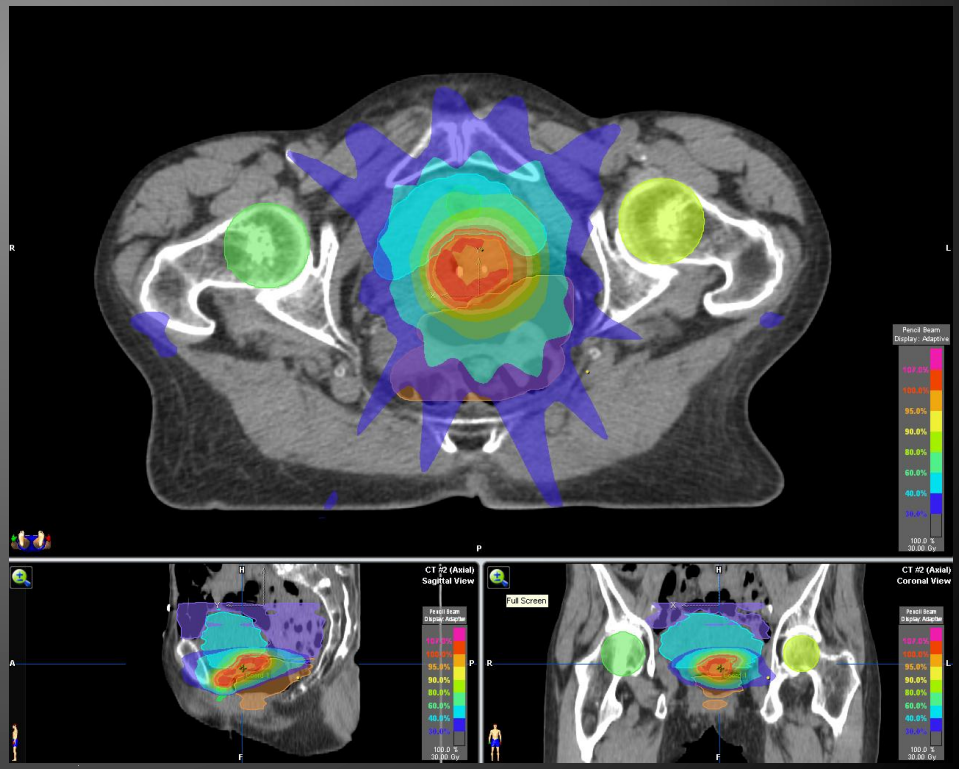
	Tumor Site	April-December 2012	January-October 2013
1.	**Metastases**	**128**	**222**
2.	**Prostate**	**86**	**167**
3.	**Thorax**	**43**	**79**
4.	**Breast**	**9**	**20**
5.	**Gastrointestinal**	**13**	**11**
6.	**Total**	**292**	**507**
		175<5 sedute	**341<5 sedute**

Clinical case: Cervical cancer

- 87 years old lady (1st patient, April 2012)
- hysterectomy for endometrial cancer in 2005
- vaginal cuff recurrence
- 5Gy x 6 fr = 30 Gy
- 7 IMRT fields
- full bladder







Prostate cancer

- ✓ **Curative RT: prostate +/- seminal vesicles**
  - ❑ **Moderate hypofractionation:**
    - 70.2 Gy/26 fr (2.7 Gy/fr) equiv to 84 Gy (α/β=1.5 Gy)
  - ❑ **Extreme hypofractionation (61 pts)**:
    - 35 Gy/5 fr (7 Gy/fr) equiv to 85 Gy (α/β=1.5 Gy)

- ✓ **Post-prostatectomy RT**
  - ❑ Adjuvant: 66 Gy/30 fr (2.2 Gy/fr) equiv to 70 Gy
  - ❑ Salvage: 69 Gy/30 fr (2.3 Gy/fr) equiv to 75 Gy

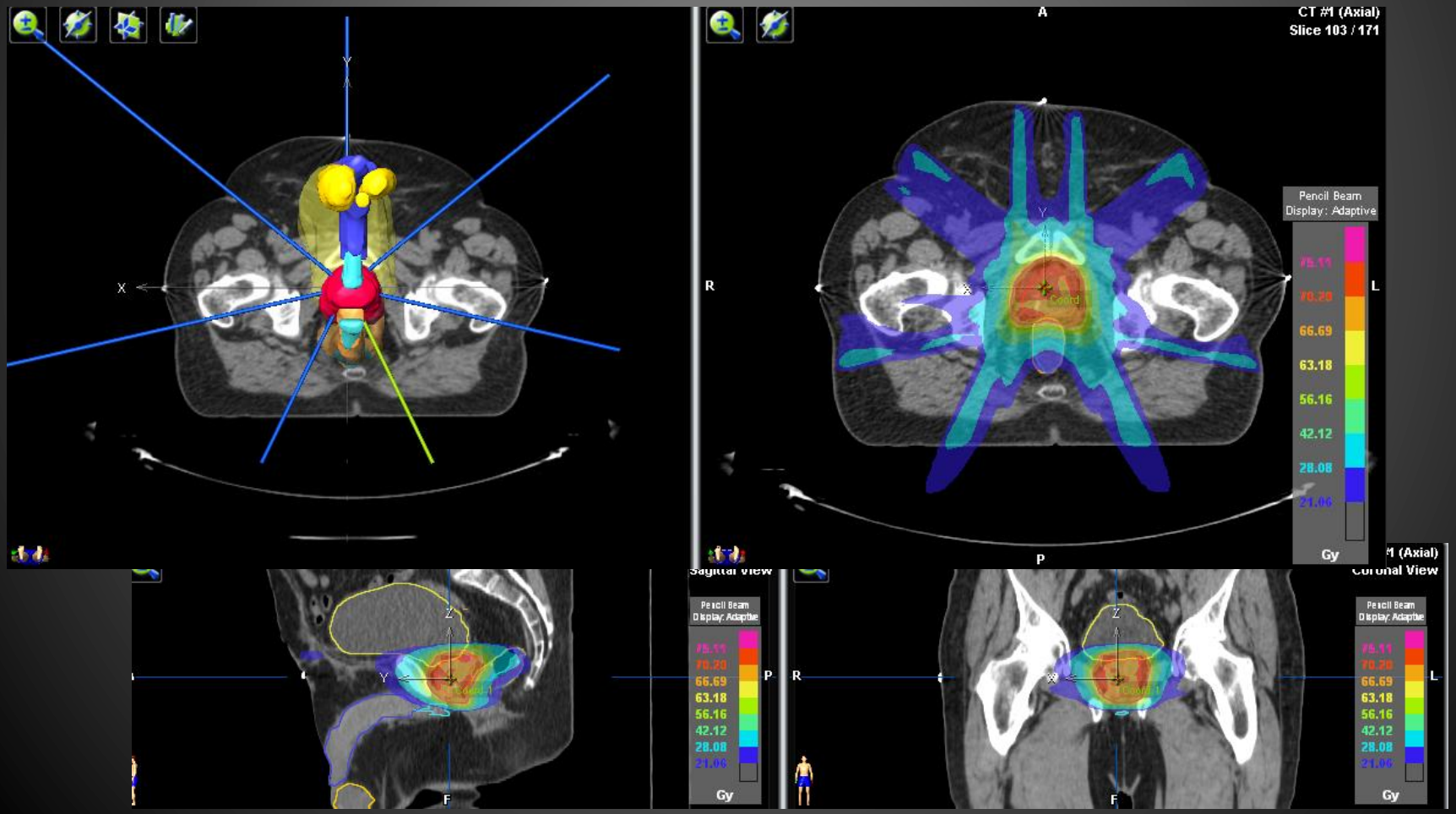
- ✓ **Re-irradiation (14 pts)**
  - ❑ 30Gy/5 fr
  - ❑ 25 Gy/5 fr
  - ❑ Strict OAR constraints

PROSTATE

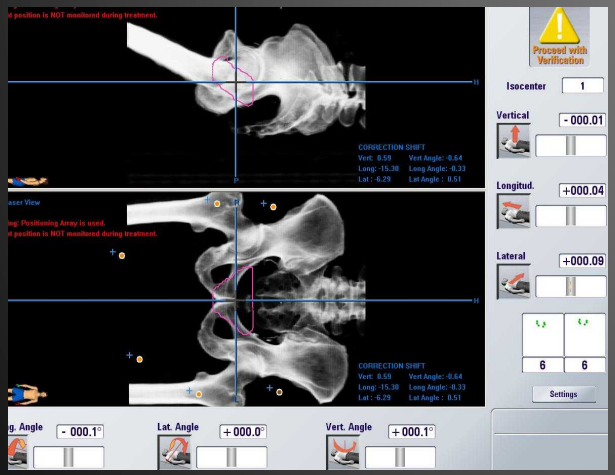
- treatment margin (5mm, 3 mm towards rectum), 5-7 IMRT fields

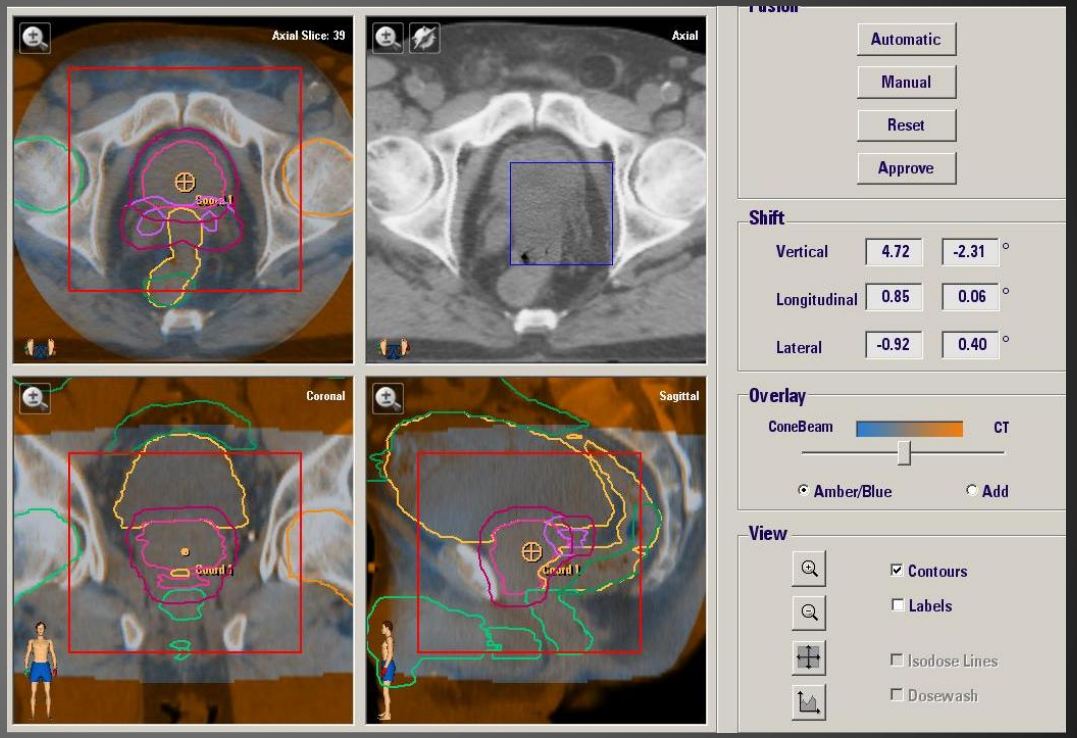
  SIB:

  Prostate: 70.2 Gy (2.7 Gy/fr), Sem Ves: 59.6 Gy (2.3 Gy/fr)



PROSTATE: daily IGRT





CBCT- planning CT registration

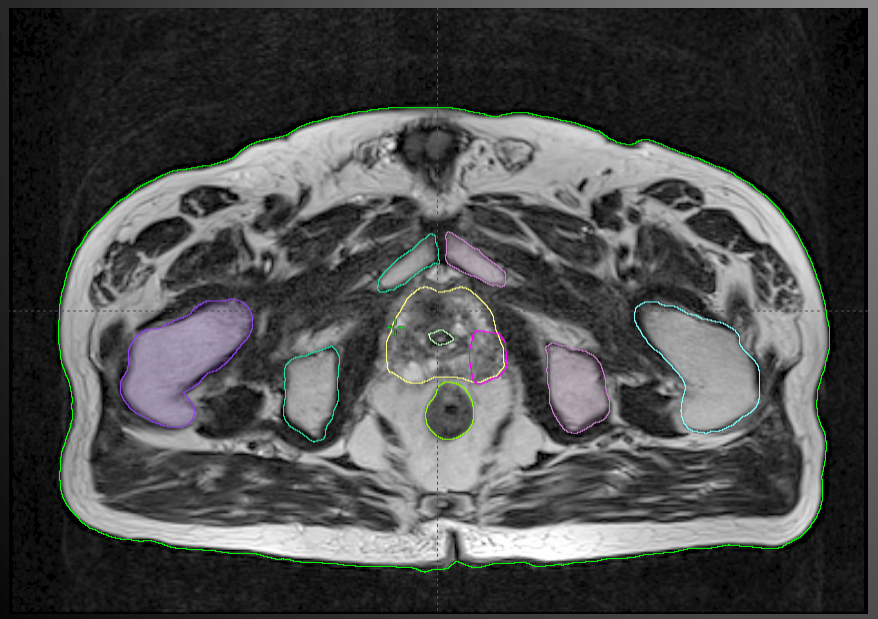
- Exactrac
- Positioning array (26 frs) or passive markers (5 fr)

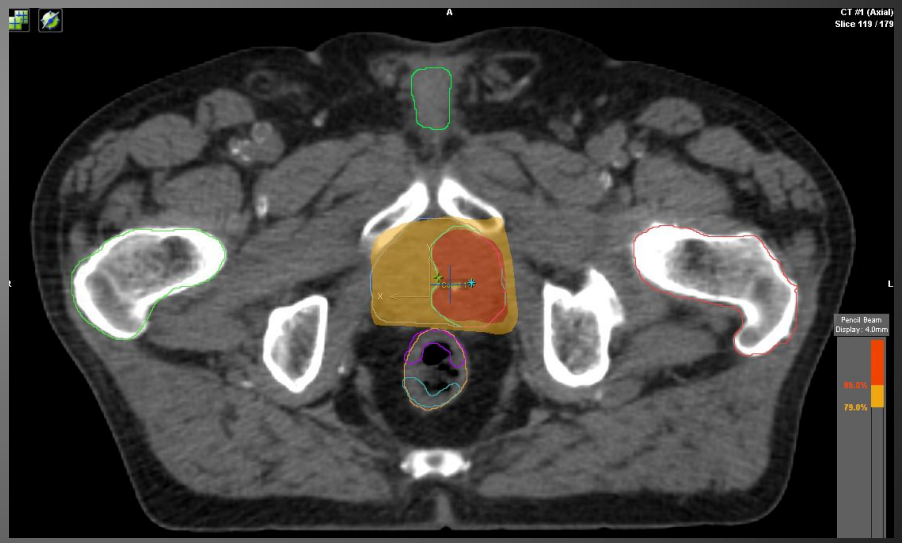
PROSTATE

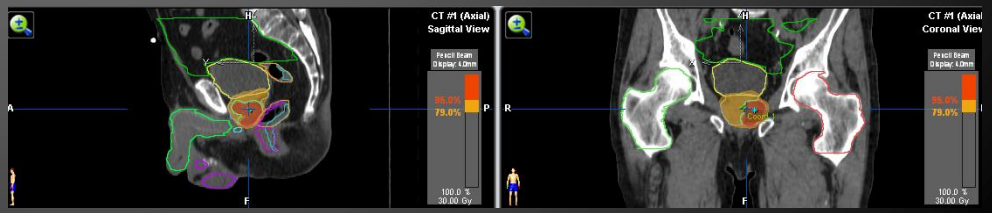
Tailored very short hypofractionated RT: AIRC project

mpMRI: dominant lesion (DIL)

SIB: 36.25 Gy/5 fr (7.25 Gy/fr) whole prostate
37.5 Gy/5 fr (7.5 Gy/fr) DIL







Prostate cancer: AIRC

Task 1: In-silico planning study comparison (based on patient- and tumor- parameters): VERO-Cyber-Trilogy (RA)-Hadrons

Task 2: Two-stage phase II, prospective, single-arm, monocentric clinical trial (65 pts)

Task 3: Modeling and organ motion

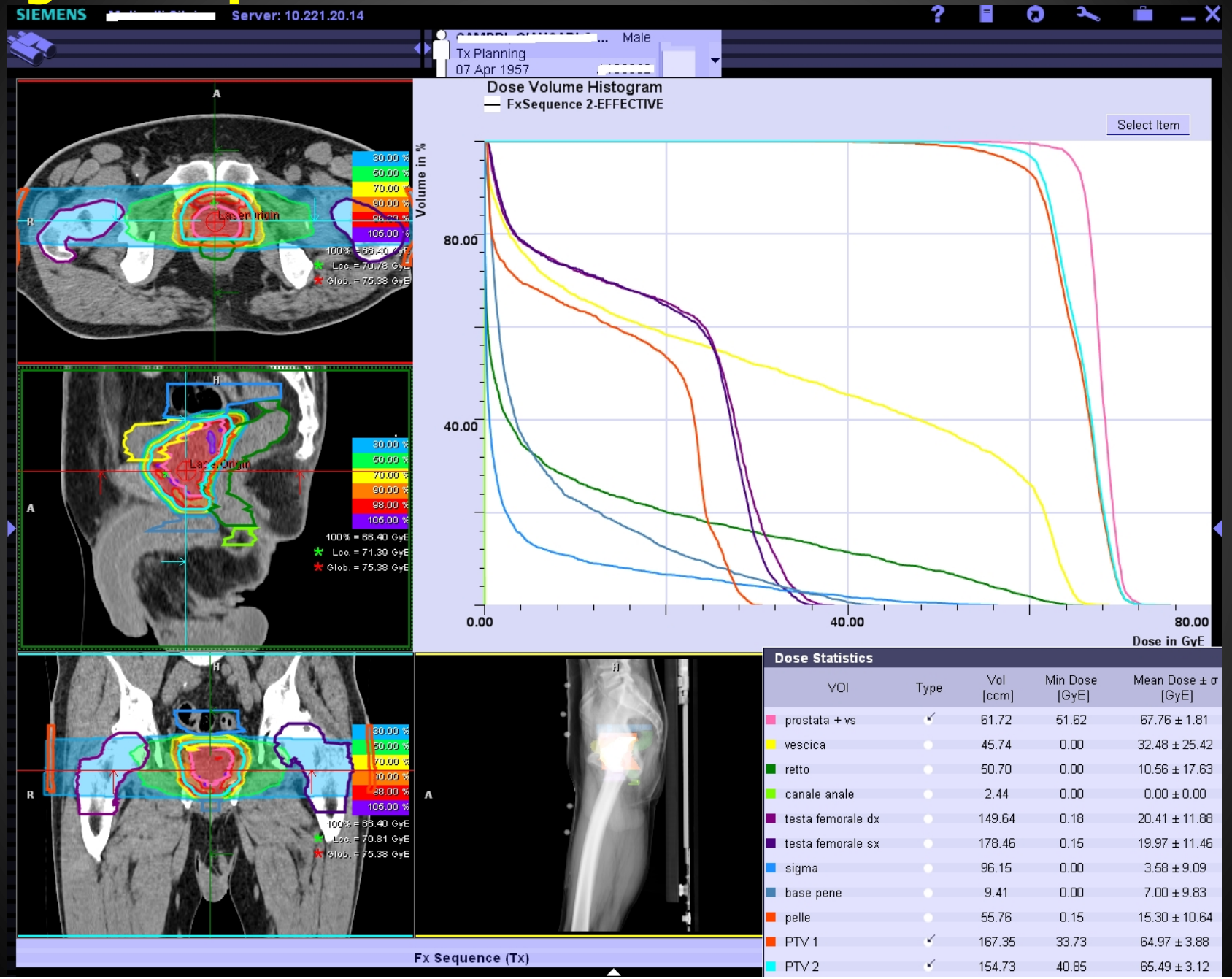
Task 4: Molecular biomarker study

- AIRC -

Associazione Italiana per la Ricerca sul Cancro

Investigator Grant - IG 2012

High risk prostate cancer. Irradiation with C-12

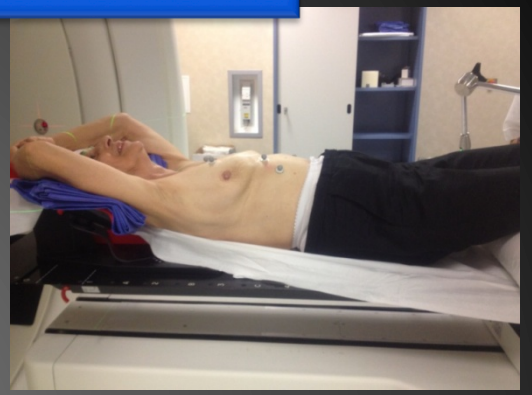


Dose Statistics

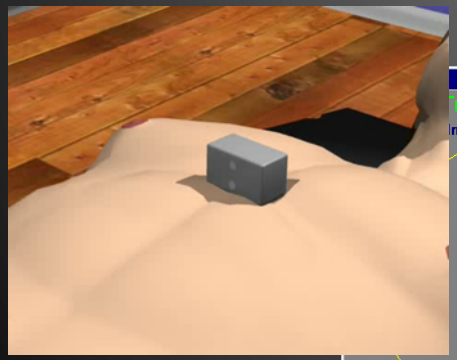
VOI	Type	Vol [ccm]	Min Dose [GyE]	Mean Dose ± σ [GyE]
prostata + vs	↙	61.72	51.62	67.76 ± 1.81
vescica		45.74	0.00	32.48 ± 25.42
retto		50.70	0.00	10.56 ± 17.63
canale anale		2.44	0.00	0.00 ± 0.00
testa femorale dx		149.64	0.18	20.41 ± 11.88
testa femorale sx		178.46	0.15	19.97 ± 11.46
sigma		96.15	0.00	3.58 ± 9.09
base pene		9.41	0.00	7.00 ± 9.83
pelle		55.76	0.15	15.30 ± 10.64
PTV 1	↙	167.35	33.73	64.97 ± 3.88
PTV 2	↙	154.73	40.85	65.49 ± 3.12

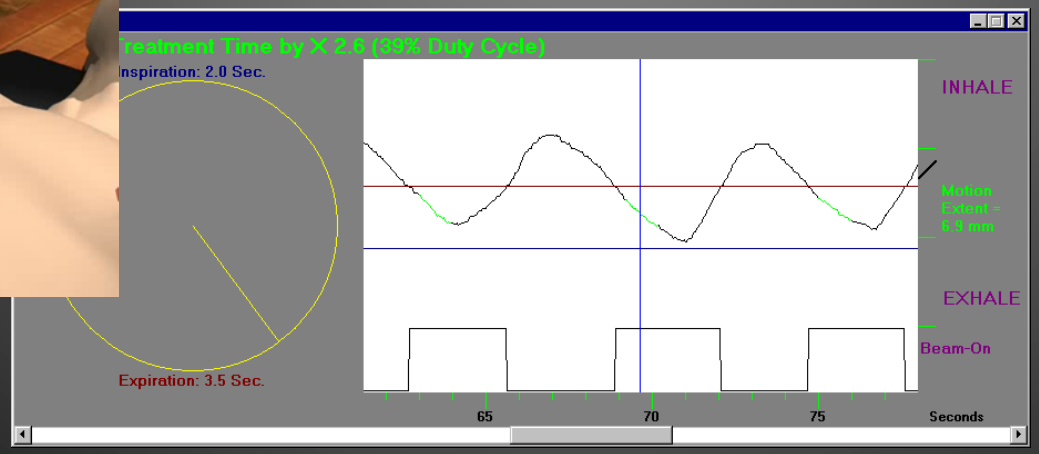
Lung cancer

- supine with an arm holder (Posirest, Civco)
- 7 reflective markers
- Helical free breathing CT (2.5 mm slice thickness)
- 10-phase 4D respiration correlated CT



- RPM (Varian)
  - wearable display showing the breathing pattern
  - patient training to achieve a reproducible breathing

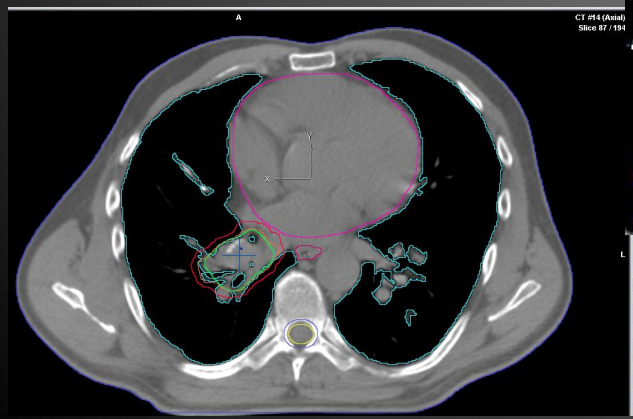


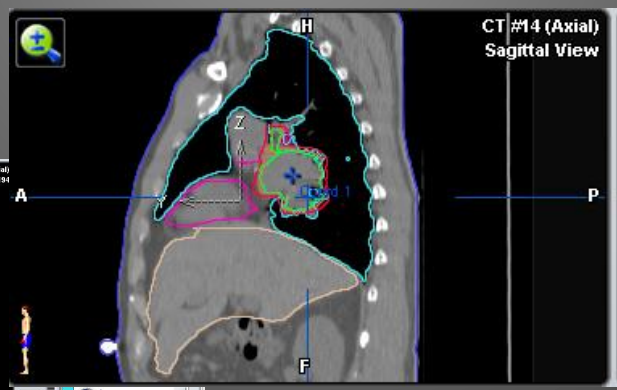


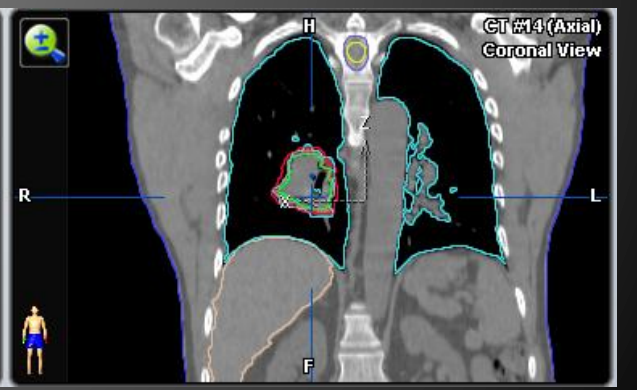
Eyewear viewer
MicroOptical Co.,
USA

LUNG SBRT: volume definition

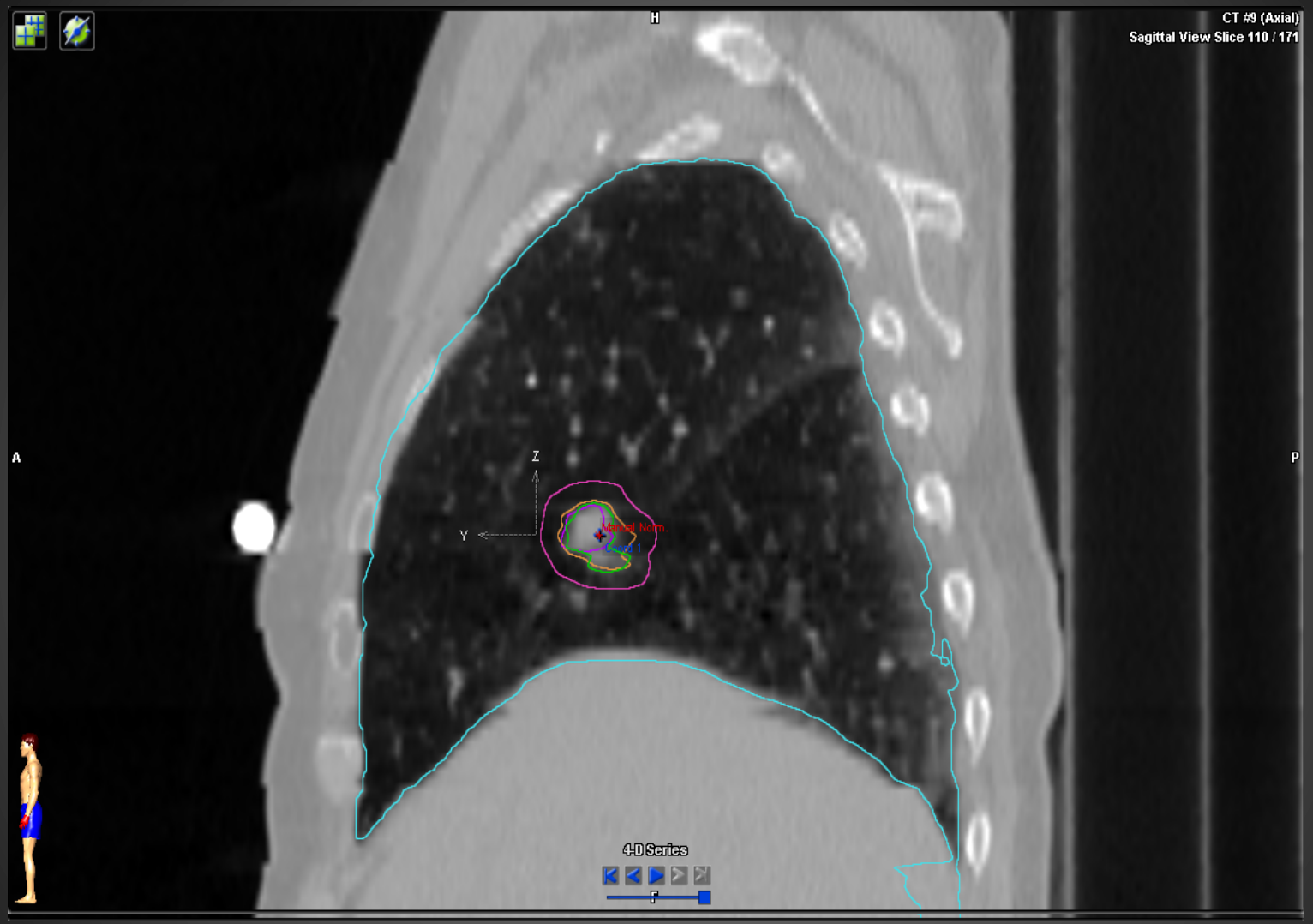
- Maximum intensity projection (MIP) CT reconstruction
- Mean Intensity projection (meanIP) CT reconstruction
- Registration MIP CT / meanIP CT
- Organs at risk delineated on the meanIP CT
- GTV drawn on end-expiration phase
- ITV derived on the MIP CT
- PTV = ITV + 5 mm







LUNG SBRT: volume definition



PTV
ITV
GTV exp
GTV insp

Appropriateness of MIP-delineation confirmed by visual inspection of projected ITV contours on EE and EI phase bins

LUNG SBRT: planning

- ✓ 1-4 no-coplanar conformal dynamic arcs (± 15°-20°)
- ✓ 7-9 no-coplanar static beams
- ✓ 5-7 step& shoot IMRT fields

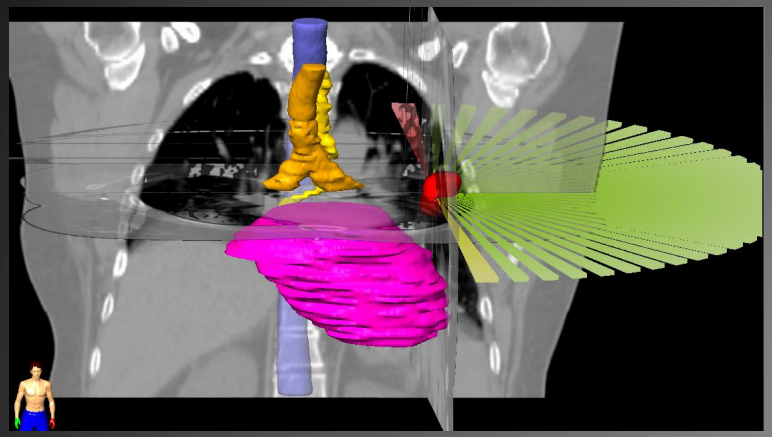
- ✓ dose calculation on the meanIP CT scan
- ✓ at least 95% of the PTV receiving the prescription dose (PB dose calculation)
  99% of PTV receiving at least 90% of prescription dose

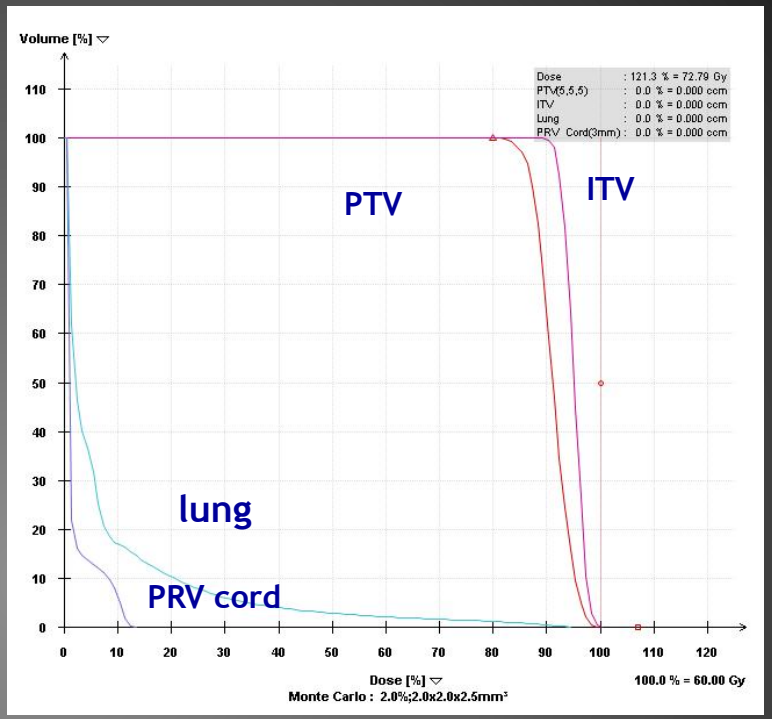
- ✓ OARs contraints (Timmerman 2008)

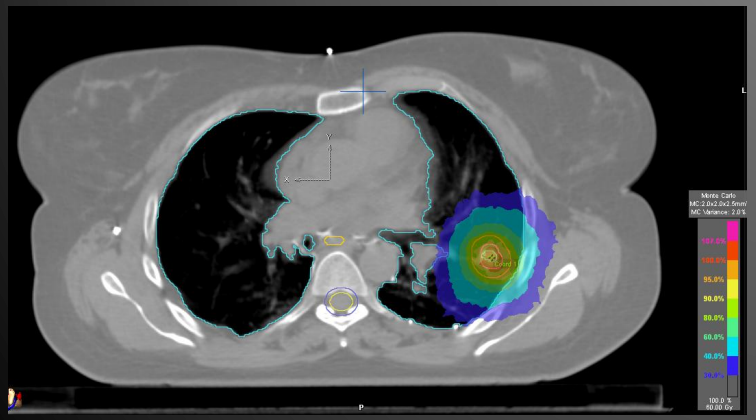
- ✓ Different regimens:

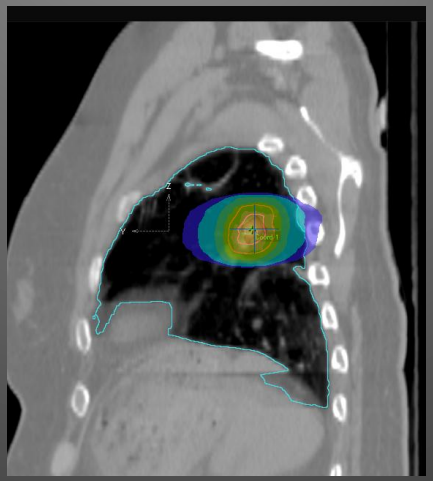
Centrally located lesions:	12 Gy x 4	BED= 105.6 Gy
	7.5 Gy x 8	BED= 105 Gy
	8 Gy x 6	BED= 86.4 Gy (near esophagus)
Peripherally located lesions:	18 - 20 Gy x 3	BED= 151.2 Gy - 180 Gy

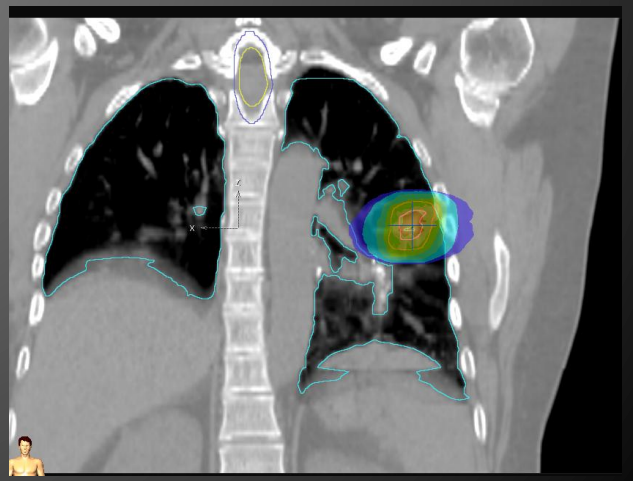
LUNG SBRT: planning







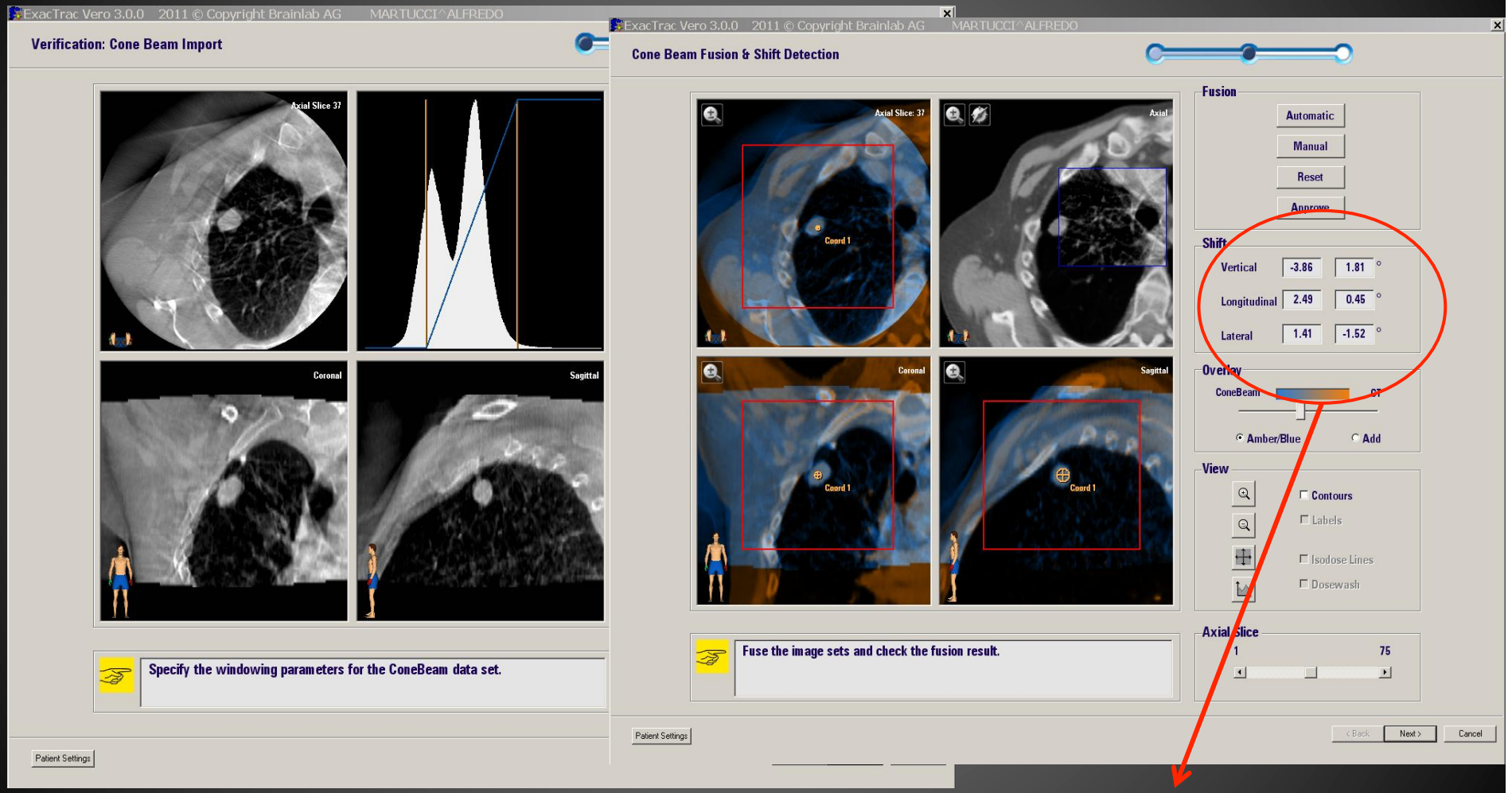




LUNG SBRT: CBCT image guidance

CBCT

CBCT- planning CT registration

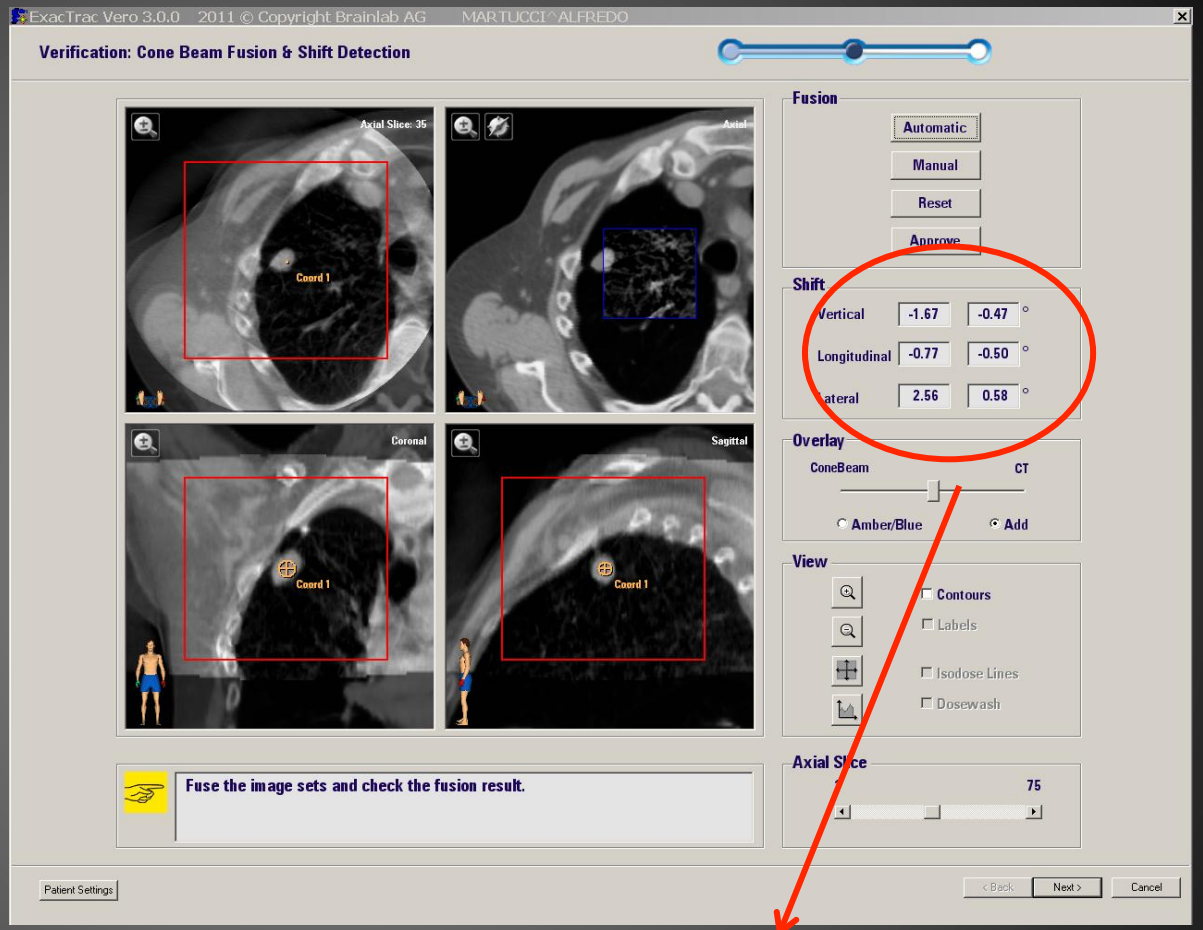


Translational and rotational localization errors

LUNG SBRT: CBCT image guidance

6D Automatic set-up correction:
Robotic couch + ring

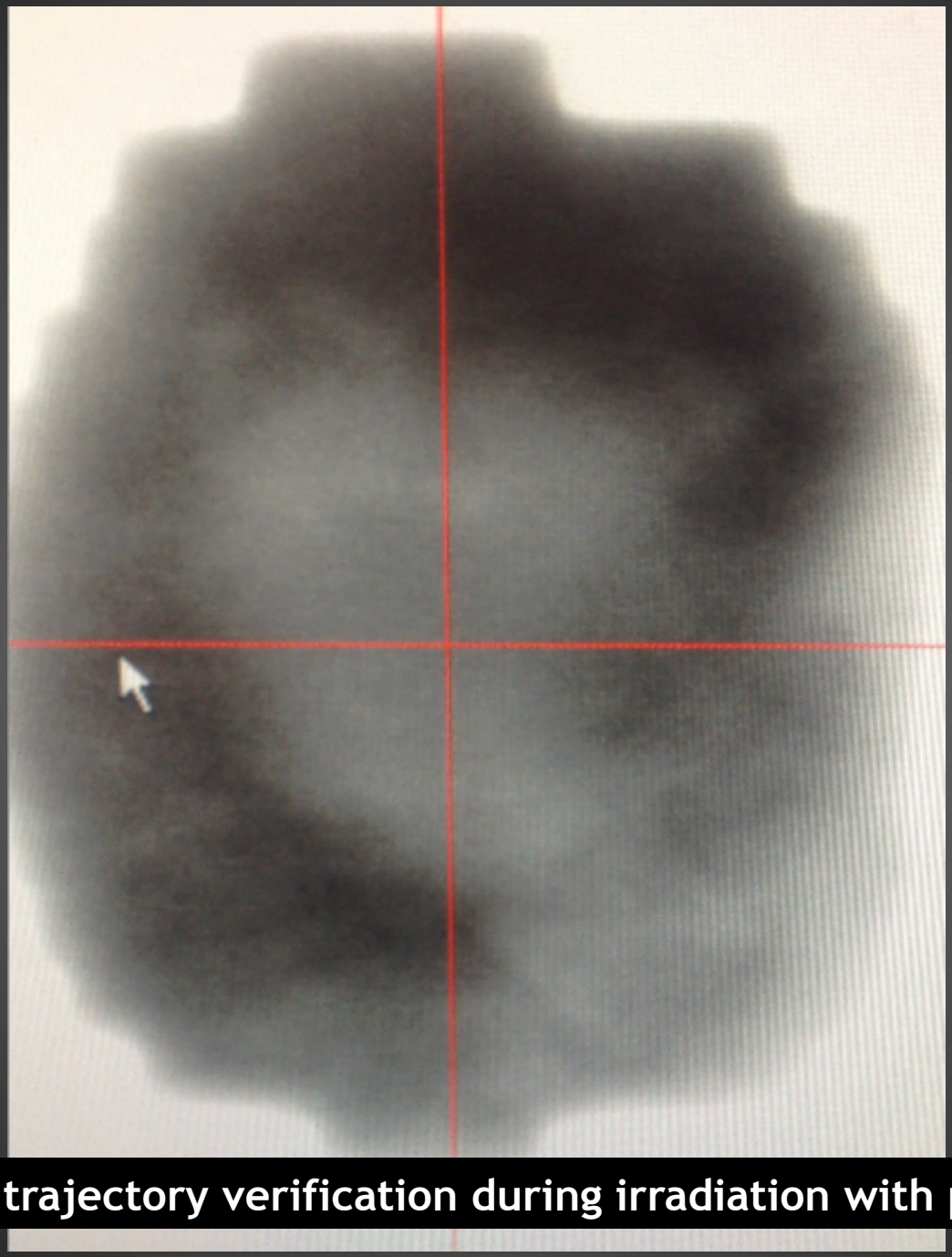
Verification CBCT



Residual translational and rotational errors

If residual errors > 2 mm and rotations > 0.5°
another 6D correction + CBCT

Currently is not possible to acquire a post-treatment CBCT to evaluate the intra-fraction tumor displacement.



Direct tumor trajectory verification during irradiation with portal imaging

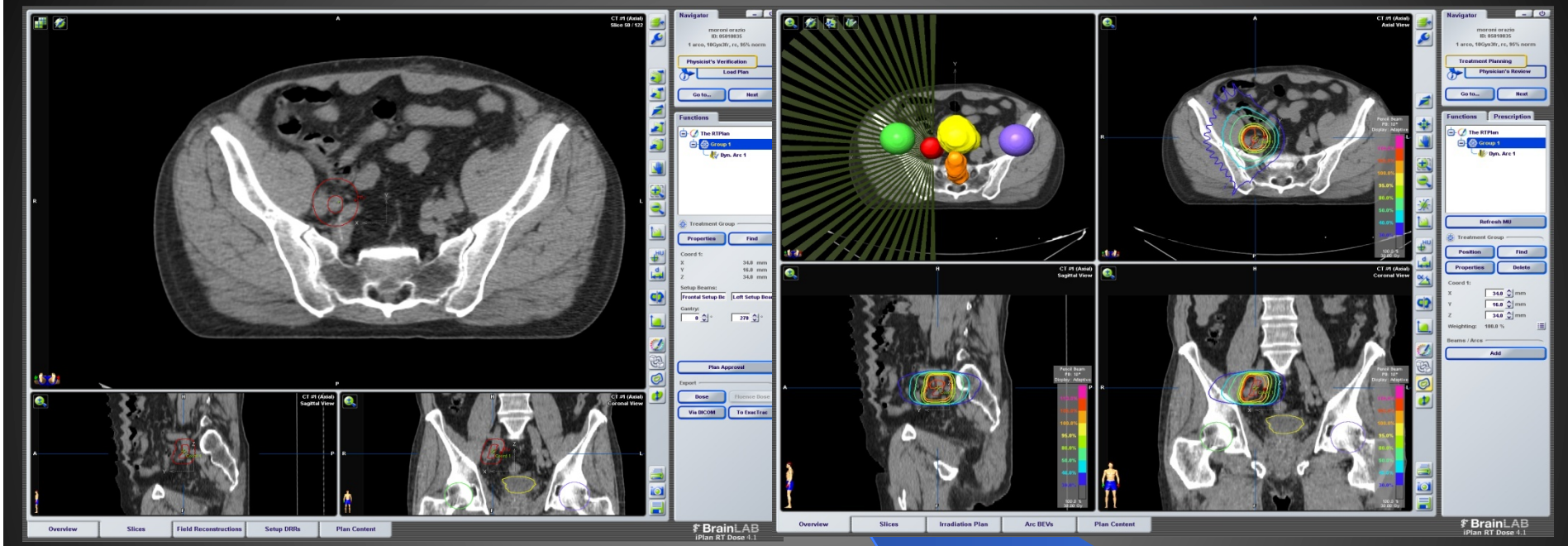
Oligometastatic cancer

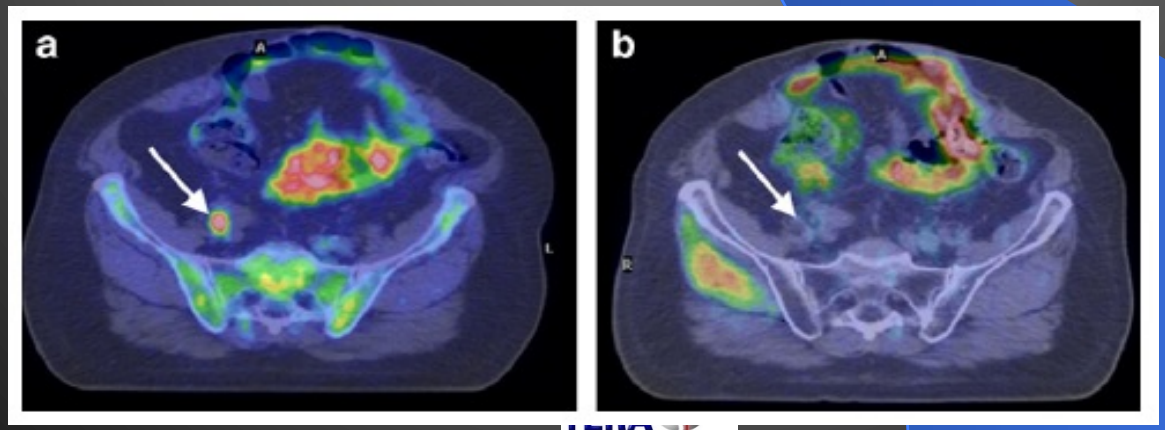
- Up to 5 lesions (Weichselbaum&Helmann 2011)
- Single metastasis or recurrent tumor, lymph node recurrence
- Short regimens:

25 Gy/5 fractions

30 Gy/3 fractions

Oligometastatic cancer

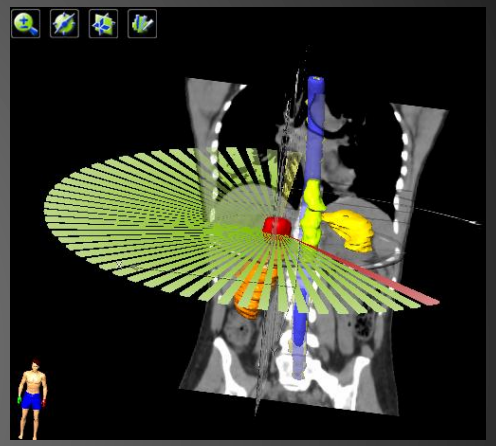




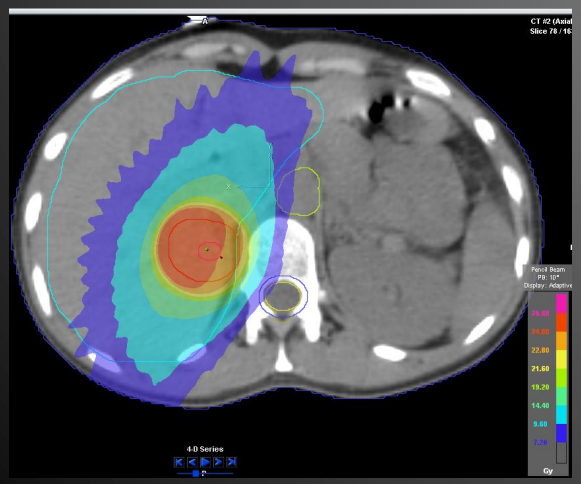
Fondazione per Adroterapia Oncologica

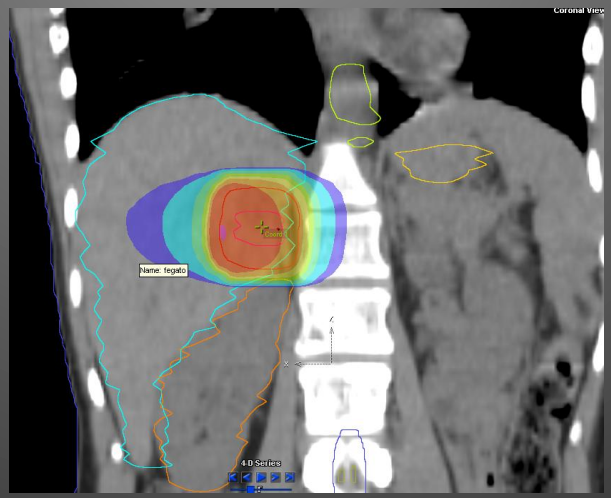
LIVER SBRT

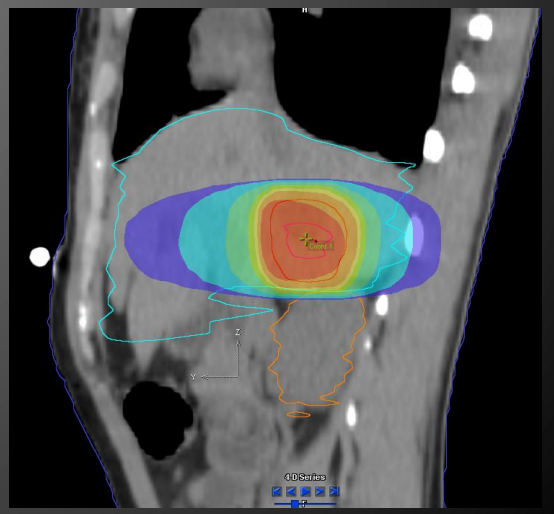
- Contrast-free FB CT scan and 3 phases contrast-enhanced CT scan
- 4D-CT scan to evaluate the motion of the liver cupola
- CT-PET / MRI fusion if necessary
- GTV drawn on the most visible CT scan



✓ 1-4 no-coplanar conformal dynamic arcs
✓ 5-7 step& shoot IMRT fields
✓ 15 Gy x 3, 12 Gy x3



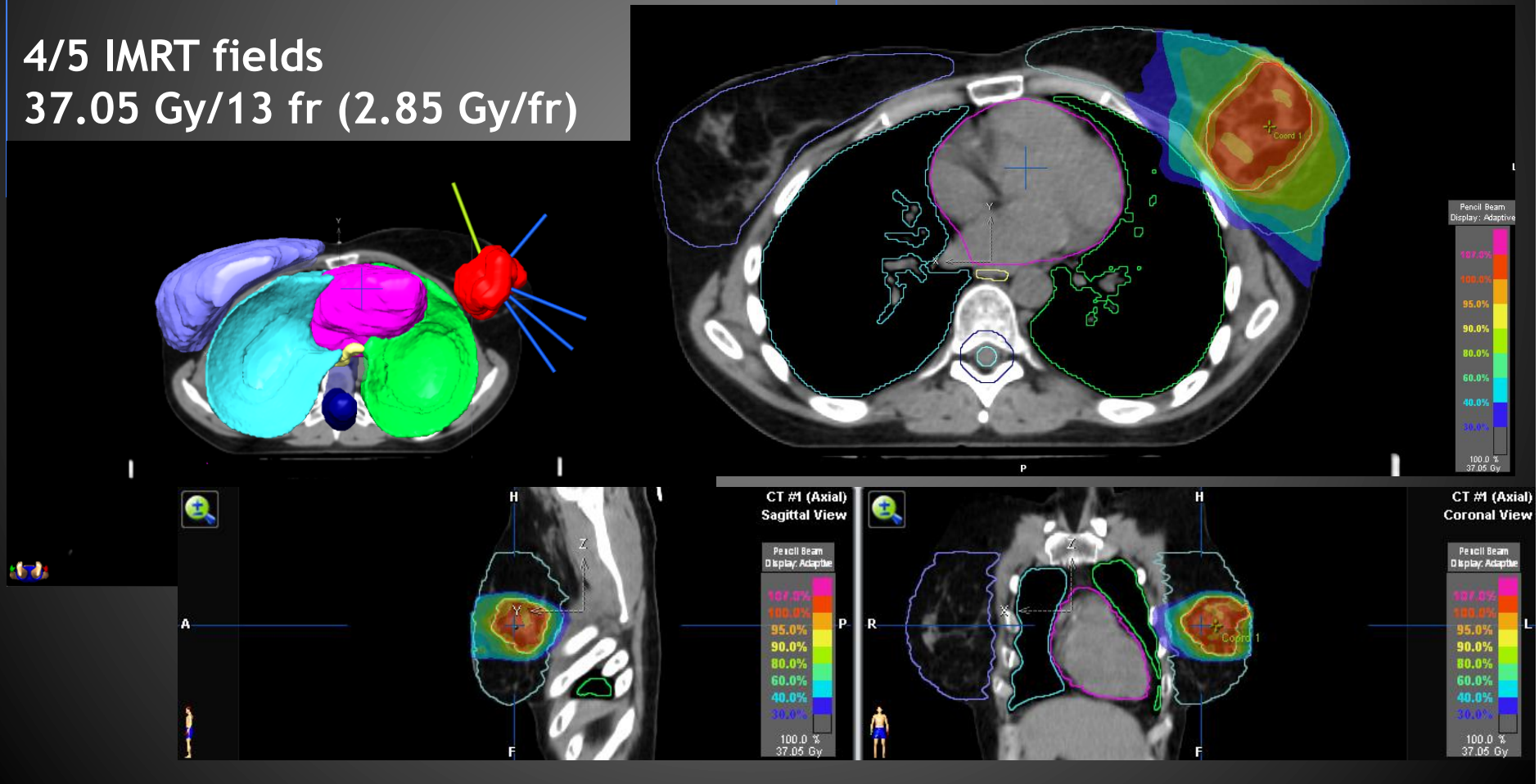




Partial breast irradiation

Re-irradiation

4/5 IMRT fields
37.05 Gy/13 fr (2.85 Gy/fr)



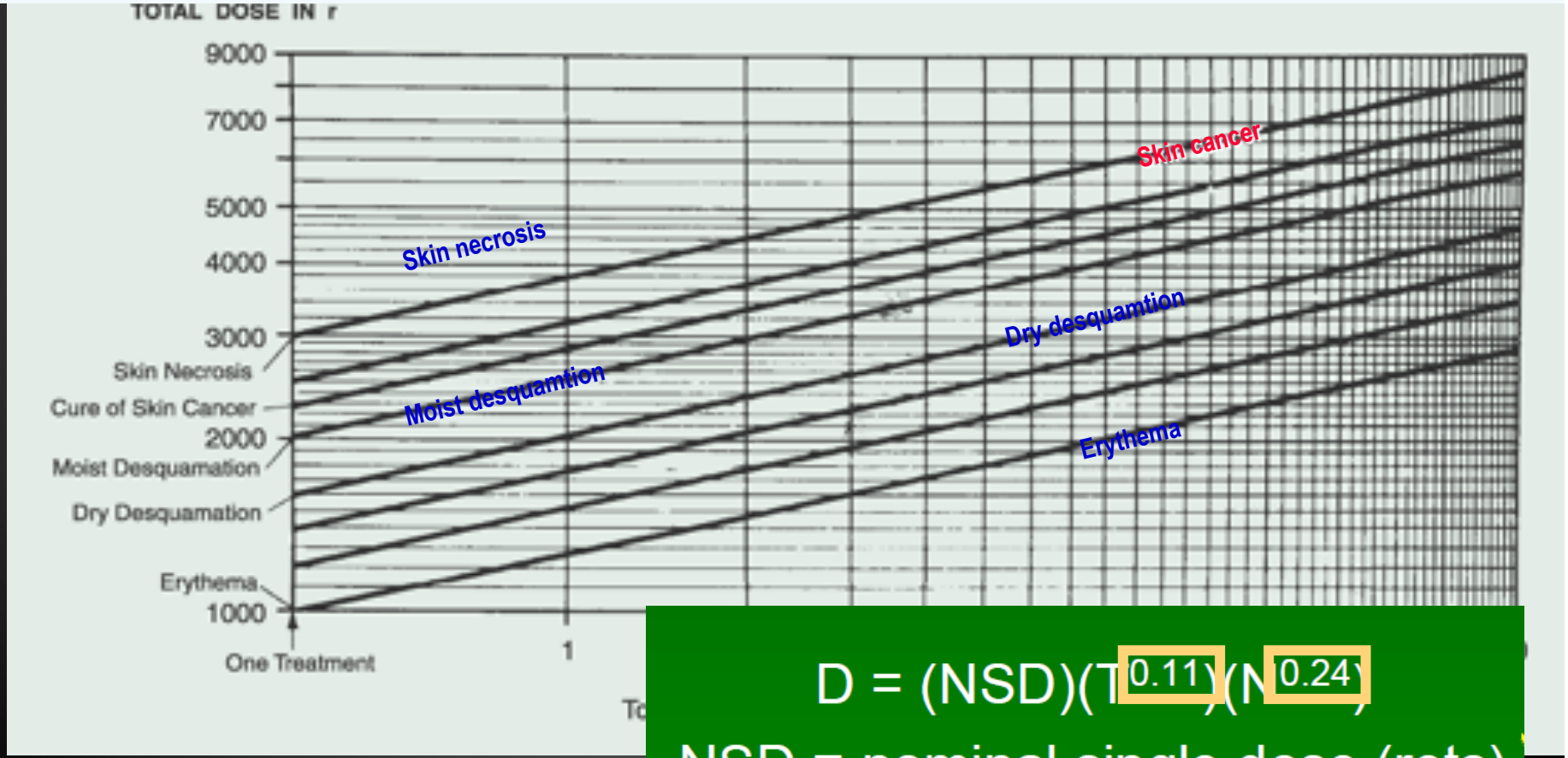
Conclusions

- ✓ Ablative Radiation Therapy
- ✓ Robotic Radiosurgery
- ✓ Personalized Treatment

Mathematical Radiobiology

Strandquist Plot - 1944

- Assume all normal tissues behave like ***skin*** and tumors like squamous cell ca.



$$D = (NSD)(T^{0.11})(N^{0.24})$$

NSD = nominal single dose (rets)

Mathematical Radiobiology

A model is no more than a representation;
is not the realty

The conseguence is that we can have no single model than accurately describes what we need to know any more than we can have any one map that tells us everything about a territory

The map is not the territory
The model is the biology

Remarks

- There can be no single regimen of treatment delivery that will be appropriate for all tumours in all patients

- Mathematical modelling without accurate clinical observation is an exsercise that is both futile and dangerous

Remarks

- Fractionation cannot be considered in isolation

- Complex interdipendence between total dose, dose-per-fraction, overall treatment time, treated volume, beam parameters, prescribing conventions and QA procedures

Remarks

- Clinical advances precede, and are preceded by, advances in our basic understanding of radiation biology

- Need to identify an evidence-based summary of acceptable dose-fractionation regimens for OAR (Organ At Risk)

Remarks

- Technical advances allow to explore new and more aggressive regimen, strongly competing with surgery (and drugs ….)

- Cost/effectiveness seems to be in favour of Radiation Therapy

Acknowledgment

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