X. Ulusal Medikal Fizik Kongresi

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Radiation biology in Radiotherapy: from theory to clinical practice

Kiki Theodorou

Lecturer of Medical Physics, University of Thessalia

Kayseri, 2005

Conformal Radiotherapy

+

Technological Advances

+

Radiobiological Models

?

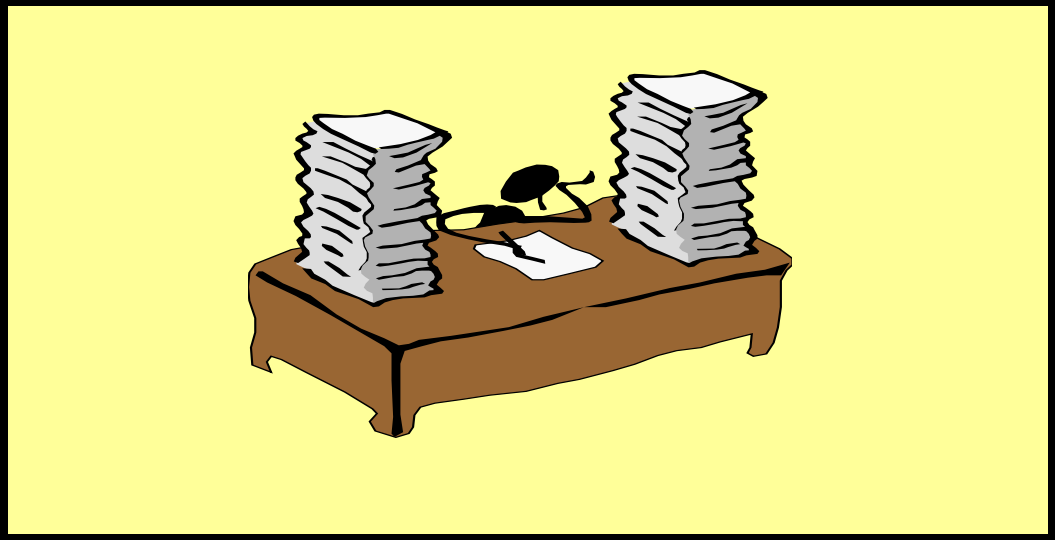
Higher TCP

+

Lower NTCP

+

Higher survival rate



Observations:

- ✓ Higher target dose → higher control rate
- ✓ Larger tumor size → higher target dose for the same TCP
- ✓ Smaller volume of irradiated normal tissues → increase the tolerance level (= *volume effect*)

- ✓ Optimum irradiation technique allows:
  - ➢ to minimize the volume normal tissues irradiated with clinically relevant dose → lower NTCP
  - ➢ to perform dose escalation → higher TCP
- ✓ Accurate dosimetry allows:
  - ➢ accuracy in prediction factors (DVHs, TCP, NTCP)
  - ➢ correct evaluation of the treatment outcome

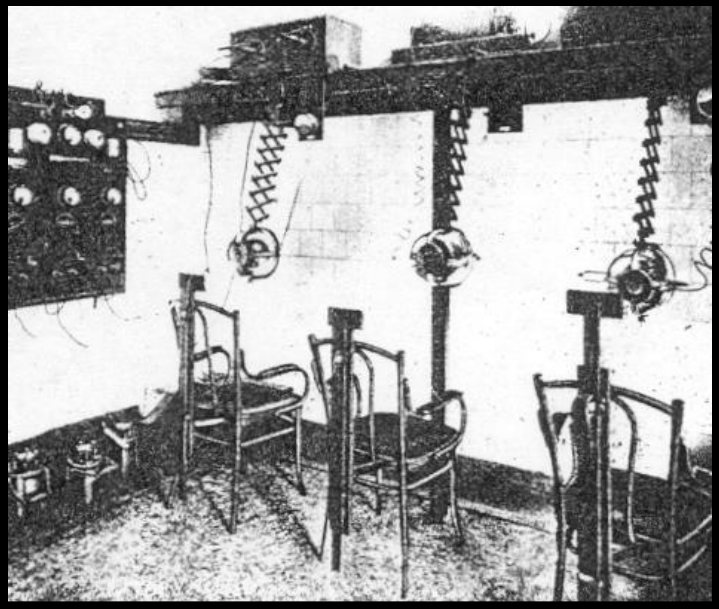
Radiotherapy Optimization

Generally, there are three main directions to improve radiotherapy:

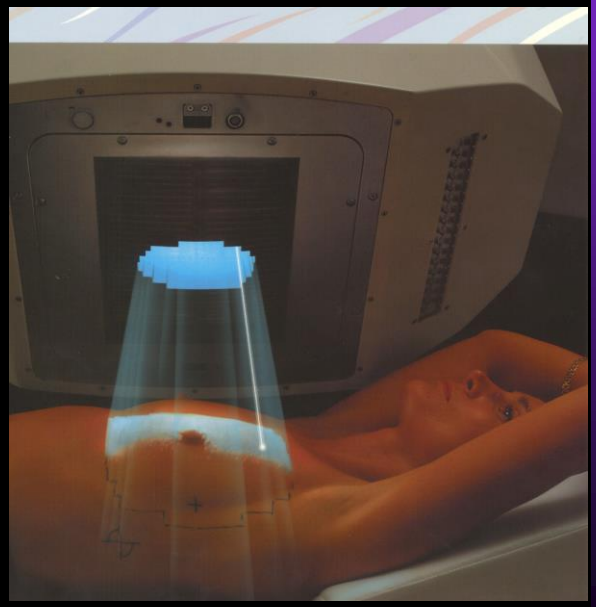
- ✓ Improving physical dose distribution
- ✓ Optimizing radiotherapy dose-time-fraction scheme
- ✓ Modifying radiation response in tumor (radiosensitizers) and/or normal tissues (radioprotectors) using chemical agents

The evolution of Radiotherapy

RADIOTHERAPY



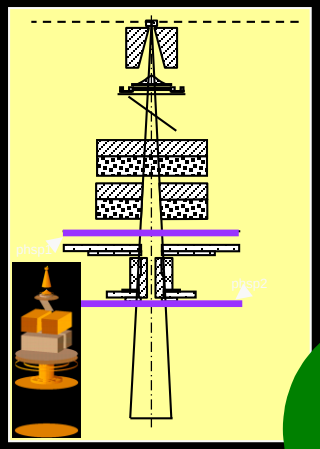
London's Radiotherapy Department 1905

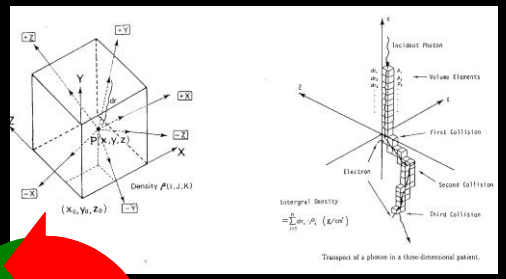


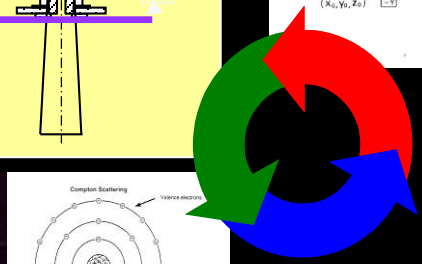
Radiotherapy 2005

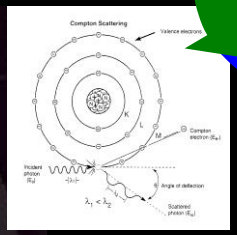
3D Patient Planning

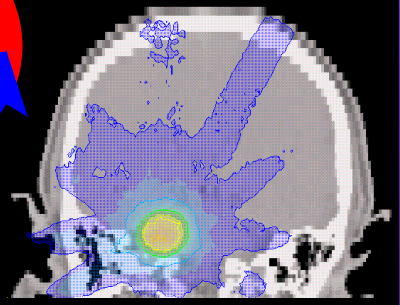
Dose Calculation

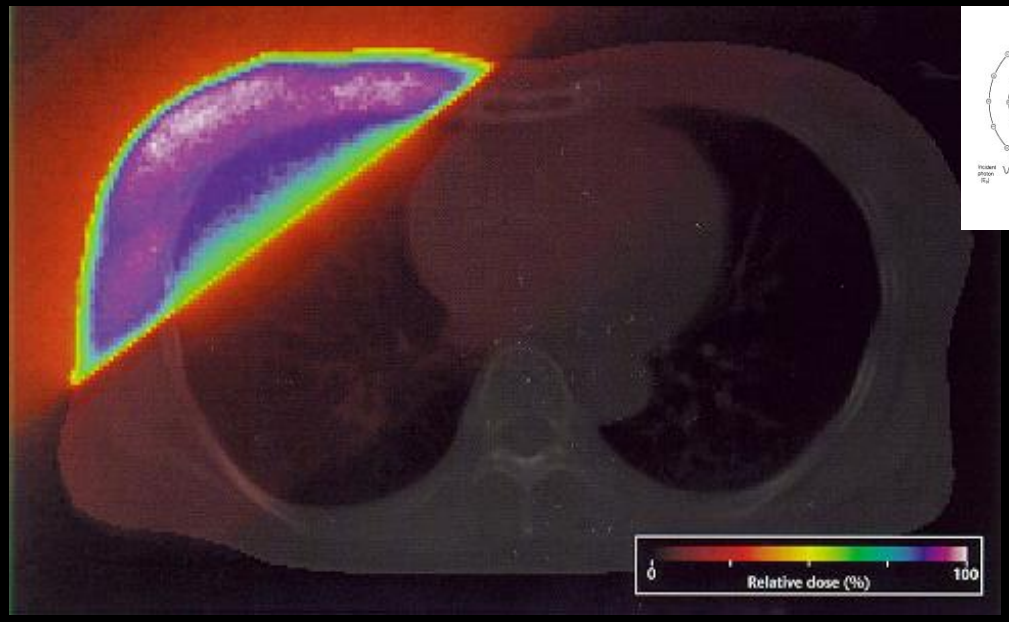








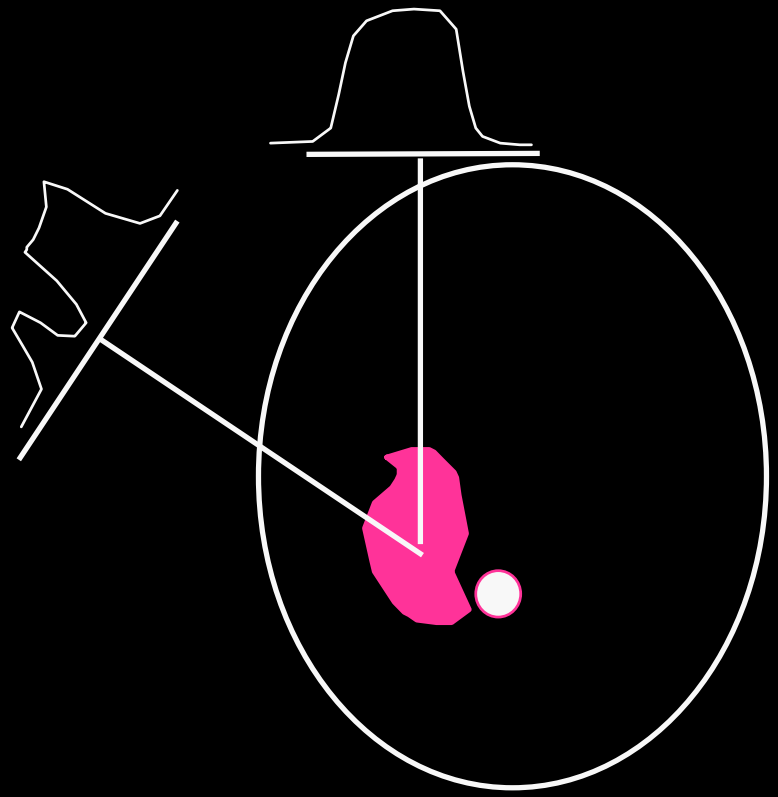




3D Dose Calculation
with Monte Carlo

3D Patient Planning

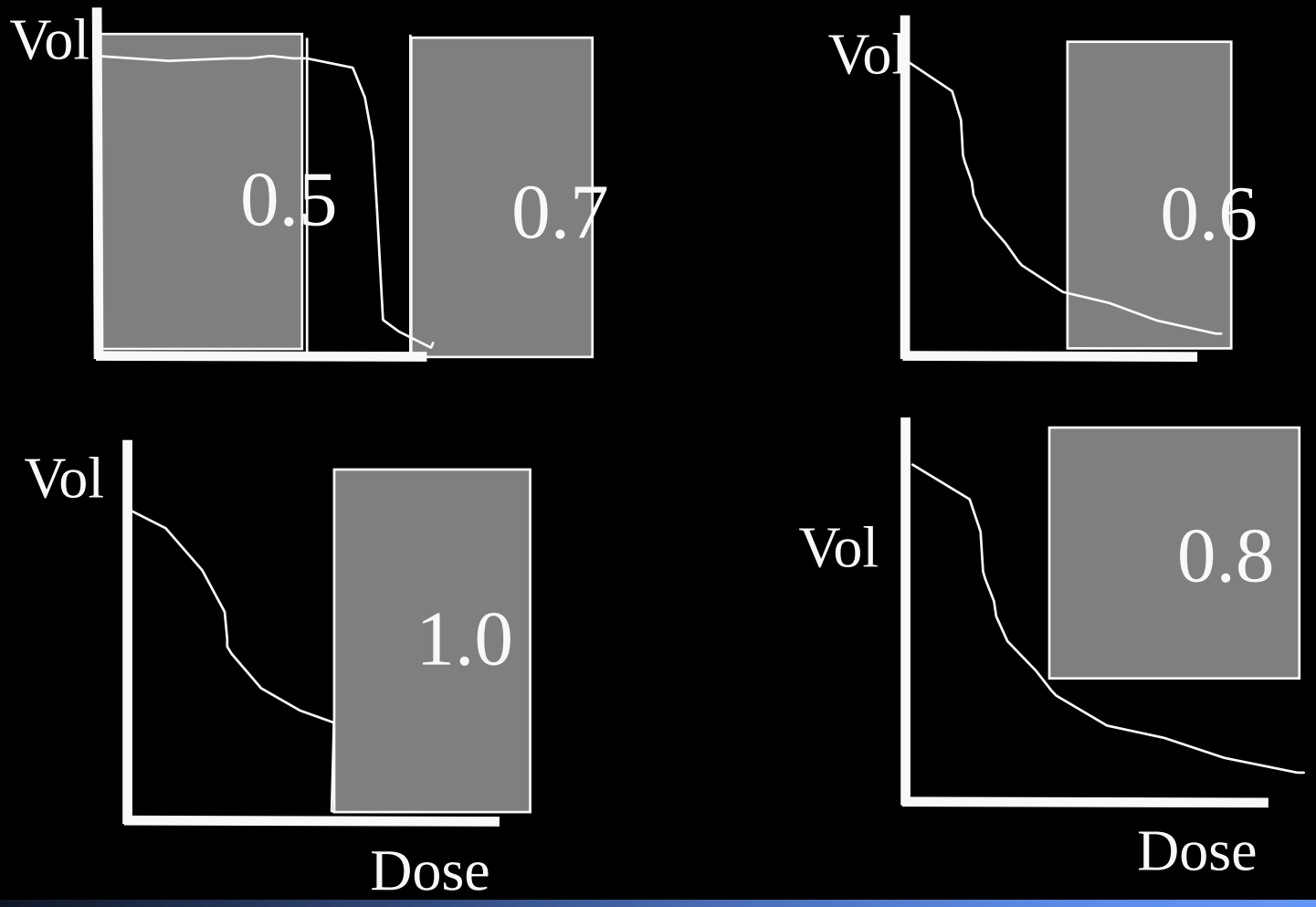
Inverse Planning



"Let's reverse the problem and
Using the power of mathematics to solve our planning challenges"

3D Patient Planning

Inverse Planning – Types of prescription



Radiation Biology
Theoretical point of view

Radiobiological models

Most of the radiobiological models are characterized by the some common features such as:

- Cell survival after irradiation follows binomial and binomial or Poisson statistics.
- Response of an organ is determined by the death or survival of its target cells (functional subunits for normal tissues and clonogents for tumors).
- All the target cells respond identically.
- Isoeffect relationships are independent of the level of response.
- Equal effects are obtained from equal fractions if sufficiently separated in time.

Radiobiological models

It is well known that the radiation response of a tissue can be characterized by the “four Rs” of radiobiology:

- *R*epair of sublethal damage
- *R*epopulation,
- *R*edistribution
- *R*eoxygenation.

Radiobiological models

Probit model

$$P(D)=\frac{1}{2}\left[1-E_{rf}\left[\sqrt{\pi\gamma}\left(1-\frac{D}{D_{50}}\right)\right]\right]$$

Logit model

$$P(D)=\left[1+\left(\frac{D_{50}}{D}\right)^{4\gamma}\right]^{-1}$$

Poisson model

$$P(D)=e^{-e^{\left[e\gamma-\left(\frac{D}{D_{50}}\right)(e\gamma-\ln\ln 2)\right]}}$$

LQ-Poisson model

$$P(D)=e^{-N_0 e^{-\alpha nd-\beta nd^2}}$$

Radiobiological models

LQ models for heterogeneous dose distributions:

$$TCP = \prod_{i=1}^{M} [[P(D_i)^s]^{\Delta v_i}]^{1/s}$$

$$NTCP = \prod_{i=1}^{M} [[1 - P(D_i)^s]^{\Delta v_i}]^{1/s}$$

Radiobiological models

LQR model for taking into account the redistribution and the reoxygenation effects:

$$S = \exp[\ -\alpha D - \beta G(\tau_R) D^2 + (\frac{1}{2}\sigma^2) G(\tau_S) D^2 + H(T_{tot}, T_k)(T_{tot} - T_k)/T_{pd}\ ]$$

$$BED = -\frac{1}{\alpha}\ln(S)$$

$$TCP \quad or \quad NTCP = \exp(-N_0 S) = \exp[-N_0 \exp(-\alpha BED)]$$

Radiation Biology
Theory → Clinical Practice

AVM radiobiological modeling

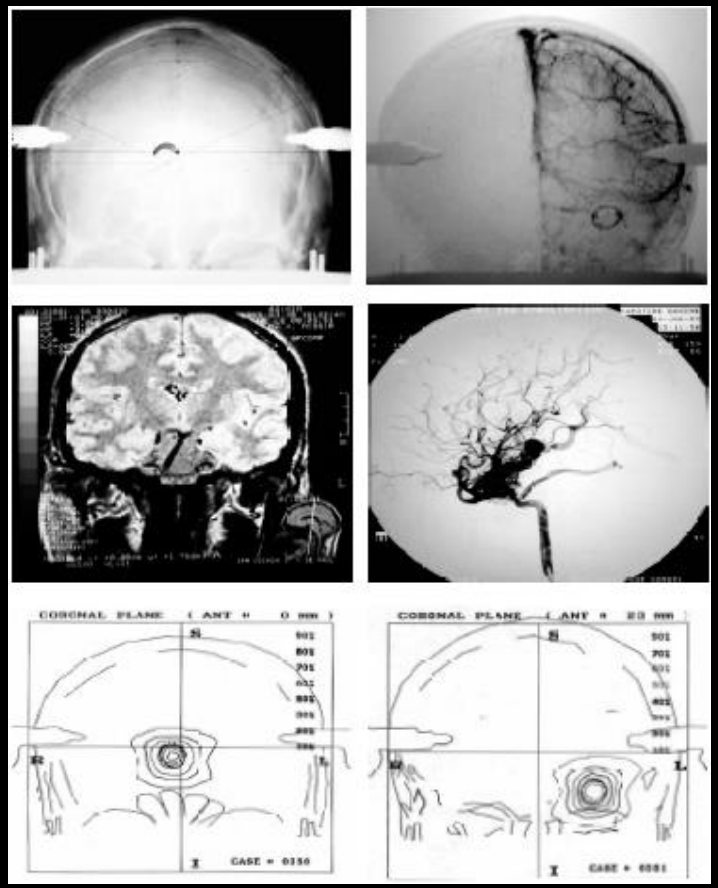


Table 1. Description of the dosimetric and clinical characteristics of the patient population.

Patients	85	Irradiation technique	
Males	52 (61.2%)	Mono-isocentric	55 (64.7%)
Females	33 (38.8%)	Multi-isocentric	30 (35.3%)
		Reference isodose	60–70%
Age		Reference dose (Gy)	
Range	6–68 years	Range	18–28
Mean	33.8 years	Mean	24.3
Median	34 years		
AVM location		Mean dose (Gy)	
Central	35 (41.2%)	Range	16–33
Peripheral	50 (58.8%)	Mean	28.4
AVM volume (cm^3)	0.3–8.8		
Haemorrhage before treatment		Follow-up	
Yes	50 (58.8%)	Angiography	85 (100%)
No	35 (41.2%)	MRI (additional)	51 (60%)
		Obliteration rate	58 (68.2%)
Other symptoms		Obliteration time	
Neurological deficit	6 (7.1%)	Range	6–54 months
Epilepsy	17 (20.0%)	Mean	20.3 months

Phys. Med. Biol. 47 (2002) 2471–2494

Radiobiological models

Linear Poisson model $$P(D) = \exp(-e^{e\gamma-(D/D_{50})(e\gamma-\ln\ln 2)})$$

Karlsson–Lax model $$P(D) = a\ln(D_{\min}) - b.$$

$$P(\vec{D}) = \prod_{i=1}^{M}[P(D_i)]^{\Delta v_i}$$

Statistics used for fitting the parameters:

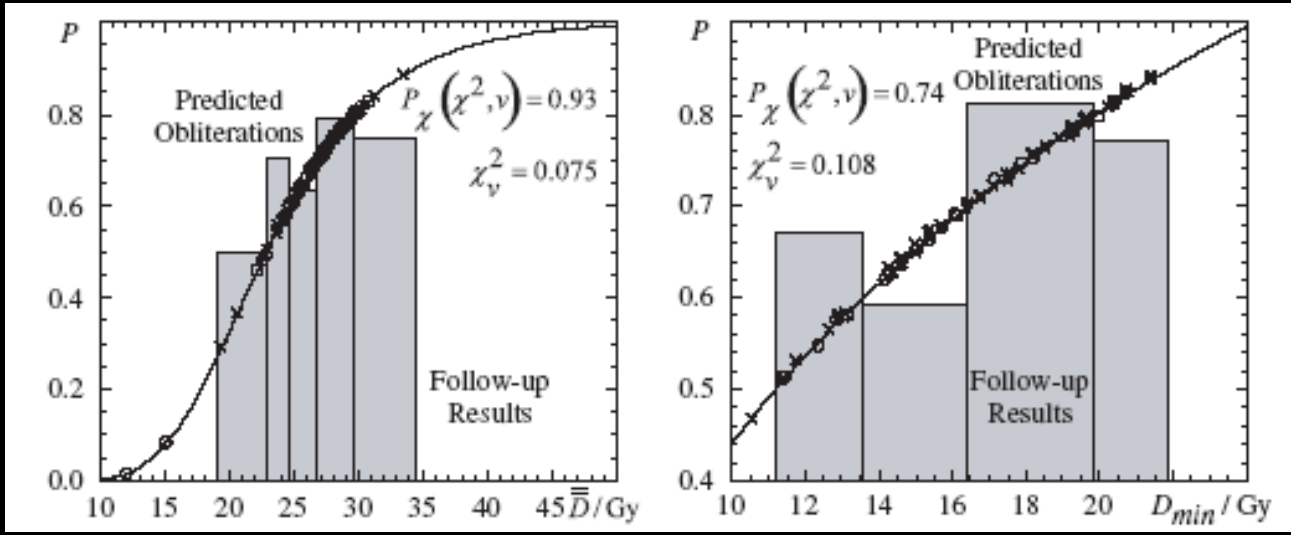
$$L(\vec{X} \mid \vec{\theta}) = L((D_{50}, \gamma), (\vec{D}, \vec{V})) = \prod_{i=1}^{m} P_{\text{obl}}((D_{50}, \gamma), (\vec{D}_i, \vec{V}_i)) \times \prod_{j=1}^{n}(1 - P_{\text{obl}}((D_{50}, \gamma), (\vec{D}_j, \vec{V}_j)))$$

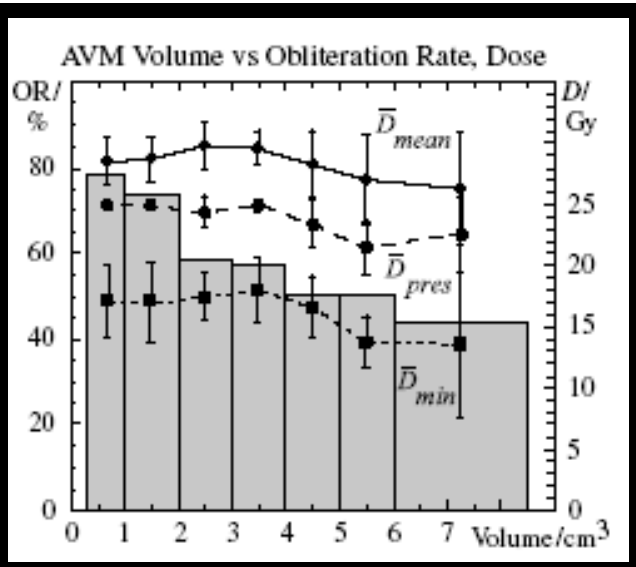
$$\begin{aligned}\ln L((D_{50}, \gamma), (\vec{D}, \vec{V})) &= \sum_{i=1}^{m}\ln(P_{\text{obl}}((D_{50}, \gamma), (\vec{D}_i, \vec{V}_i))) + \sum_{j=1}^{n}\ln(1 - P_{\text{obl}}((D_{50}, \gamma), (\vec{D}_j, \vec{V}_j))) \\ &= \sum_{i=1}^{m}\ln\left(\prod_{k=1}^{M_i}\left(\exp\left(-e^{e\gamma-(D_{ik}/D_{50})(e\gamma-\ln(\ln(2)))}\right)\right)^{V_{ik}}\right) \\ &\quad + \sum_{j=1}^{n}\ln\left(1 - \prod_{k=1}^{M_j}\left(\exp\left(-e^{e\gamma-(D_{jk}/D_{50})(e\gamma-\ln(\ln(2)))}\right)\right)^{V_{jk}}\right).\end{aligned}$$

Results

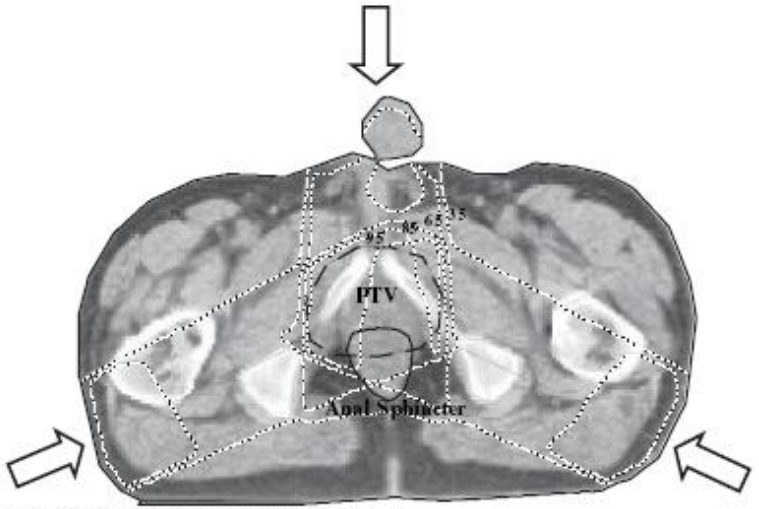
Patient subgroup	D_{50}	Confidence intervals on D_{50}	γ	Confidence intervals on γ
All AVMs ($V_{ref} = 3.0\ cm^3$) (85 patients)	22.9	68%: 21.5–24.3 Gy 95%: 20.6–24.6 Gy	1.25	68%: 0.87–1.66 95%: 0.69–1.87
Peripheral AVMs (50 patients)	24.2	68%: 21.6–26.6 Gy 95%: 20.0–35.1 Gy	0.86	68%: 0.34–1.42 95%: lim.–1.76
Central AVMs (35 patients)	20.9	68%: 18.8–22.4 Gy 95%: 17.3–23.0 Gy	1.91	68%: 1.17–2.83 95%: 0.96–3.34
Large AVMs (>2 cm^3) (41 patients)	24.6	68%: 19.7–27.3 Gy 95%: 15.4–30.2 Gy	0.67	68%: lim.–1.28 95%: lim.–1.64
Small AVMs (<2 cm^3) (44 patients)	19.7	68%: 15.8–22.2 Gy 95%: 12.8–23.1 Gy	1.37	68%: 0.82–2.26 95%: 0.69–2.71
Large AVMs (>4 cm^3) (22 patients)	23.7	68%: 20.4–26.8 Gy 95%: 15.4–30.2 Gy	0.93	68%: 0.09–1.63 95%: lim.–2.05
Small AVMs (<4 cm^3) (63 patients)	22.7	68%: 20.2–24.2 Gy 95%: 18.7–24.9 Gy	1.34	68%: 0.87–2.01 95%: 0.67–2.35
AVMs with haemorrhage (51 patients)	23.3	68%: 21.5–24.7 Gy 95%: 19.8–25.7 Gy	1.62	68%: 0.97–2.35 95%: 0.73–2.67
AVMs without haemorrhage (34 patients)	22.7	68%: 19.7–25.4 Gy 95%: 18.1–27.7 Gy	0.91	68%: 0.41–1.49 95%: 0.14–1.79
		Karlsson–Lax approach		
		a		b
All AVMs (prescribed dose)	62.28	68%: 21.80–102.76	130.42	68%: lim.–277.15
All AVMs (minimum dose)	52.07	68%: 26.68–77.45	75.84	68%: 1.90–149.79

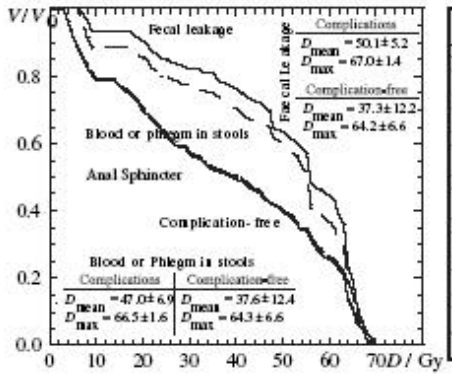
Results


P
Predicted Obliterations
$P_\chi\left(\chi^2,\nu\right)=0.93$
$\chi_\nu^2=0.075$
Follow-up Results
$\overline{\overline{D}}$ / Gy
P
Predicted Obliterations
$P_\chi\left(\chi^2,\nu\right)=0.74$
$\chi_\nu^2=0.108$
Follow-up Results
D_{min} / Gy

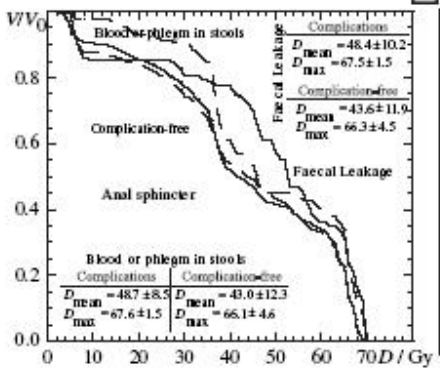

AVM Volume vs Obliteration Rate, Dose
OR/ %
D/ Gy
$\overline{D}_{mean}$
$\overline{D}_{pres}$
$\overline{D}_{min}$
Volume/cm3

Anal Sphincter radiobiological modeling





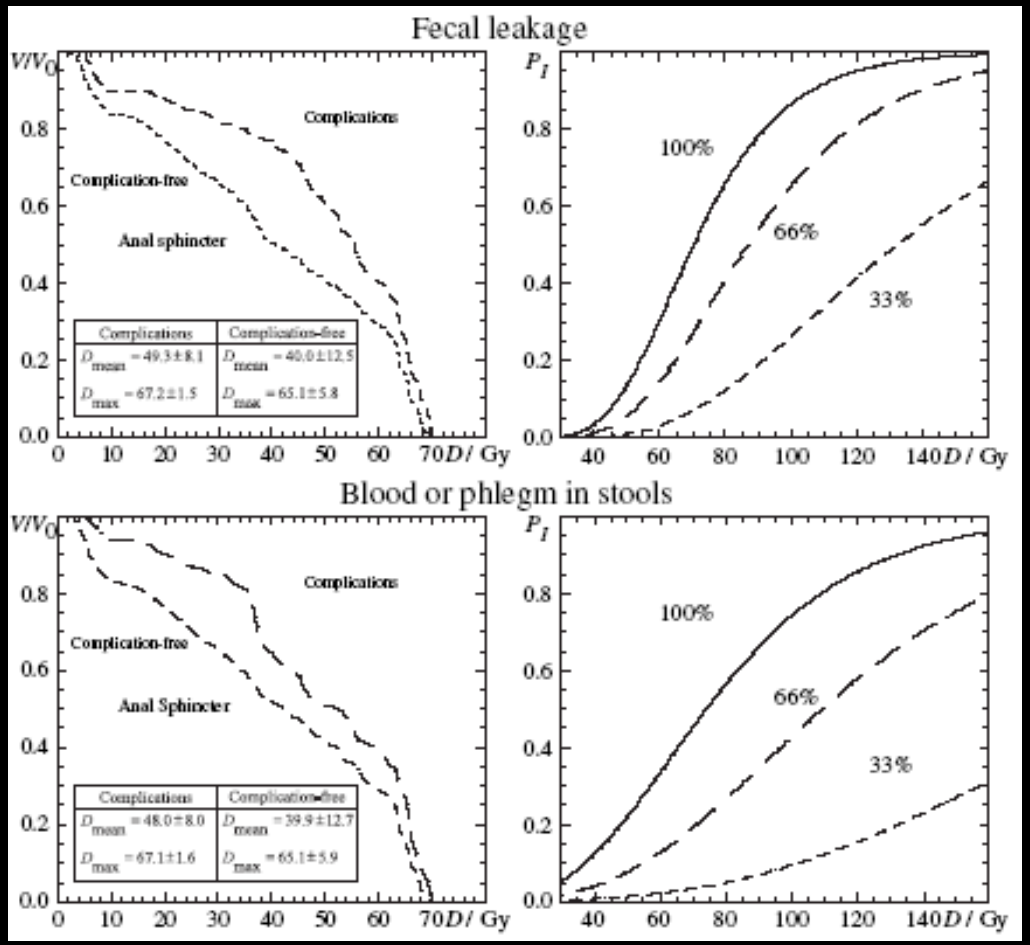
Three-field technique	
Number of patients	36
Irradiation modality	Photons
Beam energy	16 –18 MV
Beam orientation	3 fields angles: 0°, 120° and 240°
Fractions	39
Dose per fraction	1.8 Gy
Prescribed dose	70.2 Gy
Treatment period	60 ± 4 days



Four-field box technique	
Number of patients	29
Irradiation modality	Photons
Beam energy	16 –18 MV
Beam orientation	angles: 0°, 90° 180° and 270°
Fractions	39
Dose per fraction	1.8 Gy
Prescribed dose	70.2 Gy
Treatment period	60 ± 4 days

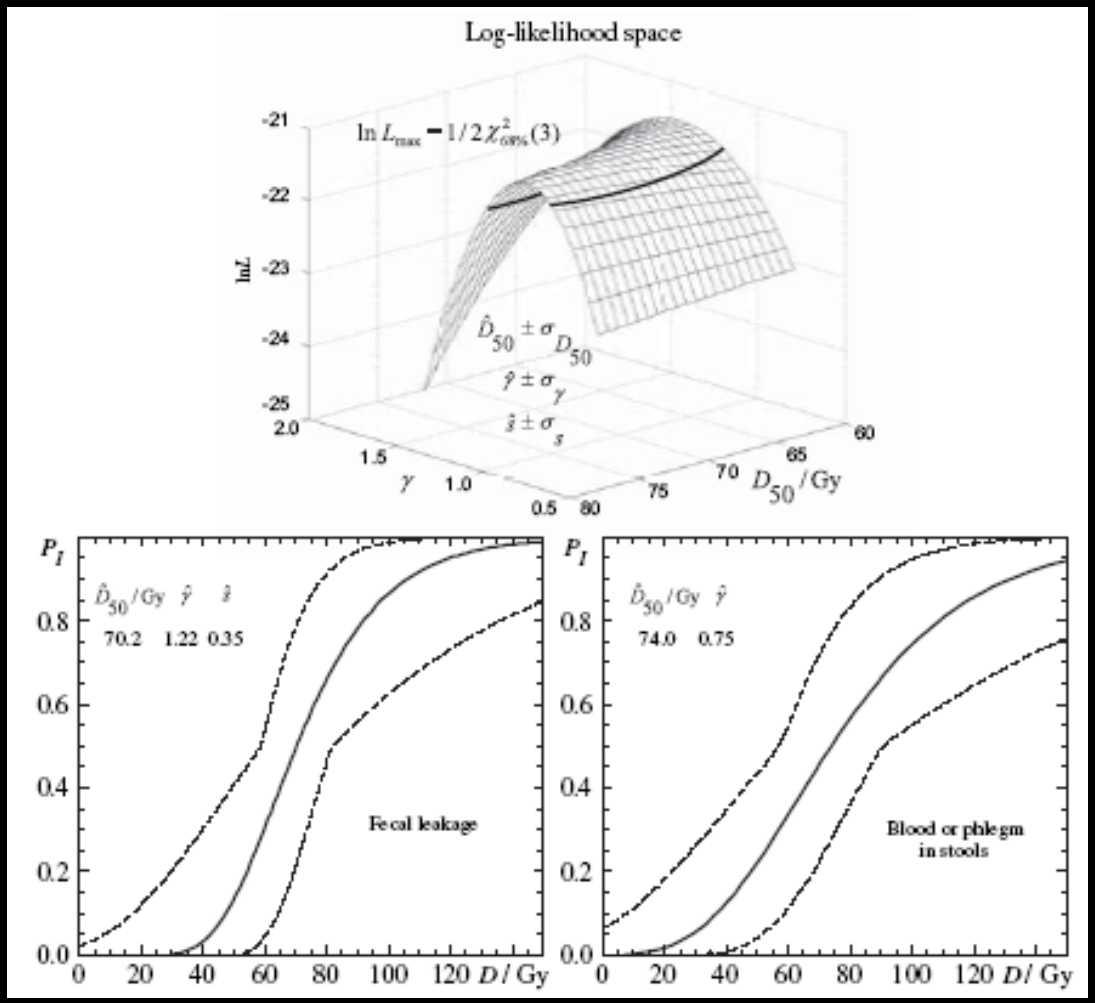
Strahlenther Onkol 2005;181:293–306

Results



Parameters	Best estimates and confidence intervals	
	Fecal leakage	Blood or phlegm in stools
D_{50} (Gy), dose for 50% complication probability	70.2 ± 16%	74.0 ± 22%
γ, maximum normalized gradient of the dose-response curve	1.22 ± 60%	0.75 ± 50%
s, relative seriality parameter	0.35 ± 90%	≈ 0 (very low)

Results


Log-likelihood space
$\ln L_{max} - 1/2\chi^2_{68\%}(3)$
lnL
-21
-22
-23
-24
-25
$\hat{D}_{50} \pm \sigma_{D_{50}}$
$\hat{\gamma} \pm \sigma_{\gamma}$
$\hat{s} \pm \sigma_{s}$
2.0
1.5
γ
1.0
0.5
60
65
70
75
80
D_{50} / Gy
P_I
$\hat{D}_{50}$ / Gy $\hat{\gamma}$ $\hat{s}$
70.2 1.22 0.35
Fecal leakage
0.0
0.2
0.4
0.6
0.8
0
20
40
60
80
100
120
D / Gy
P_I
$\hat{D}_{50}$ / Gy $\hat{\gamma}$
74.0 0.75
Blood or phlegm in stools
0.0
0.2
0.4
0.6
0.8
0
20
40
60
80
100
120
D / Gy

Evaluation of radiobiological models in breast cancer radiotherapy

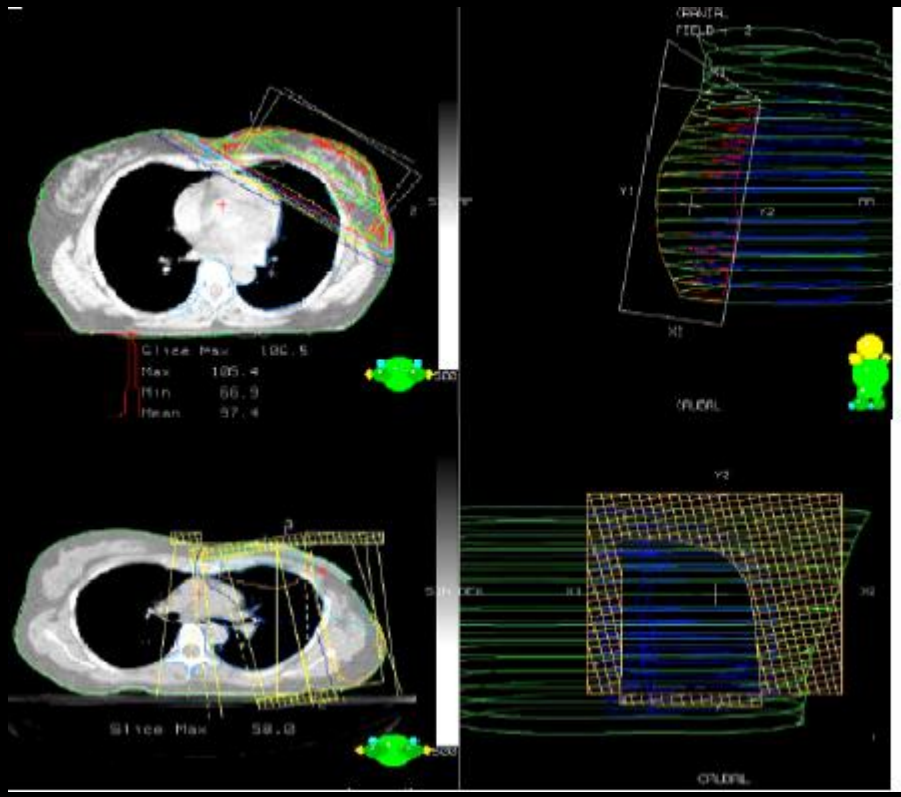
150 consecutive patients from Tempere University Hospital, Finland, treated from 1998-1999.

Age (years)	
Median	61
Range	30–83
Gender	Female
Radiation pneumonitis grade	
No–mild	135 (90%)
Medium–severe	15 (10%)
Clinical case	
Mastectomy	36 (24%)
Breast resection	114 (76%)
Side (%)	
Left	78
Right	22
Chemotherapy (%)	
Yes	20.5
No	79.5
Dose per fraction	2.0 Gy

Clinical endpoint: radiation pneumonitis

Phys. Med. Biol. **50** (2005) 3535–3554

Treatment planning



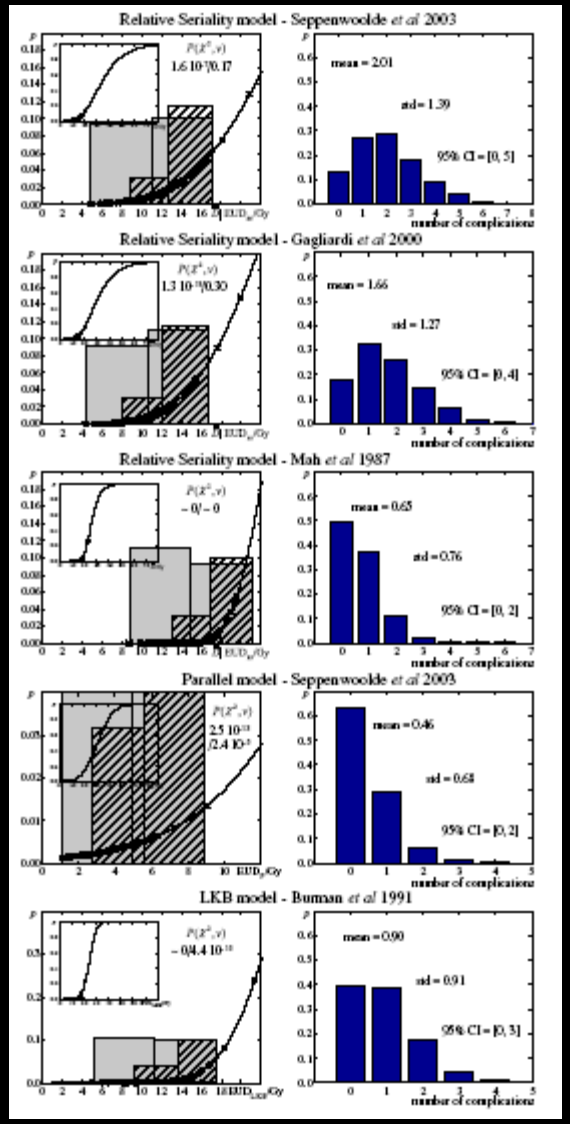
Parameters
Physical
Photons 5/6 MV
2 tangential fields
35°and 215°
50 Gy prescribed
dose in 25 fractions
Clinical
Target volume: entire breast
(fat tissue and skin)

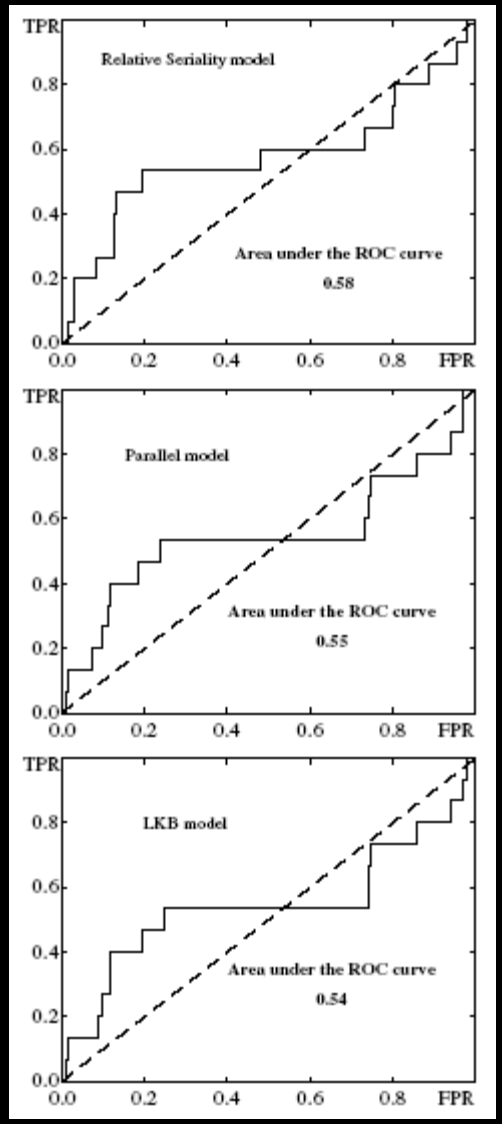
Parameters
Physical
1. Photons 6/25 MV
two anterior-posterior fields
2. Electrons 12 MeV
50 Gy prescribed
dose in 25 fractions
Clinical
Target volume: entire breast
+ regional lymph nodes
and chest wall

Radiobiological parameters

Models	Parameter values[a]			
Relative seriality model	D_{50} (Gy)	γ	s	α/β
Seppenwoolde *et al* (2003)	34	0.9	0.06	2.5–3.0
Gagliardi *et al* (2000)	30.1	0.97	0.01	3.0
Mah *et al* (1987)	26	2	0.031	–
LKB model	TD_{50} (Gy)	m	n	α/β
Burman *et al* (1991)	24.5	0.18	0.87	–
Parallel	TD_{50} (Gy)	m	n	α/β
Seppenwoolde *et al* (2003)	31	0.32	0.67	2.5–3.0

Results


Relative Seriality model - Seppenwoolde et al 2003
mean = 2.01
std = 1.39
95% CI = [0, 5]
number of complications
Relative Seriality model - Gagliardi et al 2000
mean = 1.66
std = 1.27
95% CI = [0, 4]
number of complications
Relative Seriality model - Mah et al 1987
mean = 0.65
std = 0.76
95% CI = [0, 2]
number of complications
Parallel model - Seppenwoolde et al 2003
mean = 0.46
std = 0.68
95% CI = [0, 2]
number of complications
LKB model - Burman et al 1991
mean = 0.90
std = 0.91
95% CI = [0, 3]
number of complications


TPR
Relative Seriality model
Area under the ROC curve
0.58
FPR
TPR
Parallel model
Area under the ROC curve
0.55
FPR
TPR
LKB model
Area under the ROC curve
0.54
FPR

Conclusions

Conclusion I

What we have to know in order to use biological models in the treatment planning process?

- ✓ the γ and D_{50} of the target
- ✓ the γ and D_{50} of EVERY critical organ and for EVERY complication
- ✓ The 3D dose distribution (DVHs)

ATTENTION!!!

The bibliographic data are NOT always reliable!

- ➢ wrong choice of patients – bad statistics
- ➢ not reliable clinical/physical data
- ➢ not sufficient or bad follow-up

Conclusion II

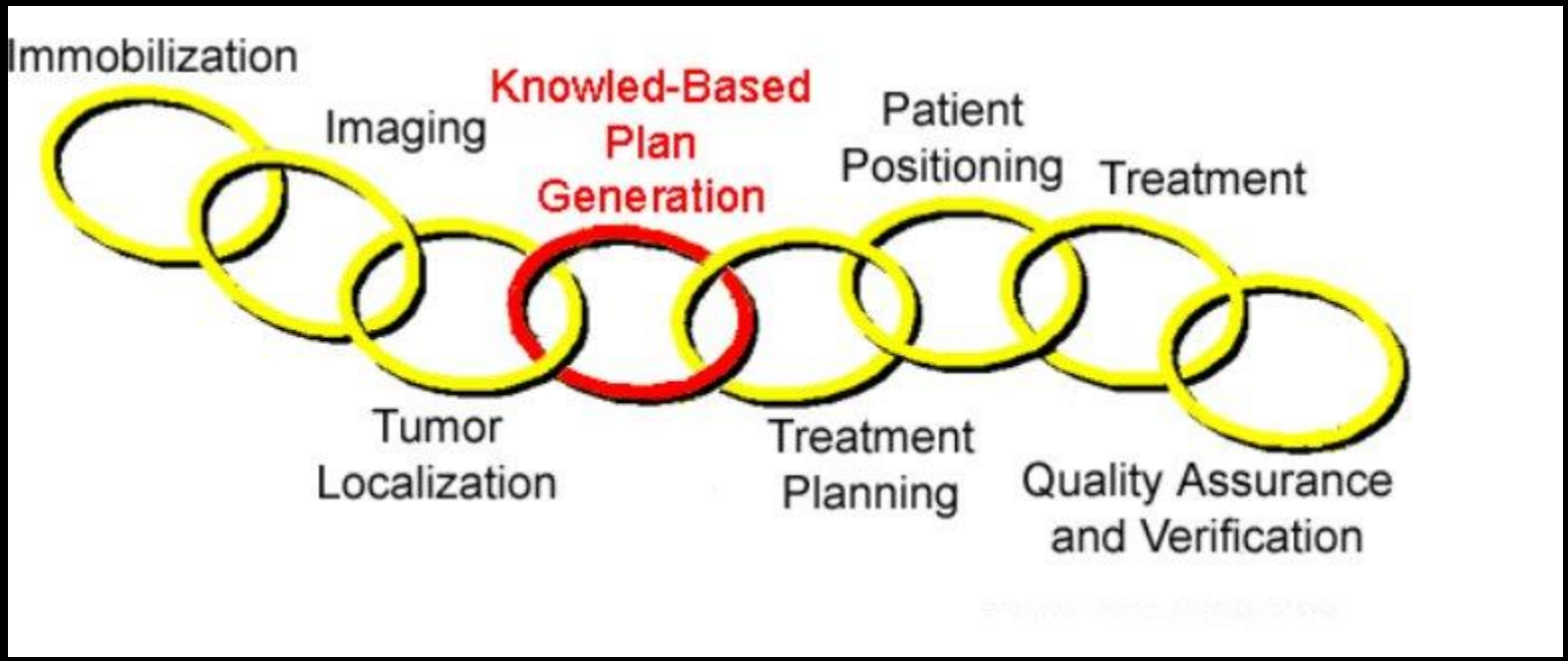
For making a study to determine our own biological parameters we have to:

- ✓ Define the target and critical organs
- ✓ Determine/record the target reference dose
- ✓ Determine the complications (endpoint)
- ✓ Produce/save the 3D dose distribution (DVH for every structure)
- ✓ Check and verify the treatment delivery
- ✓ Patient follow-up for time adequate to see the defined complications
- ✓ Have a large number of consecutive and similar patient cases

Conclusion III

- ✓ It is possible for the Medical Physicist to be involved actively in radiobiological studies and optimization
- ✓ The close collaboration between physicist and radiotherapist is imperative
- ✓ For producing your own radiobiological data, a well-defined treatment and follow-up protocol should be made
- ✓ The overall treatment accuracy is a key factor for reliable radiobiological modelling and furthermore for predictive studies

Radiotherapy Procedure



TEŞEKKÜR EDERİM