Biological optimisation of radiation therapy treatment planning – from modelling to clinical implementation

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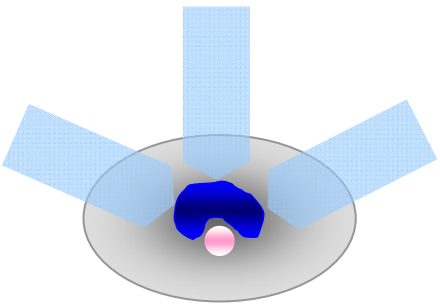
Radiation therapy optimisation

- The aim of radiation therapy is to eradicate the tumour while sparing the normal tissue as much as possible.
- Radiotherapy should follow the A.H.A.R.A. principle which is to deliver As High radiation dose As possible (Reasonably Achievable) to the clinical target while keeping the dose to other regions and organs as low as possible.

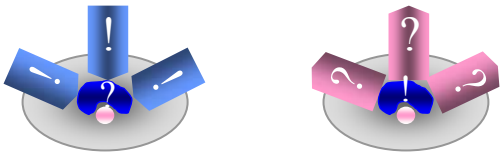


Treatment planning optimisation

Forward calculation

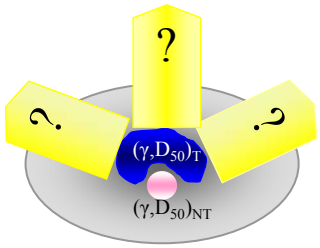
Inverse calculation

Classical beam profiles



Physically optimised beam profiles

Inverse calculation



Biologically optimised beam profiles

Treatment planning optimisation

What are the variables in treatment optimisation?

- Radiation modality (type and quality)
- Number and direction of beams
- Beam (fluence) modulation

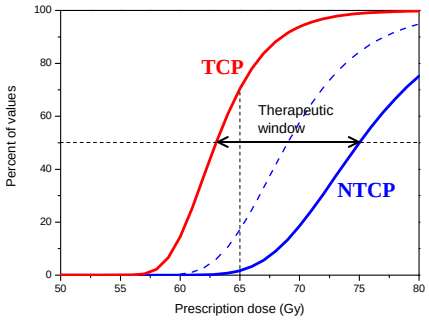
- Fractionation schedule (number of fractions and overall time)

Biological optimisation

- The generally accepted definition of optimisation in radiation therapy is to produce a treatment plan that maximizes the probability of tumour control without causing unacceptable complications in the normal tissue.
- In the current physical optimisation the outcome of the treatment expressed as tumour control and normal tissue complication probabilities does not play an active role but it is indirectly maximised through the optimised dose distribution within the clinical targets and organs at risk.
- In biological optimisation the main aim of radiation therapy expressed as clinical outcome is explicitly defined at the stage of problem formulation.

Biological optimisation

- The current physical optimisation approaches use dose and/or DVH based objective functions.
- This would imply that a higher dose would result in a higher control but the biological response to radiation is not linear.
- Example: underdosing a very small volume of the tumour would not have a significant effect on the objective value of a physical plan but TCP would be greatly diminished, hence the need for biological optimisation.



Biological optimisation

Basic requirements for the biological optimisation:

- Radiobiological models for tumour and normal tissue response
- Clearly formulated objectives and constrains
- Optimisation algorithms

Radiobiological models for TCP

Radiobiological models for tumour and normal tissue response are the result of the combination of:

- Radiobiological models for clonogenic cell survival:
  - Linear Quadratic (LQ) model
  - The lethal and potentially lethal damage (LPL) model (Curtis 1986)
  - The Repairable - Conditionally Repairable (RCR) damage model (Lind *et al* 2003)
  - etc.
- Dose-response curves fitted with various functions:
  - Poisson
  - Logistic
  - Probit

Radiobiological models for TCP

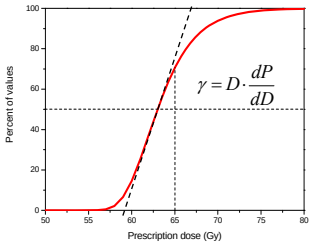
Poisson-LQ Model:

- The LQ model describes the response of individual cells to radiation in the clinical dose range and a Poisson function describes the response of a whole tissue to radiation.
- The probability of eradicating a tumour is given by:

$$P = \exp\left(-N \cdot \exp\left(-n \cdot \left(\alpha \cdot d + \beta \cdot d^2\right)\right)\right)$$

or

$$P = \exp\left(-\exp\left(e \cdot \gamma - n \cdot \left(\alpha \cdot d + \beta \cdot d^2\right)\right)\right)$$



$$\alpha = \frac{e\gamma - \ln\ln 2}{D_{50}\left(1 + \frac{d}{\alpha/\beta}\right)}$$

Radiobiological models for TCP

Poisson-LQ Model:

- In case of non-homogeneous irradiation of the tumour:

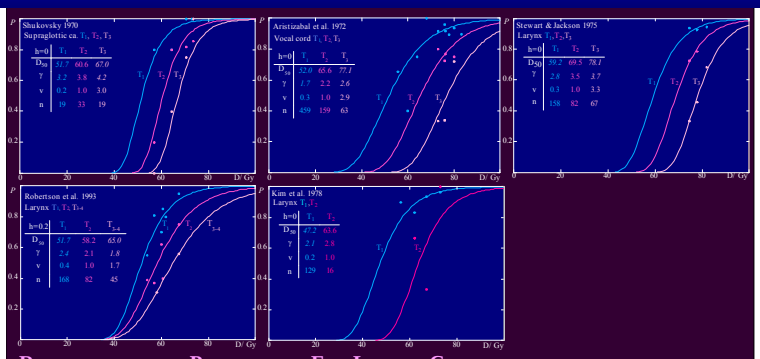
$$TCP = \prod_i P_i$$

- P_i is the control probability at the voxel level.

$$P_i = \exp\left(-\rho V_i \cdot \exp\left(-n \cdot \left(\alpha \cdot d + \beta \cdot d^2\right)\right)\right)$$

were ρ is the density of clonogenic cell in the voxel i and V_i is its volume.

Radiobiological parameters for TCP calculation



RADIOBIOLOGICAL PARAMETERS FOR LARYNX CANCER

	T1			T2			T3			
	D_{50}	γ	v	D_{50}	γ	v	D_{50}	γ	v	h
Shukovsky -70	51.7	3.2	0.2	60.6	3.8	1.0	67.0	4.2	3.0	0
Stewart et al. -75	59.2	2.8	0.2	69.5	3.5	1.0	78.1	3.7	3.3	0
Aristizabal et al.72	52.0	1.7	0.3	65.6	2.2	1.0	77.1	2.6	2.9	0
Kim et al. -78	47.2	2.1	0.3	63.6	2.8	1.0	-	-	-	0
Slevin et al. -92	-	-	-	62.2	2.0	1.0	75.9	2.4	3.3	0
Robertson et al. -93	51.7	2.4	0.4	58.2	2.1	1.0	65.0	1.8	1.7	0.2
Mean Values	52.4	2.4	0.2	63.5	2.7	1.0	72.6	2.9	2.8	-
Standard deviation	3.9	0.5	0.1	3.9	0.7	-	5.5	0.9	0.6	-
Mean Values				59.9	2.9	1.0	(59.9Gy+0.35Gy/d			
Standard deviation				2.1	0.3		above 41d at 2Gy/f)			

** By courtesy of Bengt Lind*

Radiobiological models for NTCP

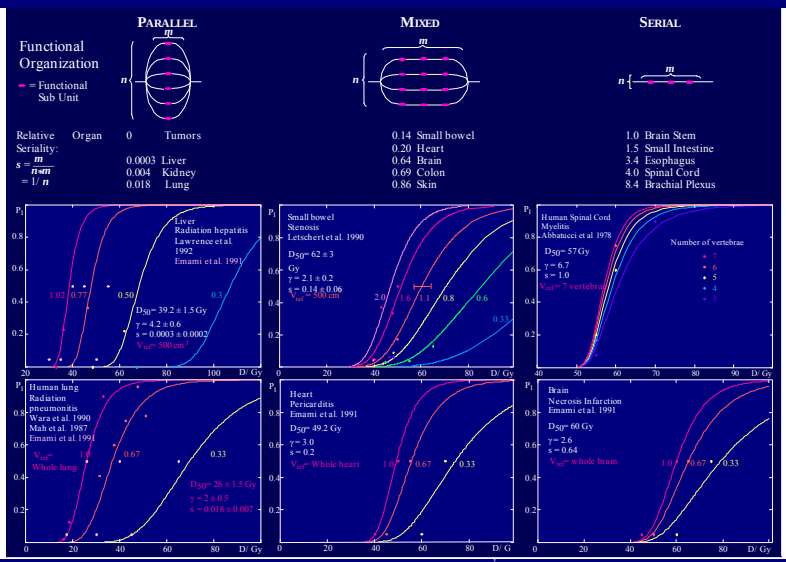
Poisson-LQ Model:

- NTCP can be calculated in a similar manner incorporating also the modelling of organ seriality, expressed by the parameter *s*.

$$NTCP = \left(1 - \prod_i \left(1 - P_i^s\right)^{v_i/V}\right)^{1/s}$$

- The radiobiological response of a serial critical organ is mainly determined by the maximum dose given to the organ while the radiobiological response of parallel critical structures is not as sensitive to hot spots.

The seriality model – influence of tissue organisation *



** By courtesy of Bengt Lind*

Radiobiological models for NTCP

Lyman-Kutcher-Burman Model:

- NTCP can be calculated based on some basic assumptions:
  - Volume dependence: power law relationship for the tolerance doses for different irradiated volumes
  - Dose dependence: described by an integral over a distribution giving a sigmoid-shaped dose response curve
  - A single step of a DVH represents the case of uniform irradiation of a subvolume

$$NTCP = \frac{1}{\sqrt{2\pi}} \int_{-\infty}^{t} \exp\left(-\frac{t^2}{2}\right) dt$$

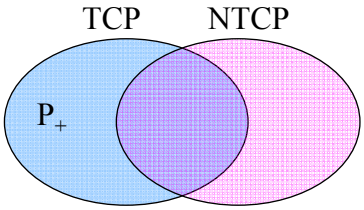
$$t = \frac{D - D_{50}}{\gamma \cdot D_{50}} \qquad D = \sum_i \left(\frac{v_i}{V} D_i^{1/n}\right)^n$$

γ is the slope of the dose-response curve and n gives the volume dependence

Composite models

- The objective function should be a scalar quantity describing the treatment outcome, eg. quality of life after treatment.
- The objective function is often simplified by using physical (dose) or biological (radiation response of tumour or normal tissue) quantities.
- A quantity that combines the probabilities of tumour control and complication free treatment into one objective function is P_+, probability of complication free tumour control.

$$P_+ = TCP - TCP \bigcap NTCP$$



Composite models

Probability of complication free tumour control P_+ could be calculated in two ways:

- Assuming that TCP and NTCP are uncorrelated

$$P_+ = TCP(1 - NTCP)$$

- Assuming that TCP and NTCP are fully correlated

$$P_+ = TCP - NTCP$$

where $NTCP = 1 - \prod_i (1 - NTCP_i)$

$$TCP = \prod_j TCP_j$$

Composite models

WARNING!

The composite models should be used with great care.

Loss of tumour control and risk of severe complications cannot be compensated by the risk of minor complications.

P_+ optimises only one NTCP at the time.

Example: $P_+ = TCP_{prostate} - NTCP_{bladder}$

or $P_+ = TCP_{prostate} - NTCP_{rectum}$

Biological optimisation

Input data:

- Patient anatomy
- Target(s) and OARs
- Individual patient radiosensitivity (if available)
- NTCP for each OAR as a function of physical dose distribution including fractionation
- TCP as a function of physical dose distribution including fractionation

Clinically relevant optimisation problems

1. Maximisation of complication free tumour control

$$\begin{cases} \text{maximise } P_+(\xi) \\ \xi \end{cases}$$

2. Maximisation of complication free tumour control followed by a constrained complication probability minimisation

$$\begin{cases} \text{minimise NTCP}(\xi) \\ \xi \\ \text{subject to } P_+(\xi) \geq \hat{P}_+(\hat{\xi}) - \Delta P_+ \end{cases}$$

3. Maximisation of complication free tumour control under NTCP constraints

$$\begin{cases} \text{maximise } P_+(\xi) \\ \xi \\ \text{subject to NTCP}^i \leq p^i \end{cases}$$

Clinically relevant optimisation problems

4. Maximisation of complication free tumour control under dose homogeneity constrains

$$\begin{cases} \text{maximise } P_+(\xi) \\ \xi \\ \text{subject to } \left(\sigma_D / \overline{D}\right)^j \leq \left(\sigma_D / \overline{D}\right)^j_{\max} \end{cases}$$

5. Maximisation of TCP under NTCP constrains

$$\begin{cases} \text{maximise TCP}(\xi) \\ \xi \\ \text{subject to NTCP}(\xi) \leq \text{NTCP}_{\text{tolerance level}} \end{cases}$$

6. Minimisation of NTCP under TCP constrains

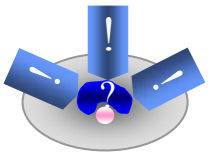
$$\begin{cases} \text{minimise NTCP}(\xi) \\ \xi \\ \text{subject to TCP}(\xi) \geq \text{TCP}_{\text{accepted}} \end{cases}$$

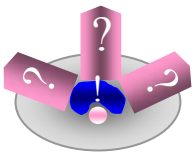
Treatment planning optimisation

Forward calculation

Inverse calculation

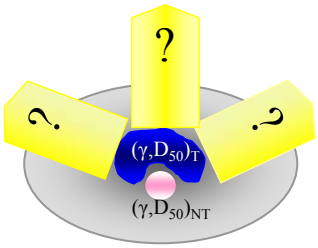
Classical beam profiles





Physically optimised beam profiles

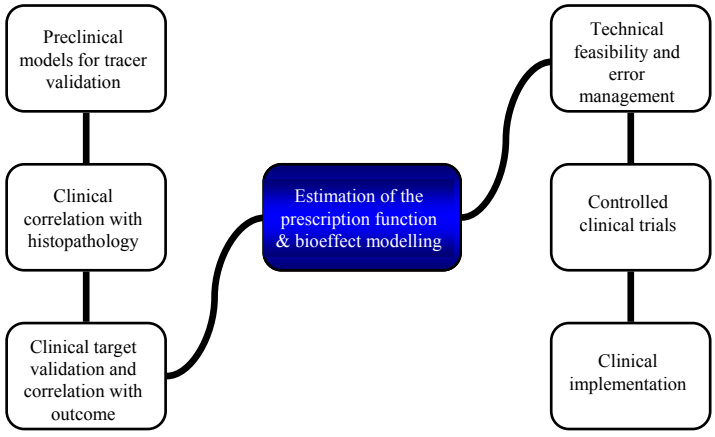
Inverse calculation



Biologically optimised beam profiles

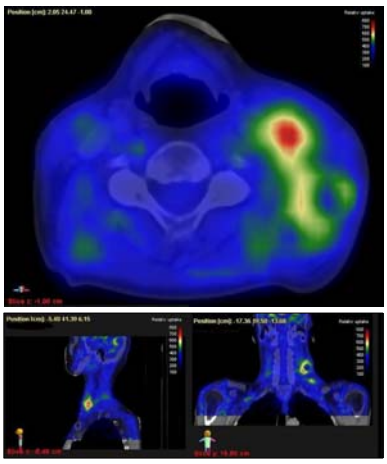
Biologically **individualised** optimised treatment planning

Biological optimisation based on functional imaging



Treatment planning based on functional imaging

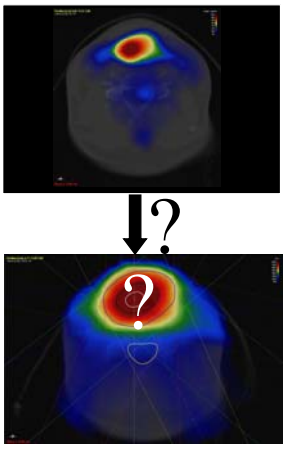
- PET-CT is a non-invasive method that can be used for imaging tumours and deriving radiobiological parameters such us tumour metabolism, proliferative activity and tumour hypoxia.
- PET tracers:
  - Metabolic tracers (e.g., FDG)
  - Proliferation tracers (e.g., FLT)
  - **Hypoxic tracers** (e.g., FMISO, CuATSM, FETA, FAZA)
- Several clinical studies have indeed shown good correlations between the amount and severity of PET hypoxia and the treatment outcome.



Treatment planning based on tumour oxygenation

- Several dose modification algorithms have been proposed for planning based on PET images:
  - empirical escalation of doses
  - dose redistributions
  - prescription of doses taking into account the dynamics of the recorded images
  - **prescription of doses taking into account the uptake properties of the hypoxic markers**

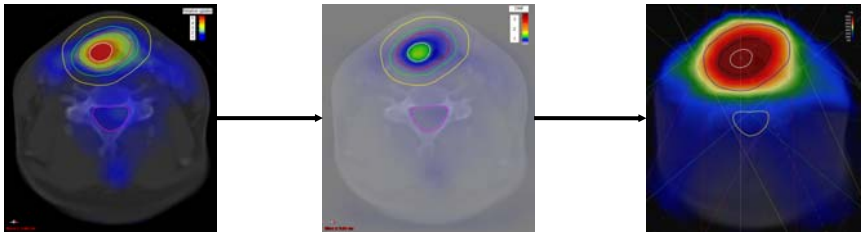
PET tracer uptake



Dose distribution

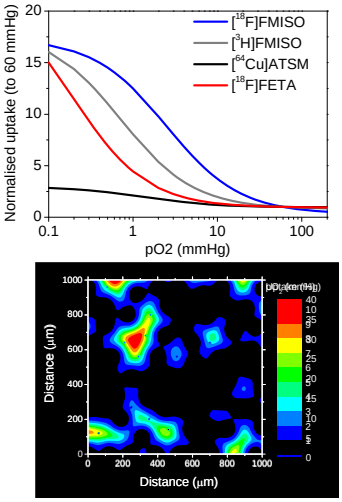
Treatment planning based on tumour oxygenation

PET tracer uptake | Dose modifying factors | Dose distribution



Hypoxic PET tracers uptake

- Cellular retention of the hypoxic PET tracers depends on oxygen concentration.
- Various PET tracers provide different levels of uptake and discrimination of the hypoxic levels.
- The uptake and the binding of the hypoxic tracer depend on complex factors but among the most important are the tumour vasculature and oxygenation.

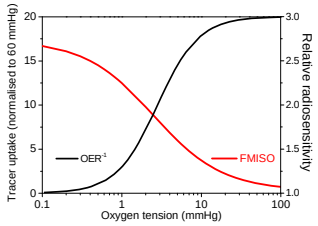


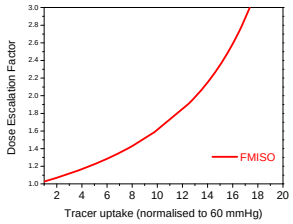
Tracer (FMISO) cellular uptake

PET hypoxia and Dose Enhancement Factors

- The normalised uptake curve for FMISO combined with the relationship between radiation sensitivity and cellular oxygenation could be used for calculating the Dose Escalation Factors.

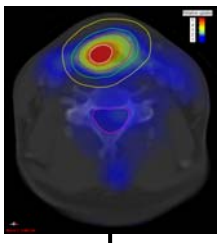
- Dose Escalation Factor as function of tracer uptake shows the non-linearity of the relationship between the two quantities.

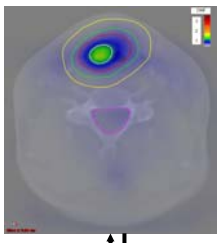


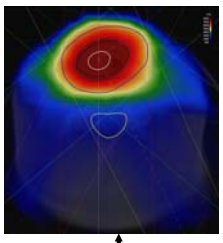


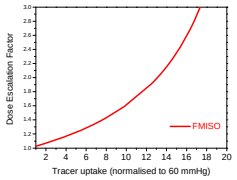
Treatment planning based on tumour oxygenation

PET tracer uptake | Dose modifying factors | Dose distribution









$$D_P = \frac{\overline{D}}{\left[1 - \frac{\gamma}{2P(\overline{D})}\left(\frac{\sigma_D}{\overline{D}}\right)^2\right]}$$

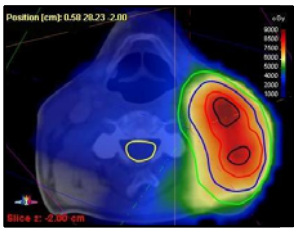
(Toma-Dasu *et al* 2009)

Treatment planning based on tumour oxygenation

How does this work on patients?

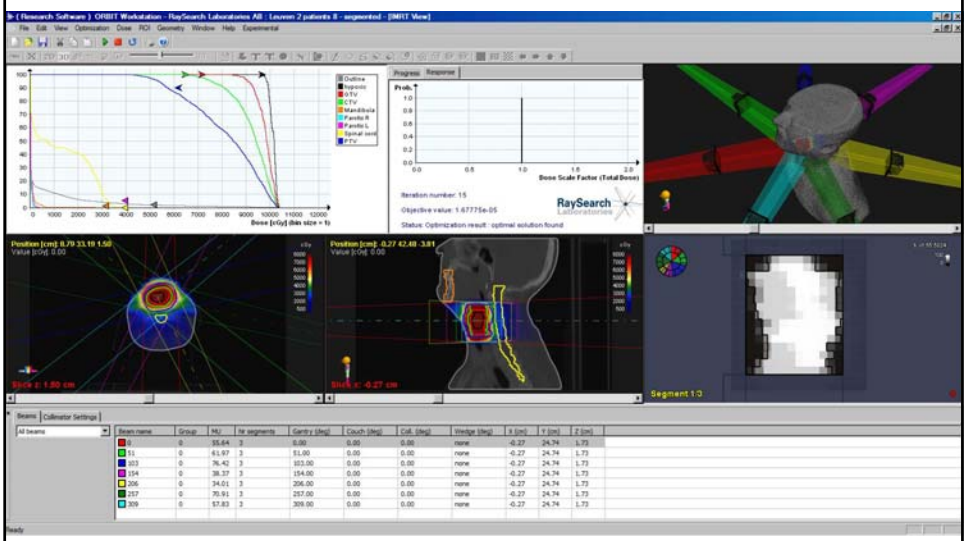
- Acquisition of PET image;
- Calibration of the uptake relative to a reference region;
- Converting uptake levels into radiation sensitivities;
- Target segmentation;
- Calculation of the prescribed doses for segments;
- Treatment plan optimisation;

- Treatment verification;
- Assessment of tumour responsiveness;
- Replanning based on subsequent PET images.



Hypoxic target 98 Gy
GTV 73 Gy
CTV 66 Gy

Treatment planning based on tumour oxygenation

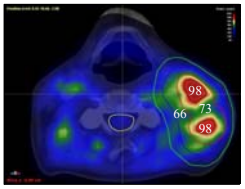


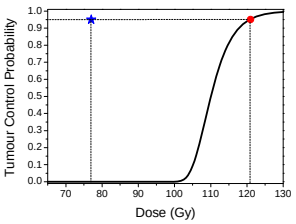
Treatment planning based on tumour oxygenation

Patient no.	Primary tumour site	Age	Gender	Clinical T classification	Clinical N classification
1	Larynx	48	M	3	0
2	Larynx	60	M	4a	2c
3	Larynx	61	M	1	2c
4	Oropharynx	57	M	3	2b
5	Oropharynx	60	M	2	2c
6	Oropharynx	48	M	4a	1
7	Oropharynx	55	M	4a	1

Treatment planning based on tumour oxygenation

Patient no.	Calculated dose (Gy)				
	Static oxygenation	Dynamic oxygenation	Segmented method		
	Clinical target	Clinical target	CTV	GTV	HTV
1	121	77	66	73	98
2	70	70	66	70	72
3	71	68	65	70	73
4	67	69	64	69	71
5	68	66	64	67	70
6	67	65	64	66	70
7	76	75	72	76	78





OARs constrains				
Spinal cord	Mandibula	Left parotid gland	Right parotid gland	Non-specific normal tissue
Maximum dose 38 Gy	Maximum DVH 30 Gy to 1% volume	Maximum DVH 38 Gy to 5% volume	Maximum DVH 38 Gy to 5% volume	Maximum DVH 50 Gy to 1.5% volume

Feasibility of planning based on PET hypoxia

- Treatment planning based on segmentations methods incorporating information about PET hypoxia leads to better results than highly heterogeneous dose distributions especially for rapidly reoxygenating tumours.
- Customisation of radiation delivery by focusing the radiation dose to the hypoxic areas has the potential to reduce the average tumour dose needed to achieve a certain level of local control.
- The particular features of hypoxia dynamics might require further imaging throughout the treatment and when needed replanning should be employed for further individualisation of the treatment.

Future studies

- Comparison between various optimisation approaches
- Planning study using different techniques for dose delivery
- Testing the feasibility of the method for various tumour locations
- Clinical study on H&N patients
- Planning accounting for tumour hypoxia and proliferation derived from FLT PET

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