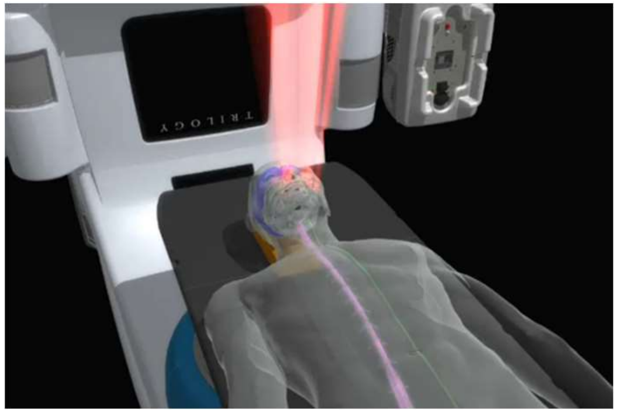
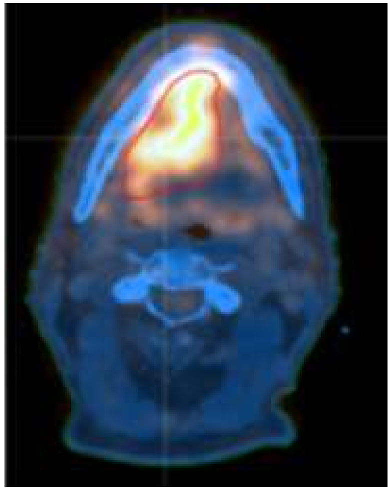
Individualizarea radioterapiei cu fotoni pe baza imagisticii funcționale



Iuliana Toma-Dasu

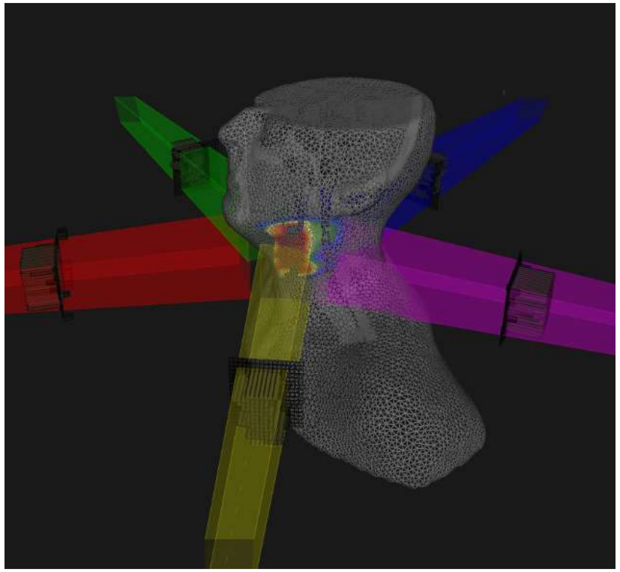
Medical Radiation Physics

Stockholm University and Karolinska Institutet



Radiotherapy

- **Radiotherapy** - the use of ionising radiation in the management of malign and benign diseases



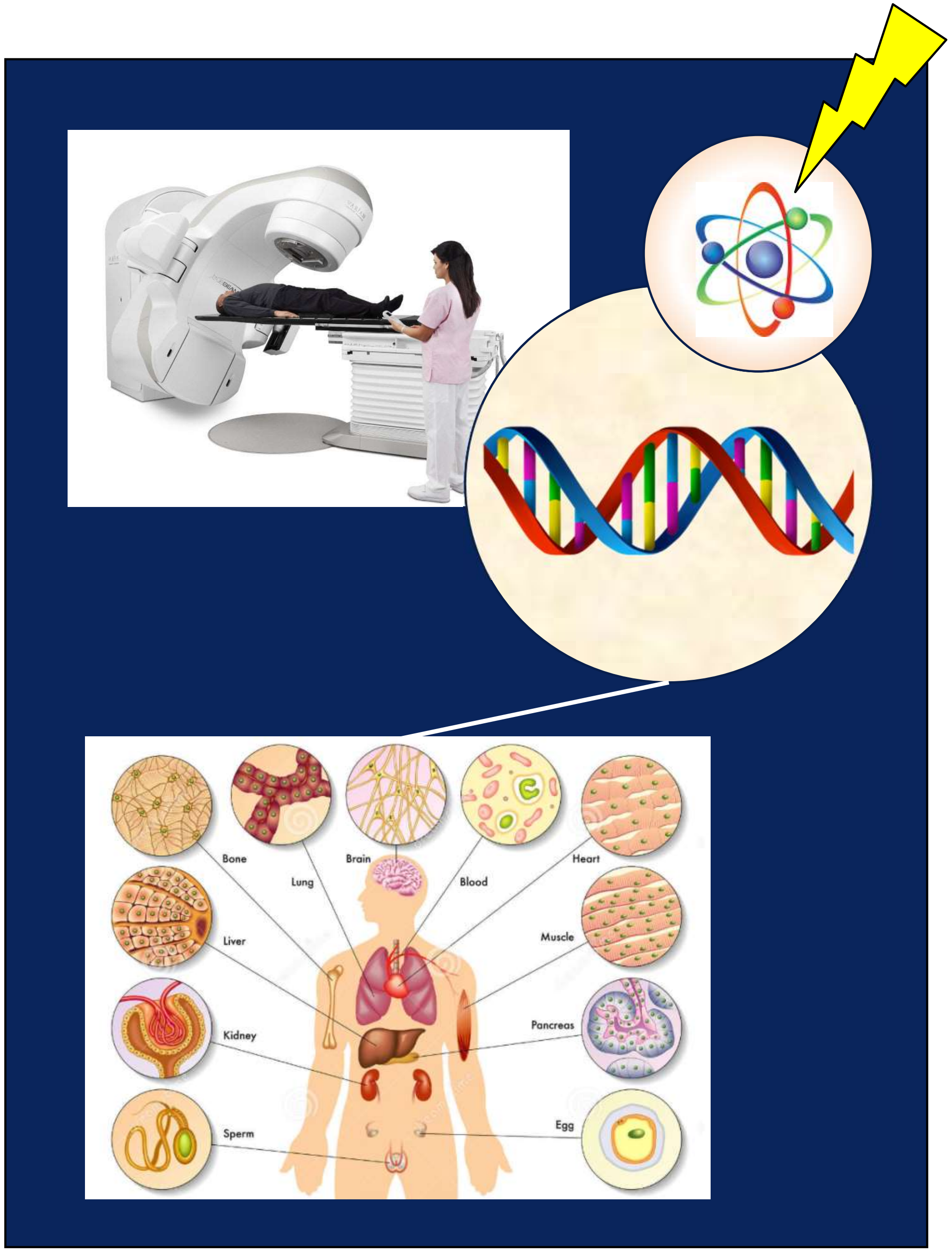
- Radiotherapy is used alone or in combination with surgery and/or chemotherapy in about **50% of the cancer treatments**

- Contribution towards cure by the major cancer treatment modalities:
  - 49% are cured by surgery
  - **40% by radiotherapy**
  - 11% by chemotherapy

Radiobiology and Radiotherapy

What happens when living matter is exposed to ionizing radiation?

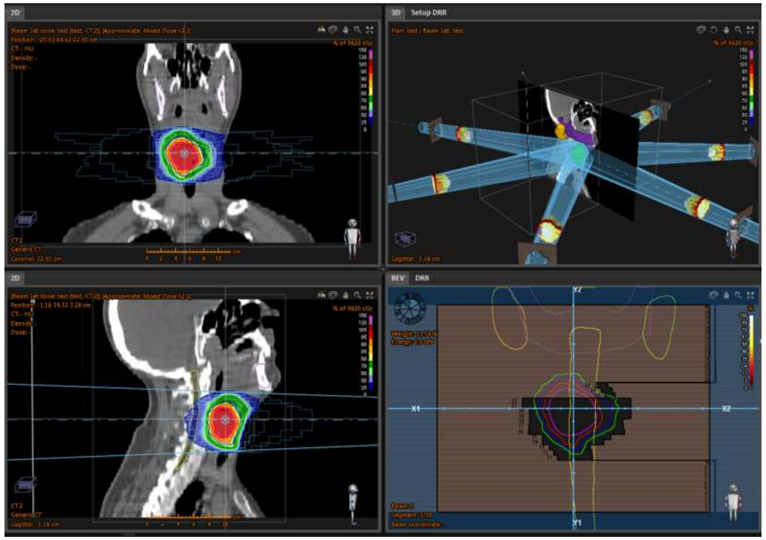
- Physical interaction between radiation and the atoms or molecules in the matter
- Possible biological damage to cell functions could follow
- At the tissue level the effects of radiation are caused by cellular depletion



RT treatment planning

- The aim of radiation therapy is to eradicate the tumour while sparing the normal tissue as much as possible

  - ➢ To deliver the prescribed dose to the targets while the doses to the OARs and the normal tissue do not exceed the tolerance levels



RT treatment planning

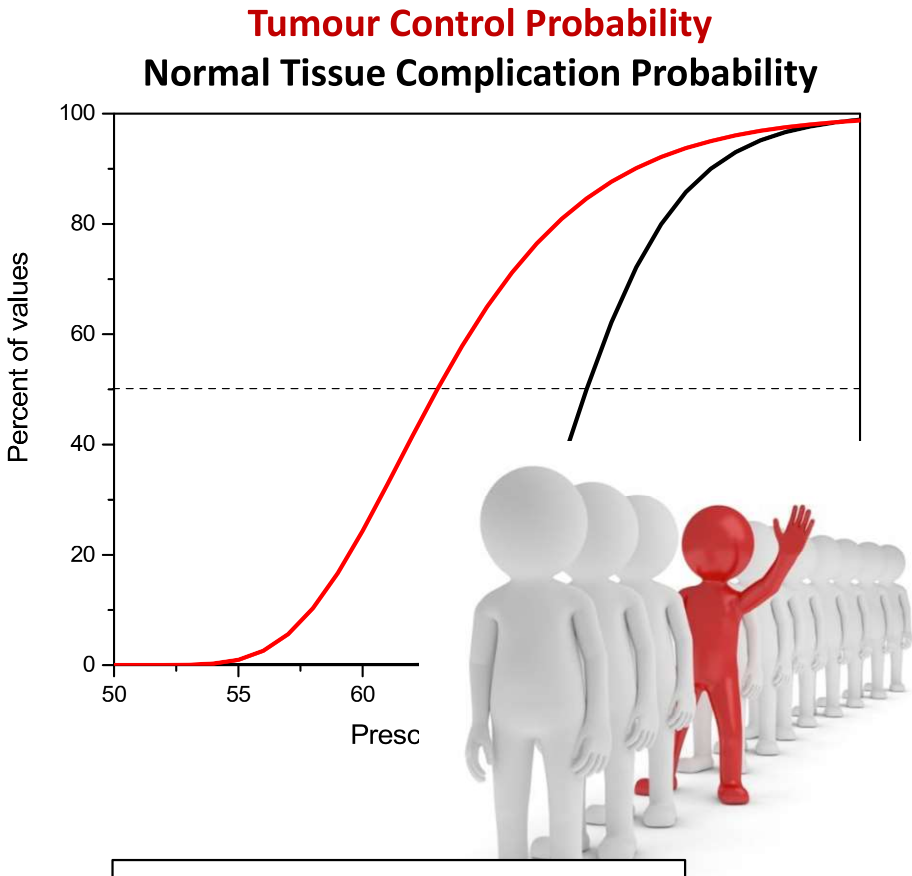
- The aim of radiation therapy is to eradicate the tumour while sparing the normal tissue as much as possible

  - ➢ To deliver the prescribed dose to the targets while the doses to the OARs and the normal tissue do not exceed the tolerance levels

  - ➢ To maximise the TCP while the NTCP is minimised

  - ➢ Generic curves derived from a population of patients

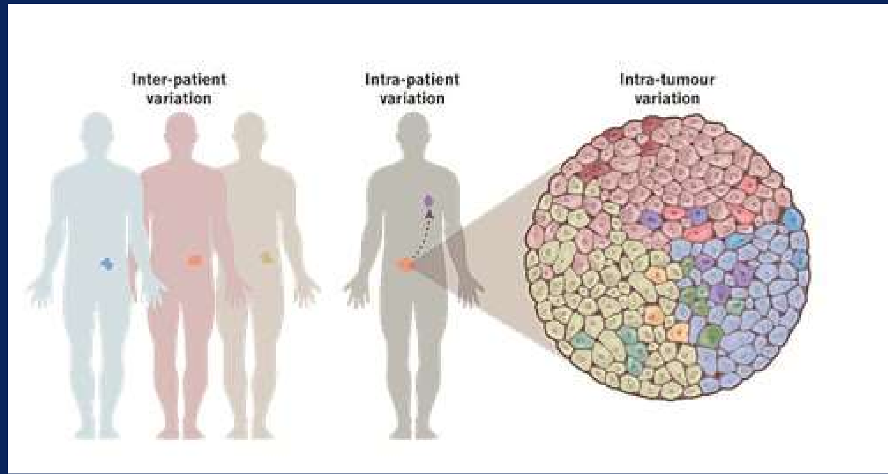
  - ➢ ***Where is our individual patient?***



There is a need for treatment individualisation!

Biological heterogeneity of tumour tissue

- **Cancer heterogeneity** may occur at multiple levels
  - Inter/intra patient variation



- Evidence is accumulating that a major cause of ***clinically observed radiation resistance*** lies in the ***biological heterogenity of the tumour***

Personalized molecular fingerprint

Meaningful radiobiological targets

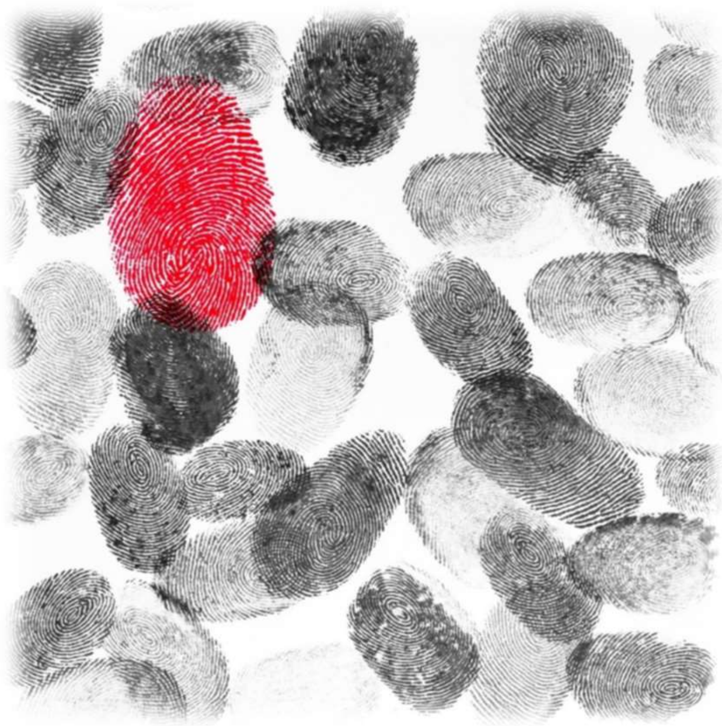
Functional imaging

Targeting radiation resistant sub-volumes of the tumour

Dose painting

Increasing local control

PERSONALIZED IMAGE-BASED MOLECULAR FINGERPRINT



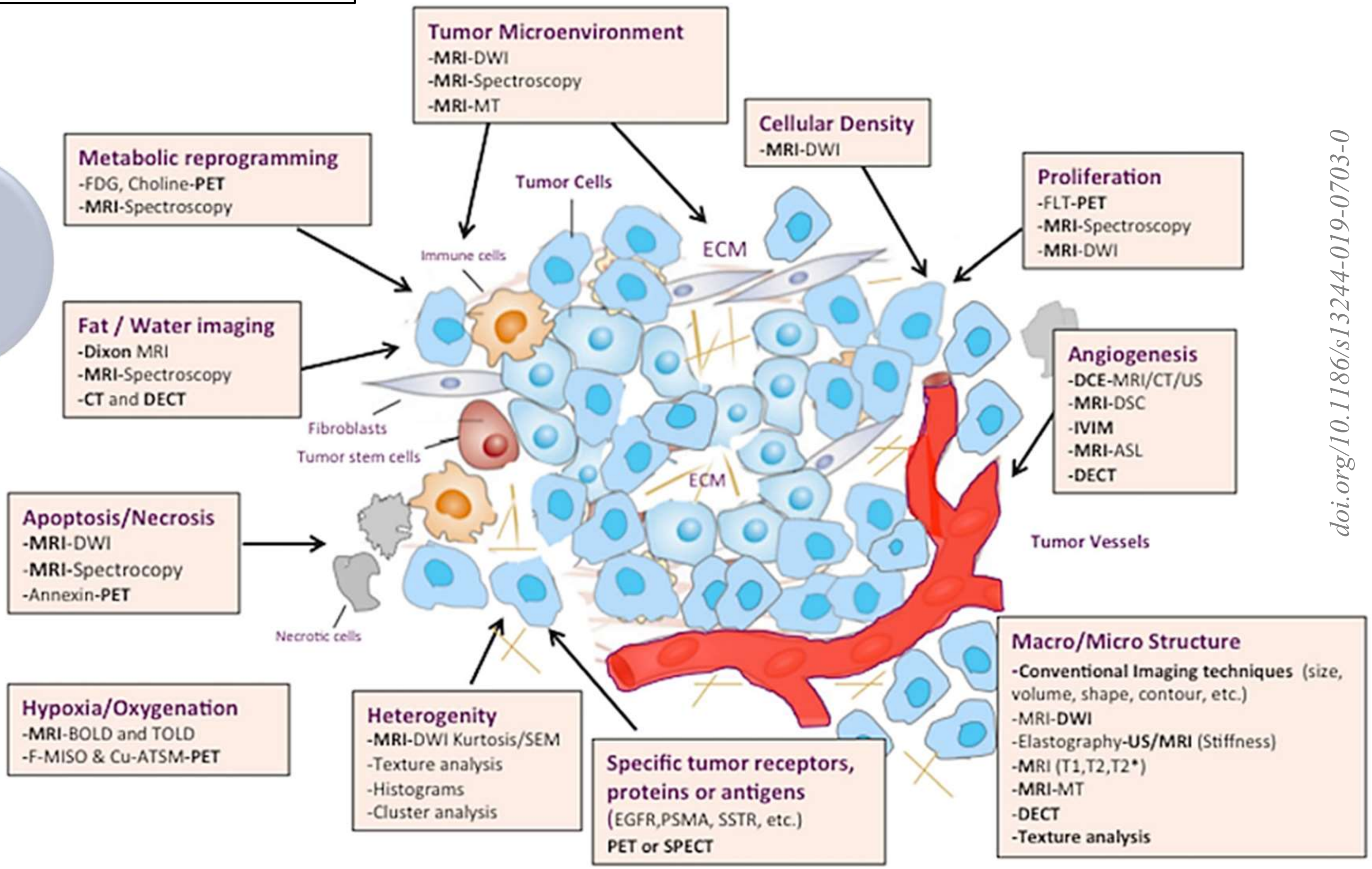
Individualised RT - Era of Precision Medicine

Functional imaging techniques such as
Positron Emission Tomography (PET)
Magnetic Resonance Imaging (MRI)
allow tumour characterization ***in vivo*** and
non-invasively, before and **during RT**

PET

MRI

US
SPECT
…



doi.org/10.1186/s13244-019-0703-0

RT planning based on PET imaging

Hypothesis 1

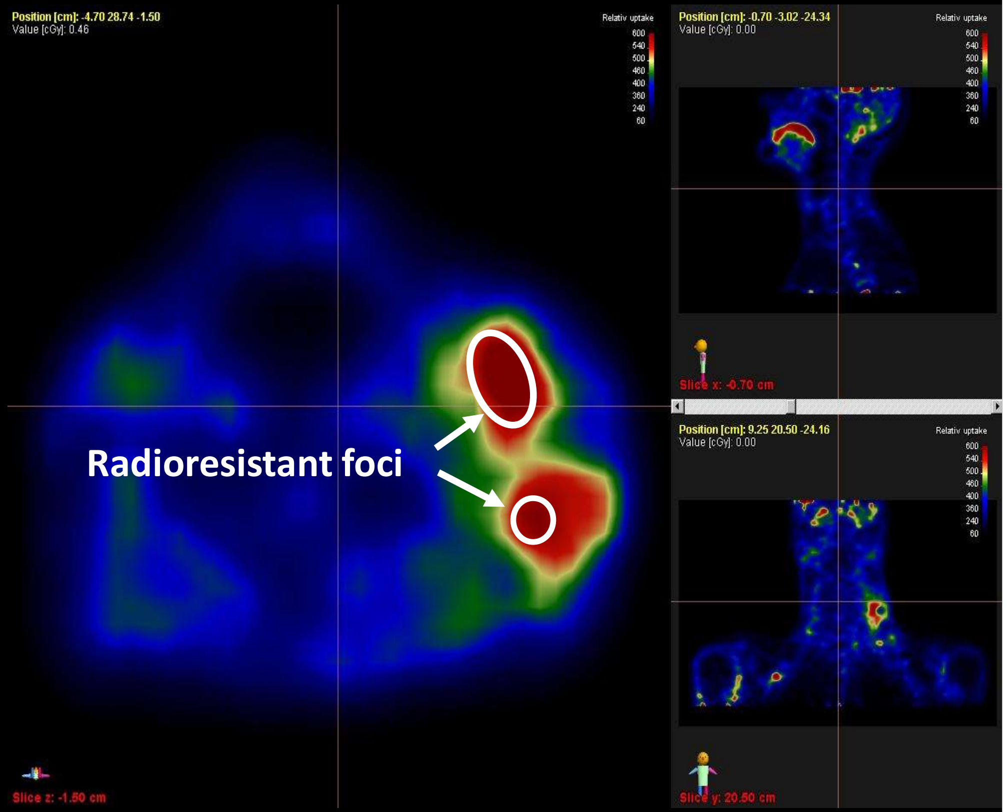
Local recurrence is related to resistant foci not eradicated by the currently prescribed and delivered uniform doses.

Hypothesis 2

PET imaging allows mapping the target in terms of radioresistance.

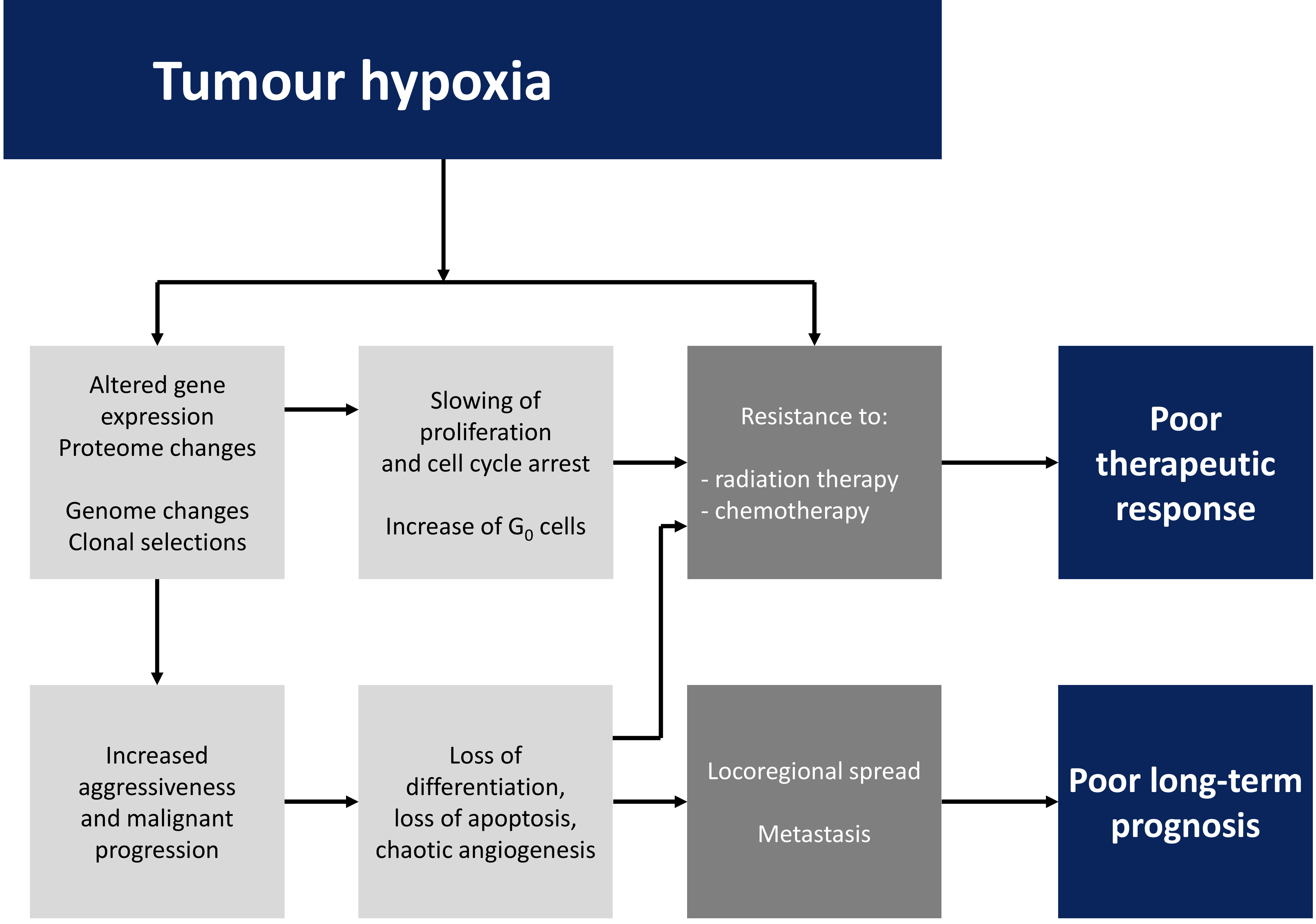
Hypothesis 3

Progress in treatment planning and delivery allows non-homogeneous target irradiation while the irradiation of the normal tissue and OARs is kept below the tolerance levels.

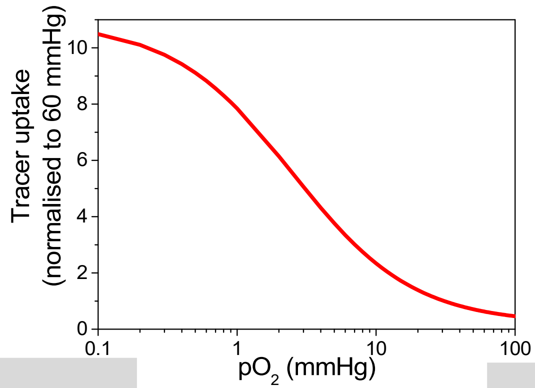


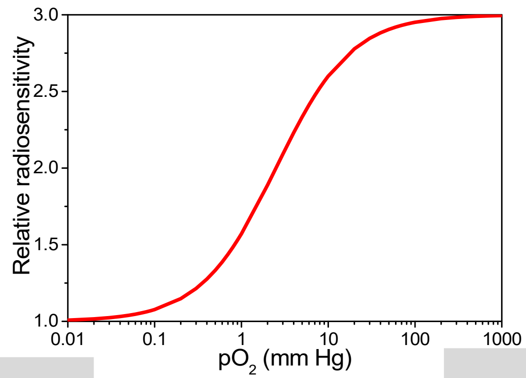
Radioresistant foci:

- **Tumour hypoxia**
- **High density of clonogenic cells**
- **Highly proliferating cells**


Tumour hypoxia
Altered gene expression
Proteome changes
Genome changes
Clonal selections
Slowing of proliferation
and cell cycle arrest
Increase of G_0 cells
Resistance to:
- radiation therapy
- chemotherapy
Poor therapeutic response
Increased aggressiveness and malignant progression
Loss of differentiation,
loss of apoptosis,
chaotic angiogenesis
Locoregional spread
Metastasis
Poor long-term prognosis

RT planning accounting for hypoxia





PET IMAGE → **TUMOUR HYPOXIA MAP** → **DOSE ESCALATION MAP**

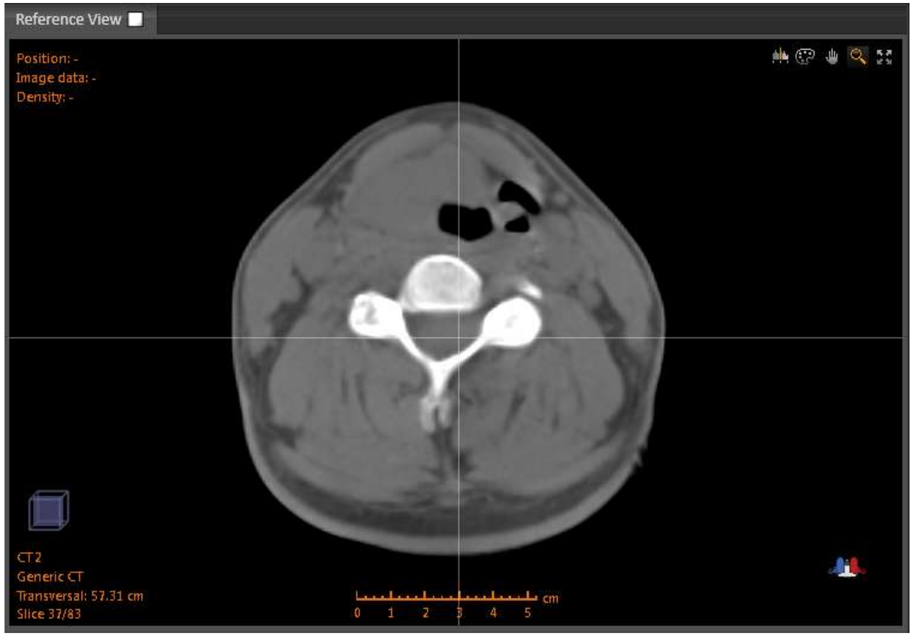
Prescription algorithm* → **OPTIMISED DOSE DISTRIBUTION**

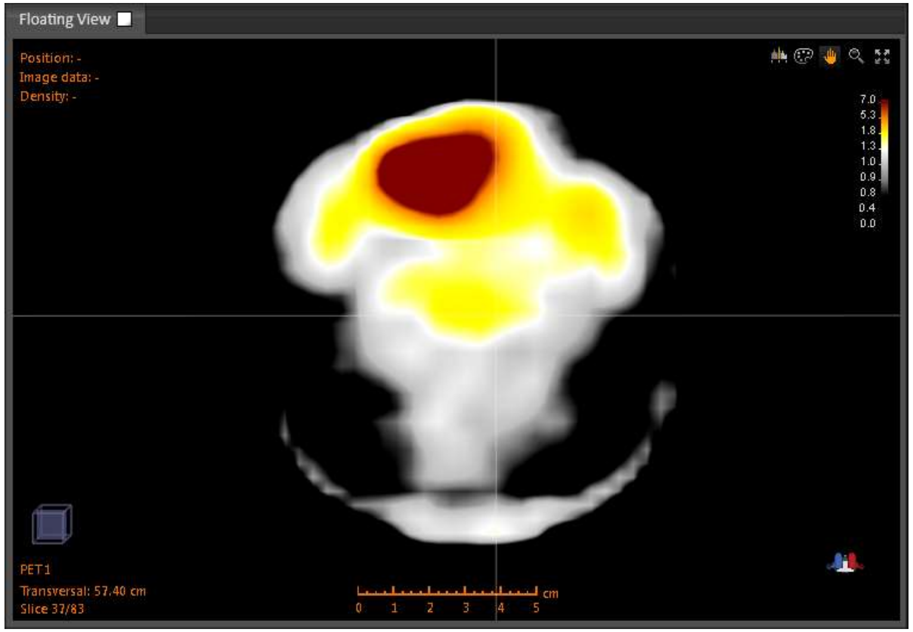
RT planning accounting for hypoxia

Locally advanced HNSCC

Age	Gender	Clinical T classification	Clinical N classification
48	M	3	0

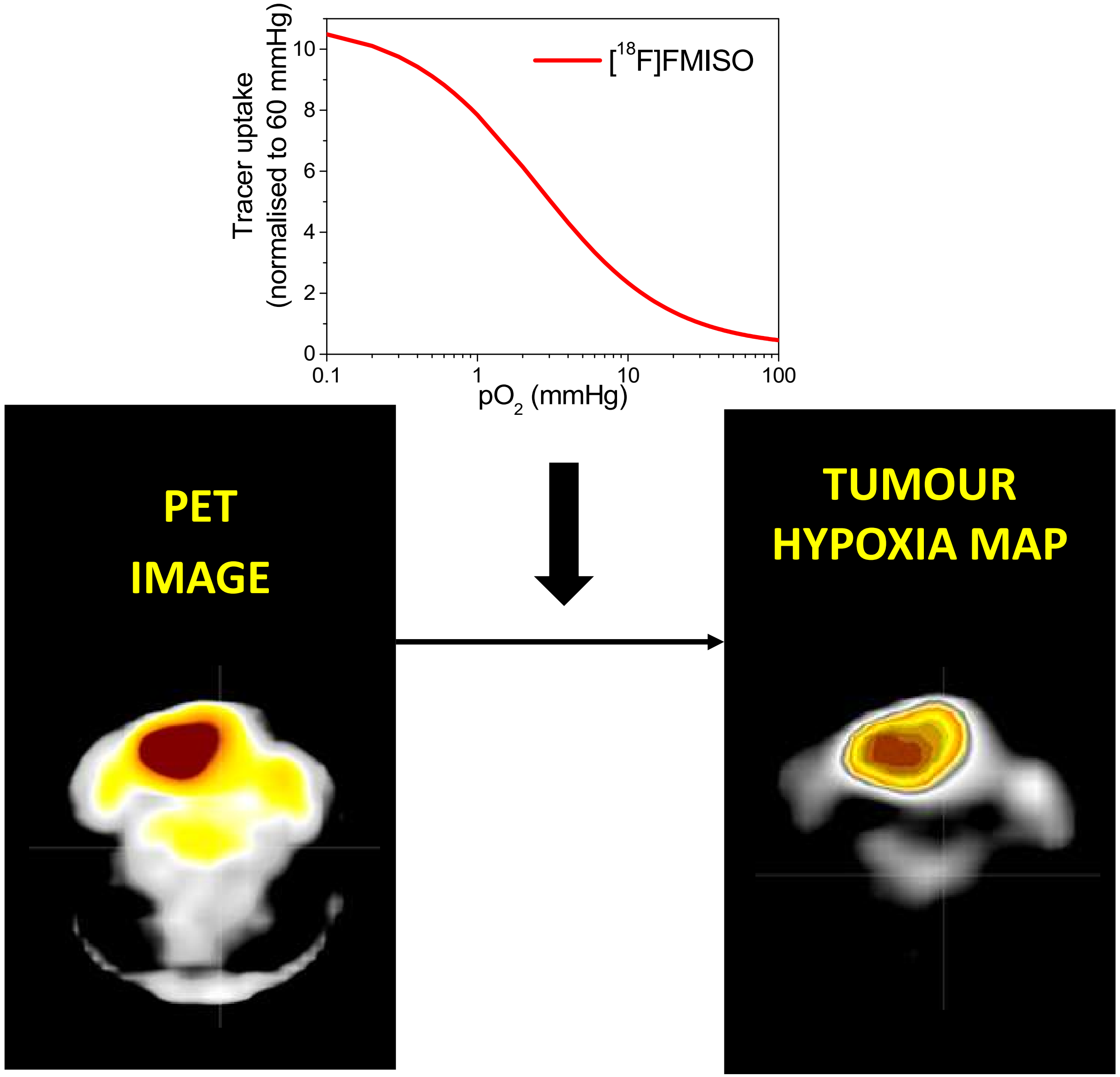
Pre-treatment CT and FMISO-PET/CT





RT planning accounting for hypoxia

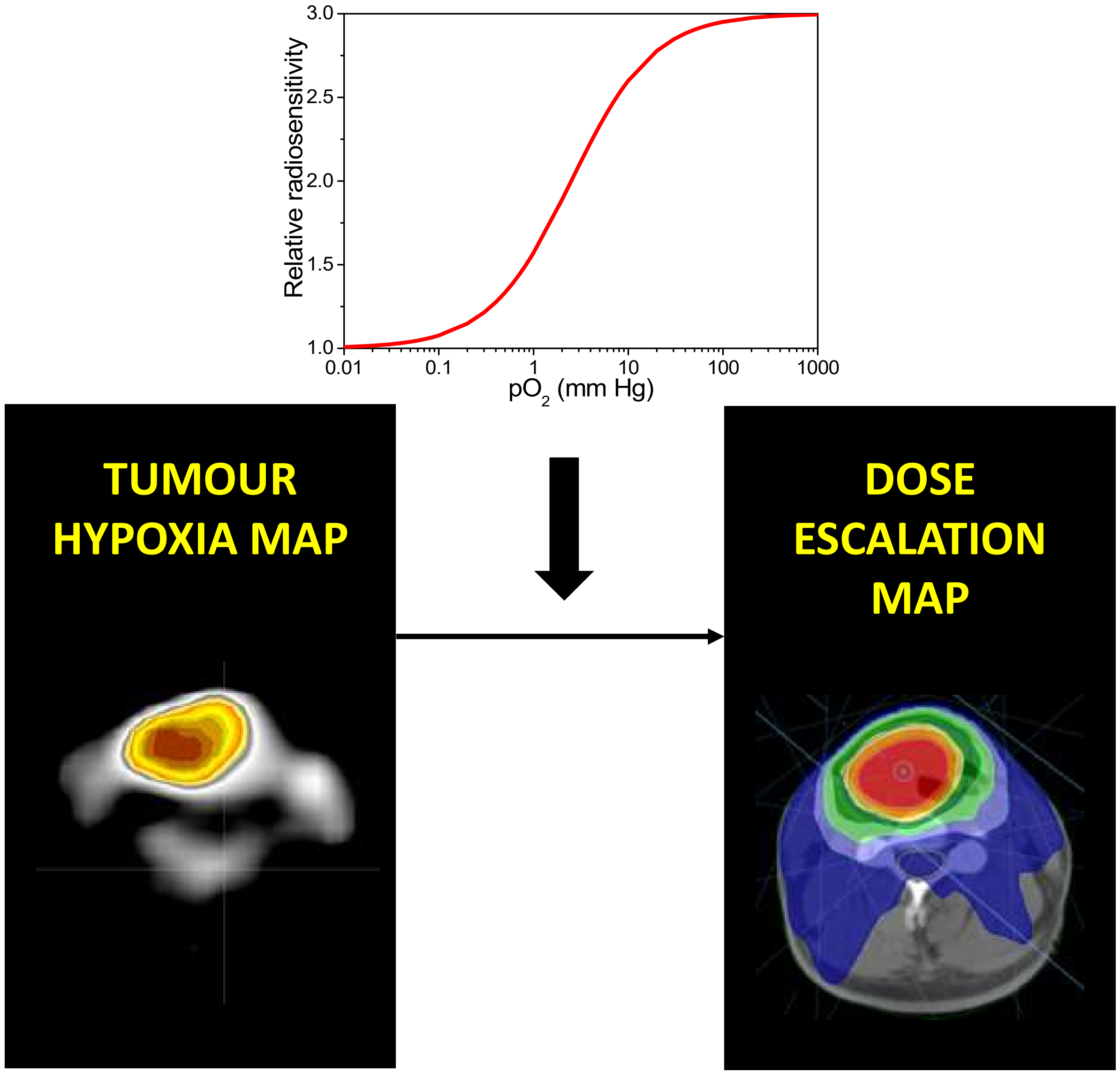
- Set the reference value for tracer uptake in the well oxygenated tissue
- Scale the values in the PET image based on the tracer uptake curve
- Set the threshold for the hypoxic target (10 mmHg) and delineate the Hypoxic Target Volume (HTV)



RT planning accounting for hypoxia

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

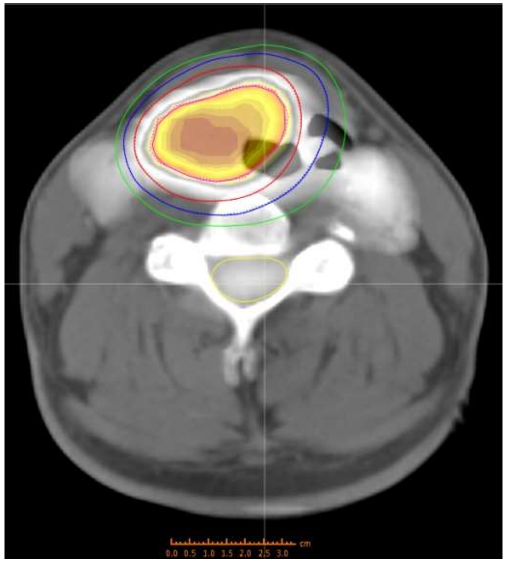
- Dose Escalation Map as function of tracer uptake shows the non-linearity of the relationship between the two quantities.



RT planning accounting for hypoxia

Target physical objectives for 95% TCP			
PTV	CTV	GTV	HTV
Minimum dose 60 Gy	Minimum dose 66 Gy	Minimum dose 73 Gy	Minimum dose 98 Gy

pO_2 registered on CT

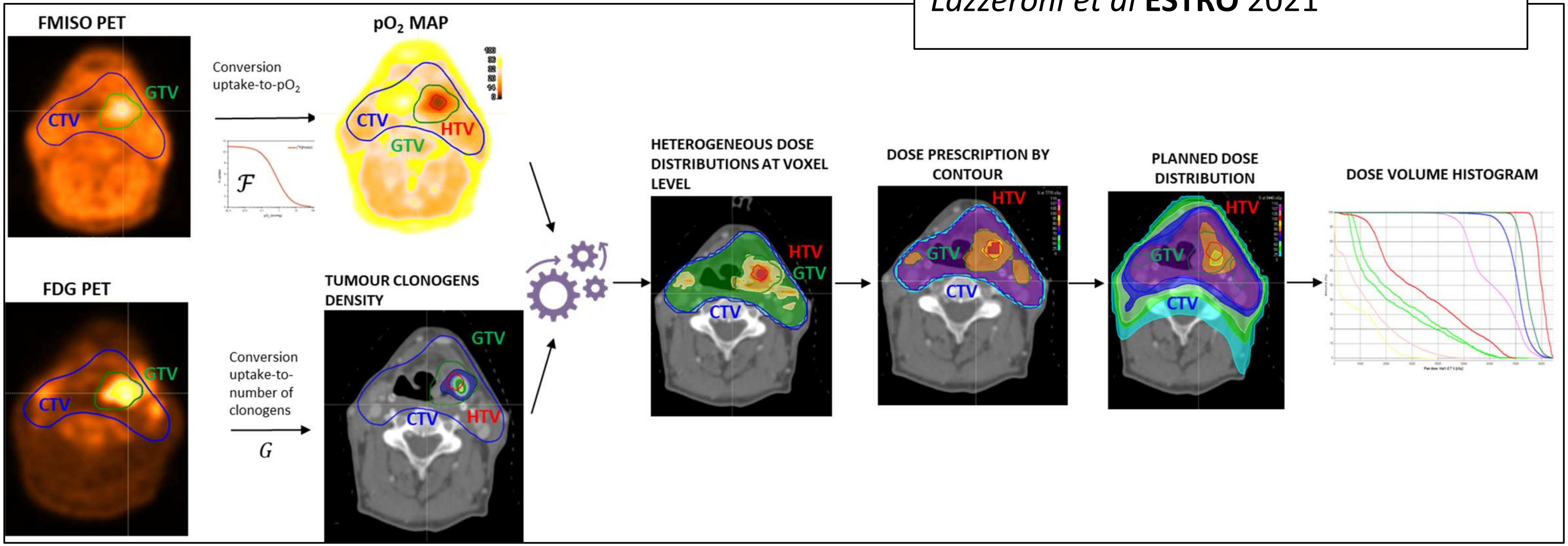


OARs constraints				
Spinal cord	Mandibula	Left parotid gland	Right parotid gland	Non-specific normal tissue
Maximum dose 38 Gy	Maximum DVH 30 Gy to 1% volume	Maximum DVH 38 Gy to 5% volume	Maximum DVH 38 Gy to 5% volume	Maximum DVH 50 Gy to 1.5% volume

RT planning accounting for hypoxia and N_0

Synergistic use of combined FDG and FMISO PET/CT imaging for personalized dose prescription

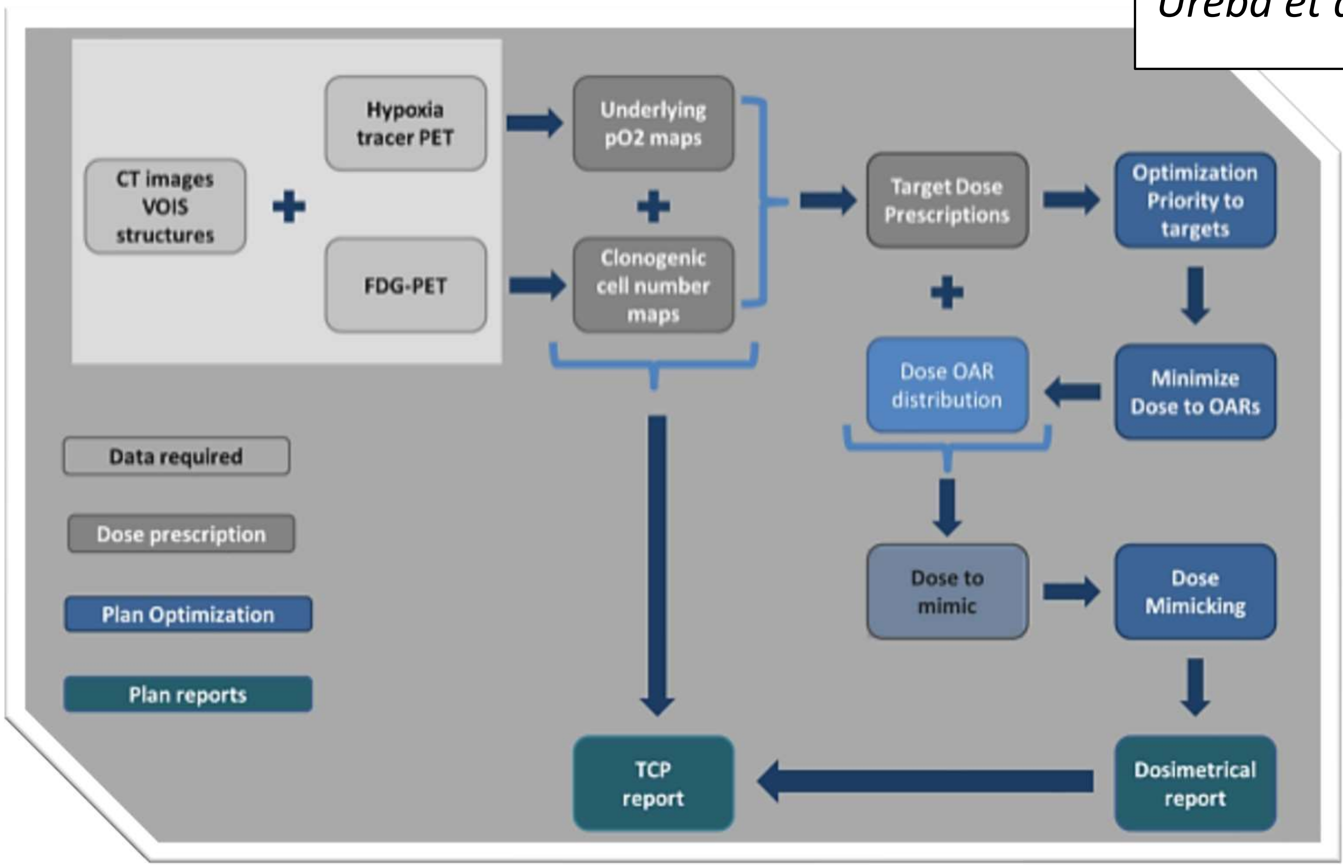
Lazzeroni et al **ESTRO** 2021



RT planning accounting for hypoxia and N_0

Automated treatment planning using dose mimicking for biologically guided dose prescription

Ureba et al **ESTRO** 2022



Challenges and limitations

IMAGING

- Choice of the tracer
- Method for quantification of tracer uptake
- Optimal imaging time

- Spatial resolution
- Partial volume effects
- Image reproducibility

- Temporal artefacts
- Movement artefacts

- *etc.*

RADIOBIOLOGY

- Definition of the BTV

- Choice of the model for interpreting the tracer uptake

- Choice of dose prescription function or level

- Accounting for the dynamics of the system

- *etc.*

TREATMENT DELIVERY

- Need for delivering highly heterogeneous dose distributions
- High gradients in the dose
- Penumbra issues

- Need for re-planning or adaptive treatment

- *etc.*

Is it time for a paradigm shift?

Move the focus from dose painting approaches to
personalised adapted radiation therapy
based on tumour responsiveness assessed with functional imaging

Adaptive strategies to account for functional changes

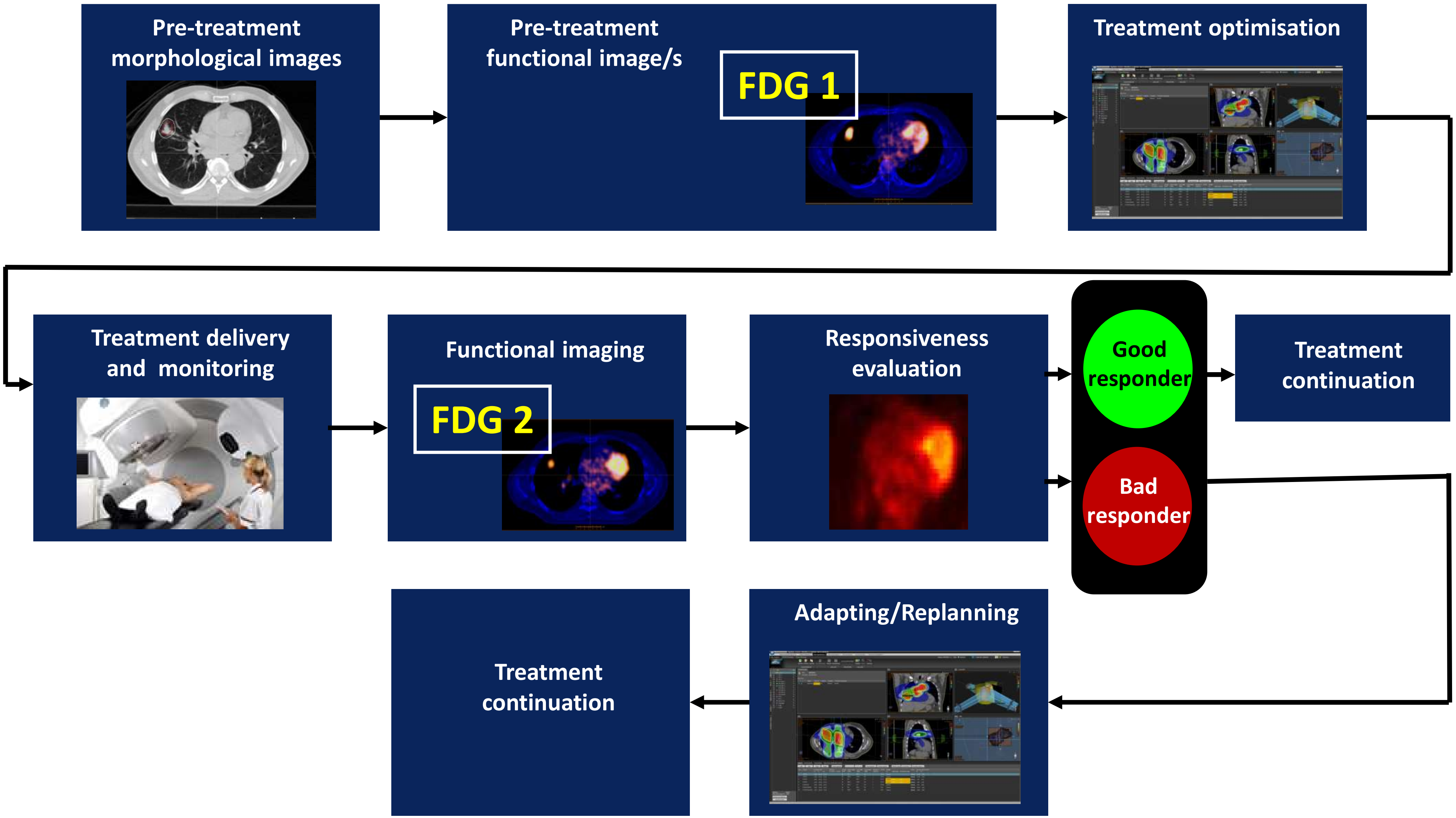
How?

Where?

When?

Who?

Who?

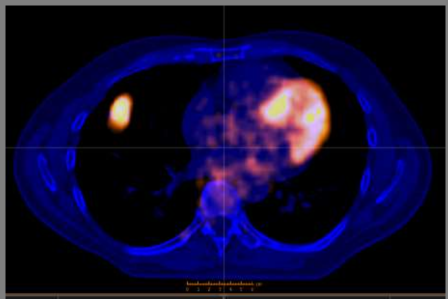


Pre-treatment morphological images
Pre-treatment functional image/s
FDG 1
Treatment optimisation
Treatment delivery and monitoring
Functional imaging
FDG 2
Responsiveness evaluation
Good responder
Bad responder
Treatment continuation
Adapting/Replanning
Treatment continuation

How?

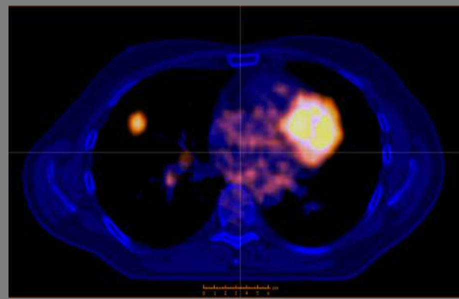
t=-1 | t=0 | t=8

CT1 + PET1

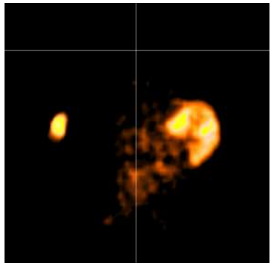


Delivered dose

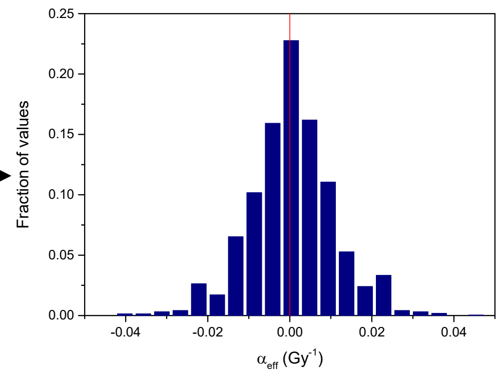
CT2 + PET2



Response assessment

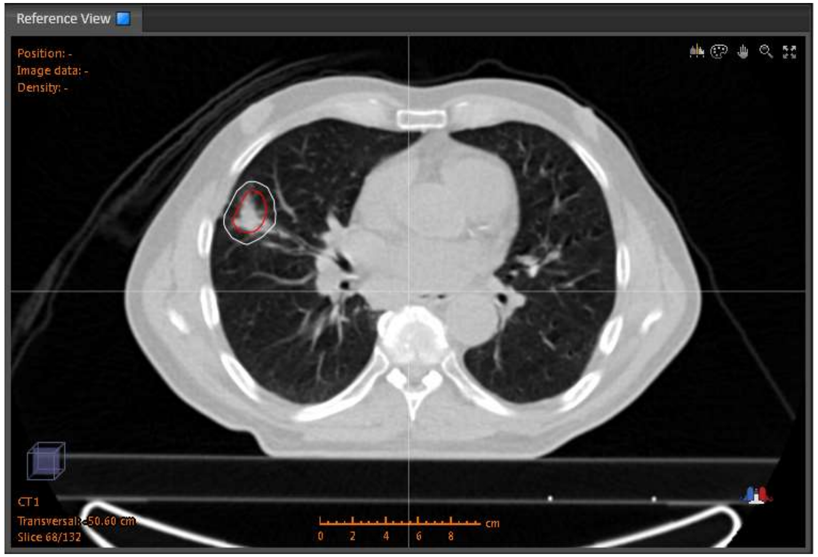


$$\alpha_{eff} = \frac{\ln\left(PET_1 / PET_2 \right)}{nd\left[1 + d / (\alpha/\beta) \right]}$$



Effective radiosensitivity

Response assessment

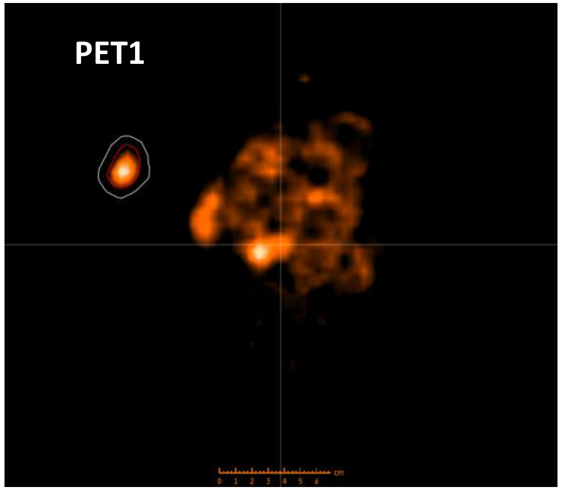


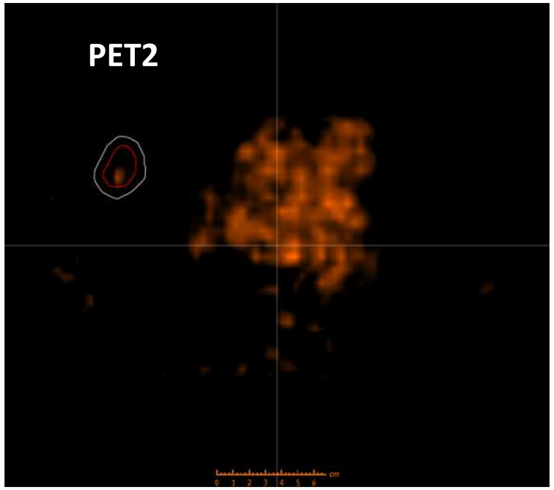
Patient 1

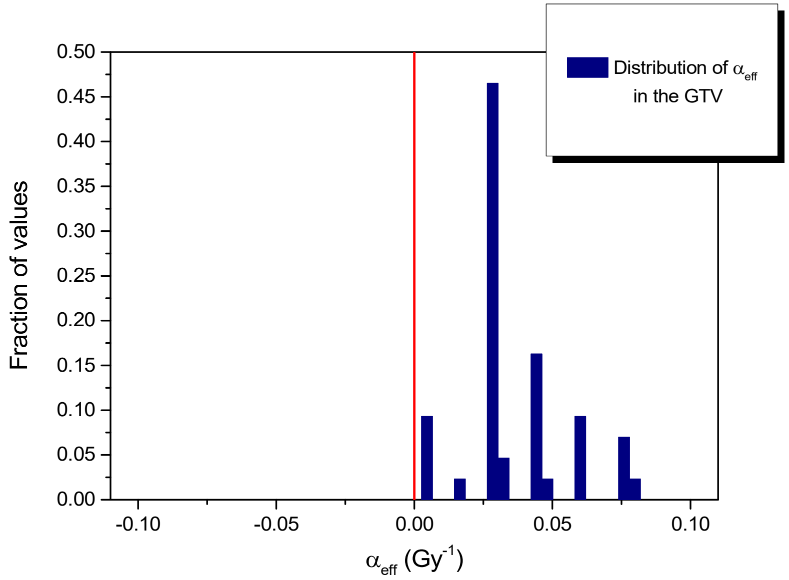
NSCLC T1N3M0 IIIb
RT+ Sequential chemo

1.5Gy*13 by the time of PET2

OS@2Y 1 (31.3 months in follow-up)







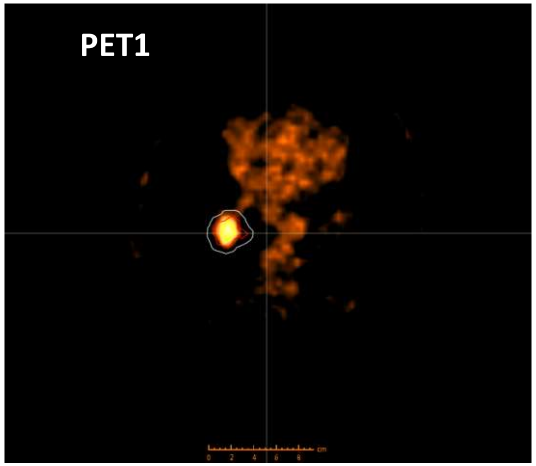
Response assessment

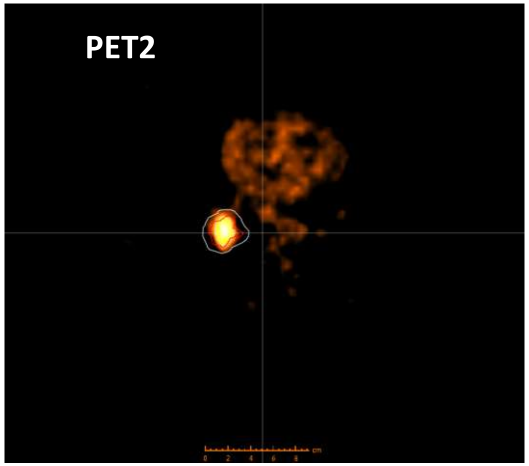
Patient 2

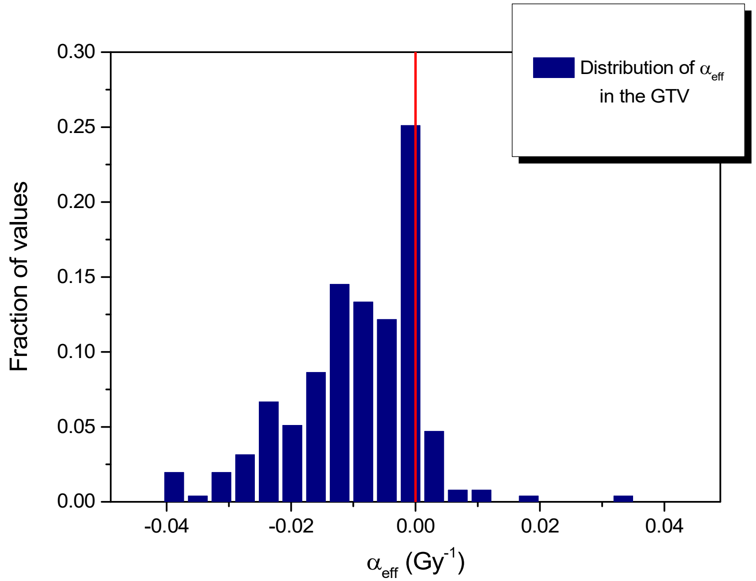
NSCLC T2N2M0 IIIa
RT+ Sequential chemo

1.8Gy*13 by the time of PET2

OS@2Y 0 (15.9 months in follow-up)







Response assessment

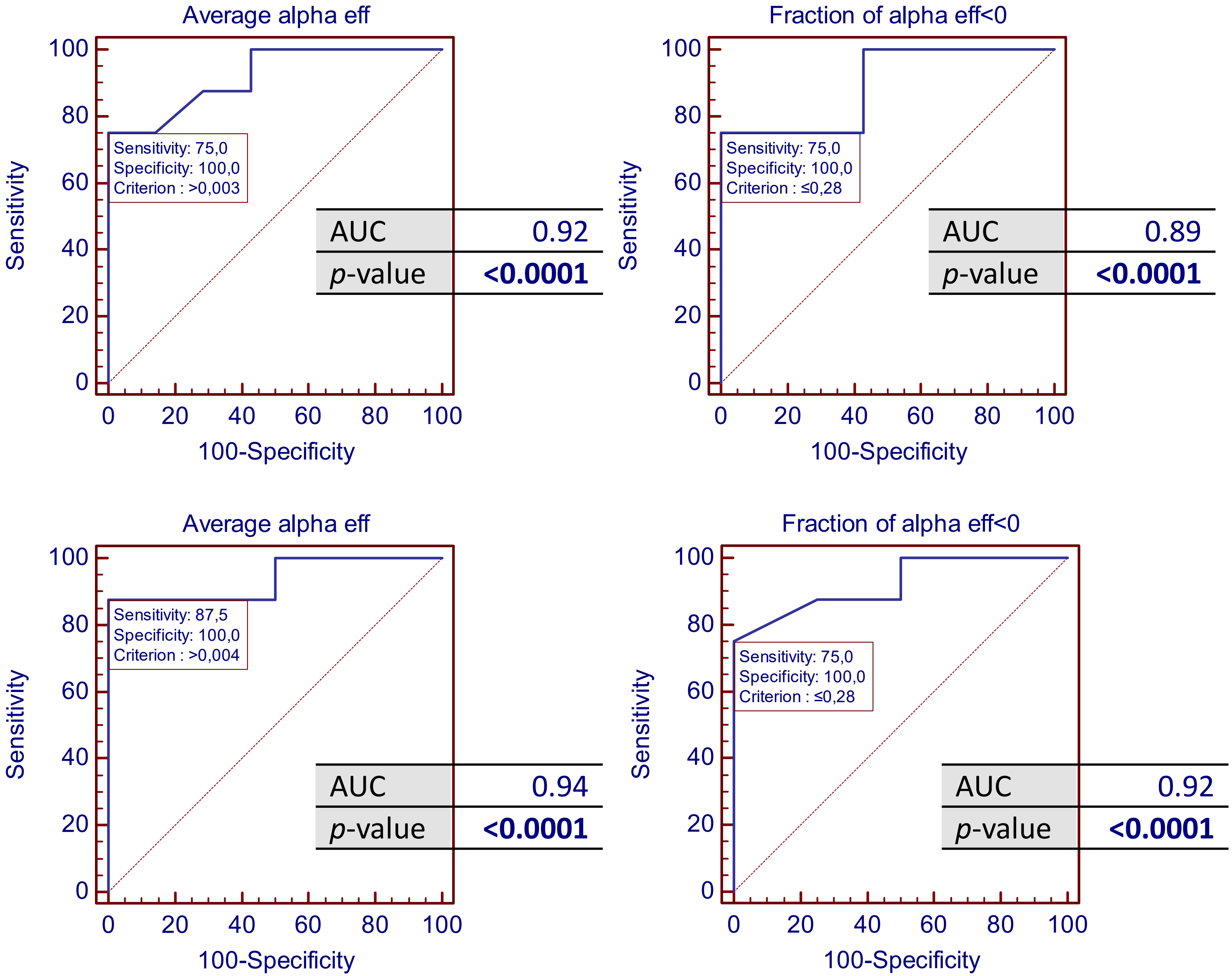
RT + sequential chemo

How well does the effective radiosensitivity predict OS?

Example:

Effective radiosensitivity analysis for NSCLC patients

RT + concurrent chemo



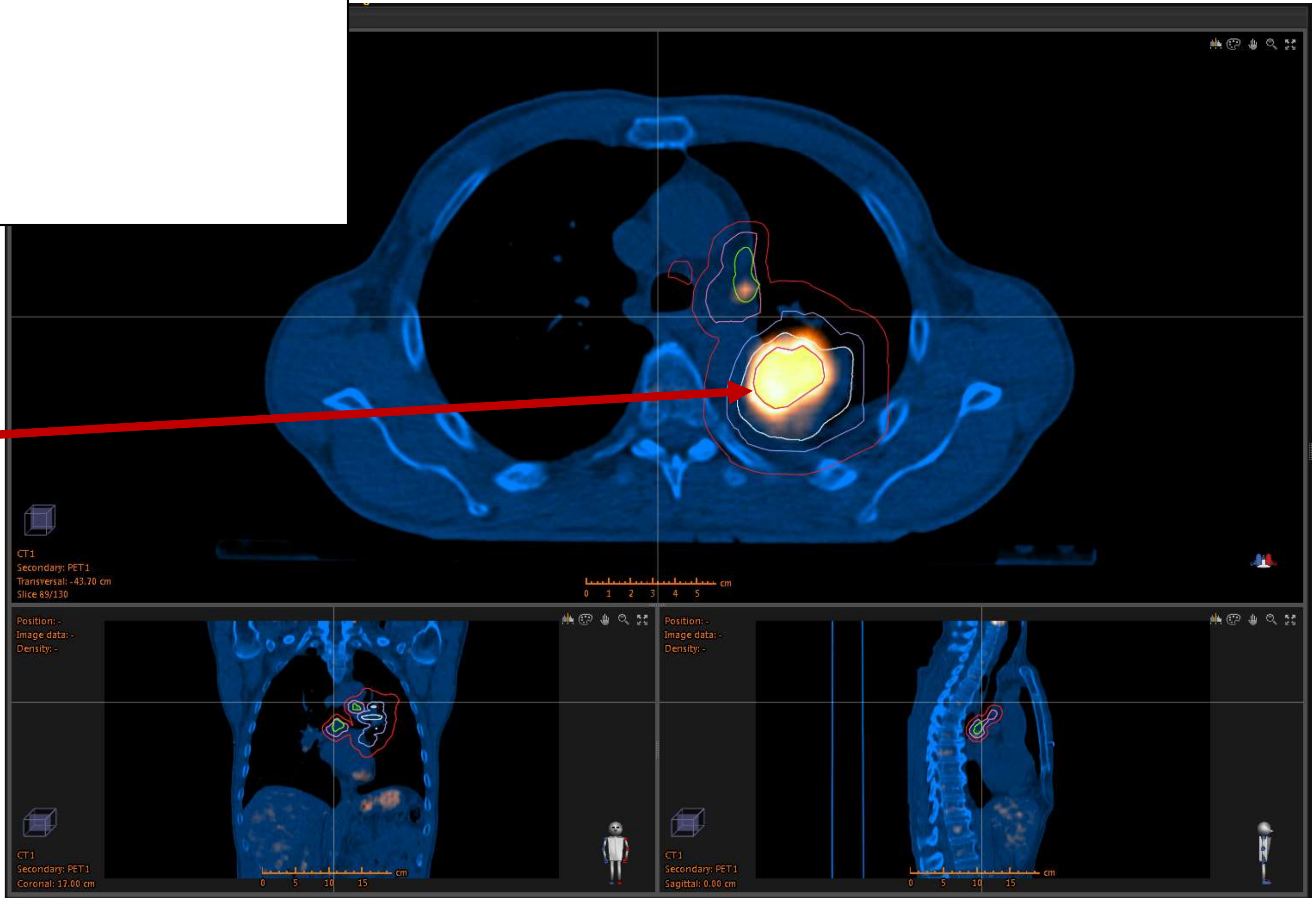
Where?

Where shall we look for the response?

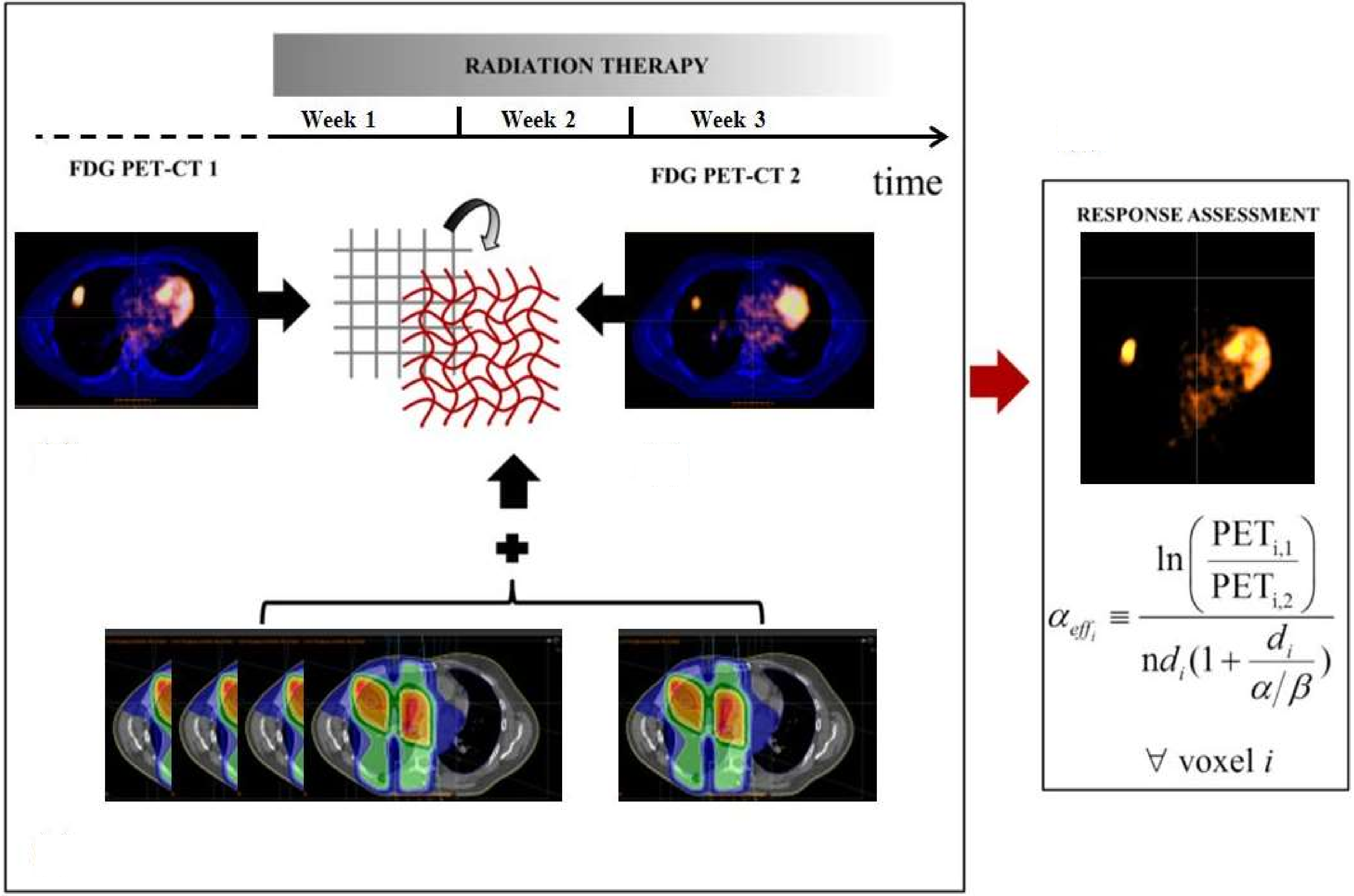
GTV_{prim} and/or GTV_{lymph}?

CTV_{prim} and/or CTV_{lymph}?

***Answer:* GTV_{prim}**



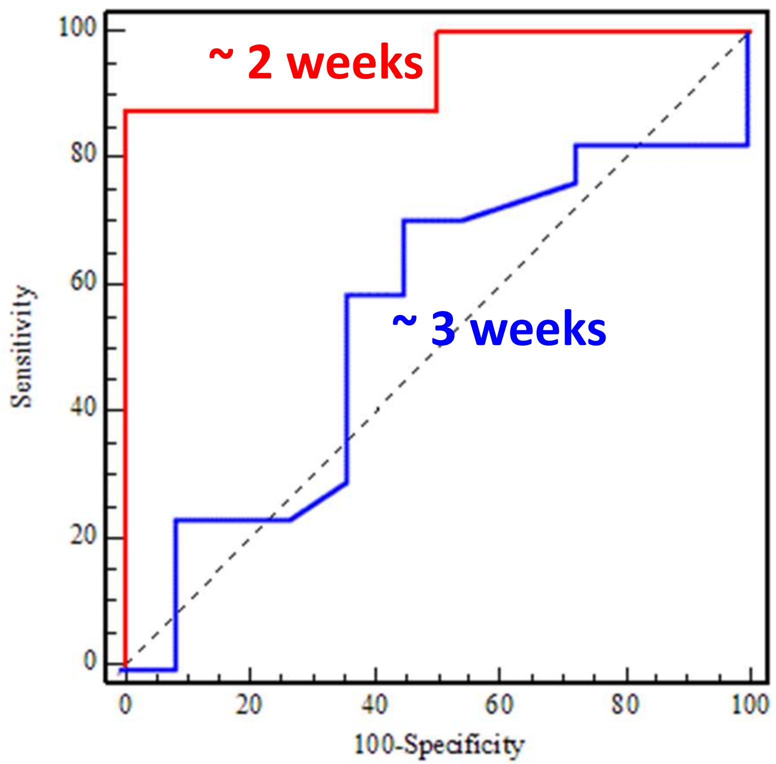
When?



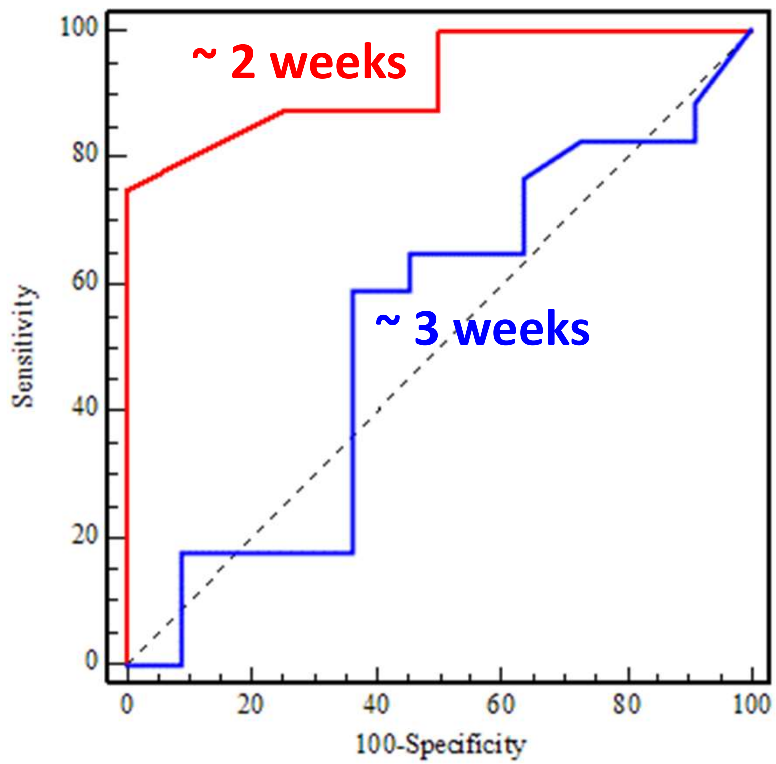
RADIATION THERAPY
Week 1
Week 2
Week 3
FDG PET-CT 1
FDG PET-CT 2
time
RESPONSE ASSESSMENT
$$\alpha_{eff_i} \equiv \frac{\ln\left(\frac{PET_{i,1}}{PET_{i,2}}\right)}{nd_i(1+\frac{d_i}{\alpha/\beta})}$$
$\forall$ voxel i

When?

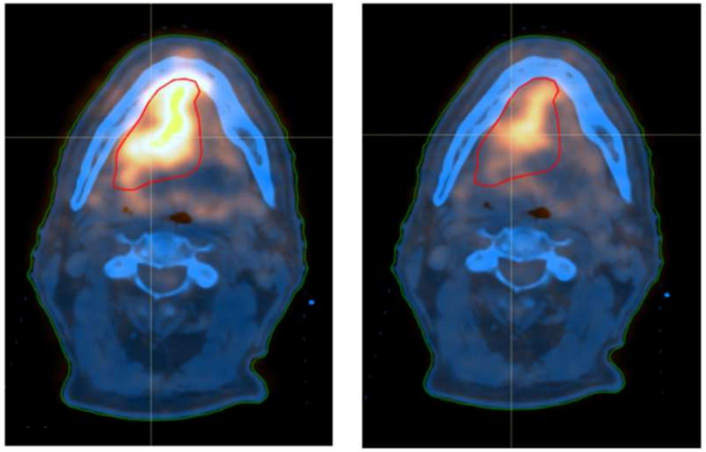
Average α_{eff} *vs* OS

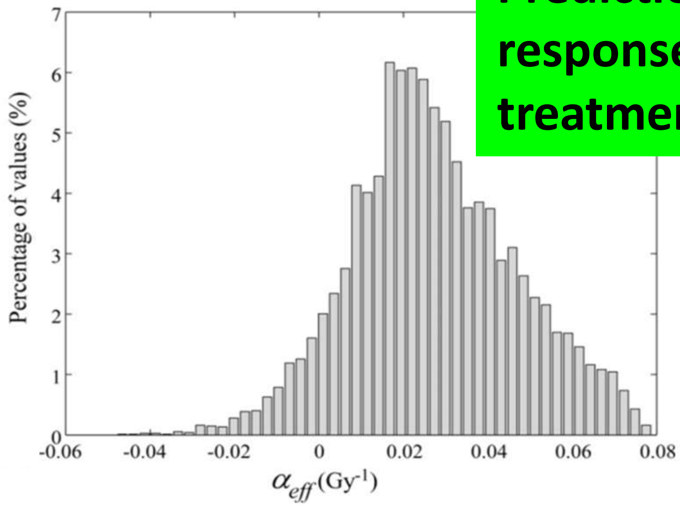


Fraction of α_{eff} <0 *vs* OS

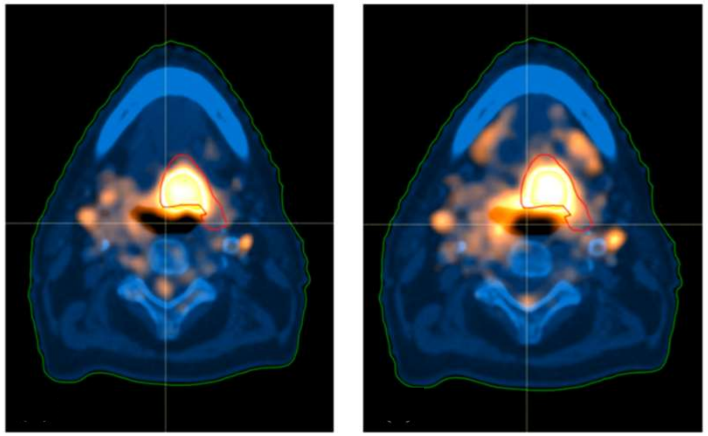


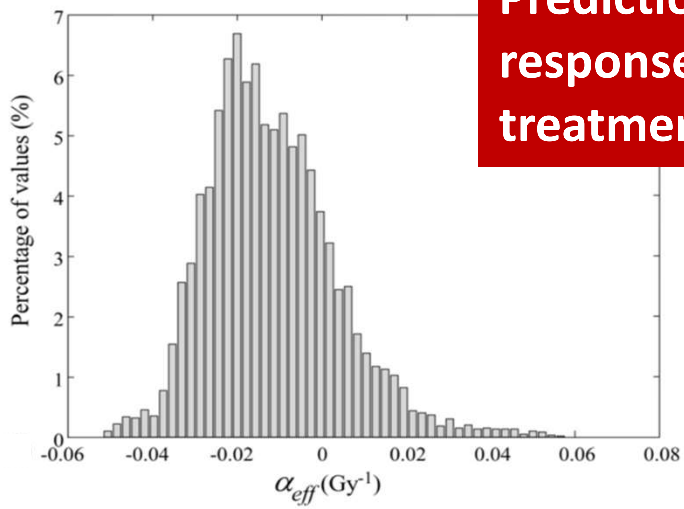
Response assessment





Prediction of good response to the treatment





Prediction of poor response to the treatment

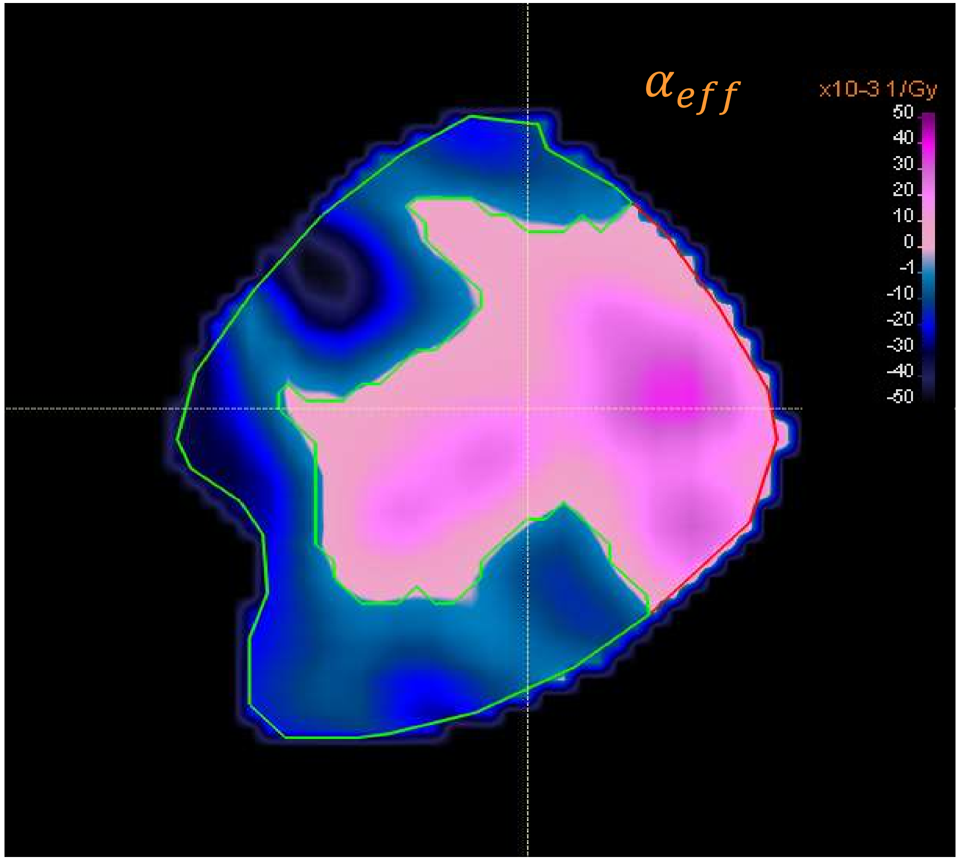
Adaptive RT for bad responders

- Effective radiosensitivity map of a selected slice of GTV_{prim}

  pink area: $\alpha_{eff} > 0$

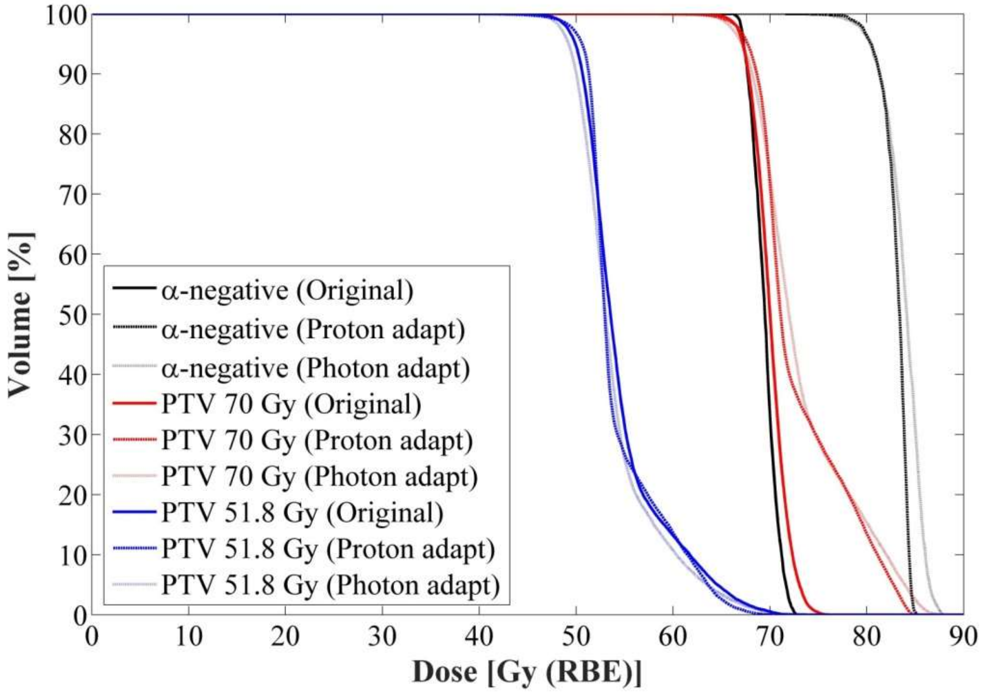
  blue area: $\alpha_{eff} < 0$

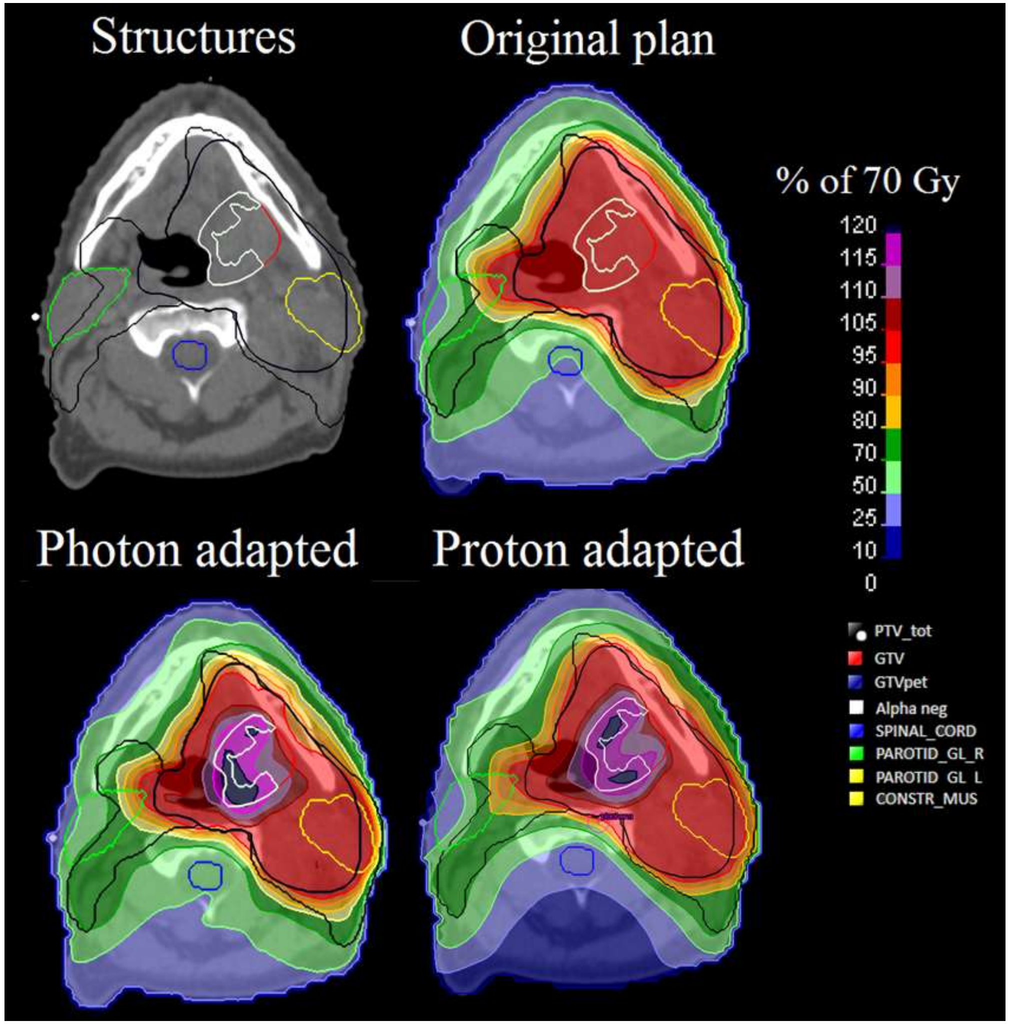
- Adapt the treatment by ***boosting the volume were α_{eff}<0***



Adaptive RT for bad responders

Original plan = 70 Gy
Boost to 84 Gy

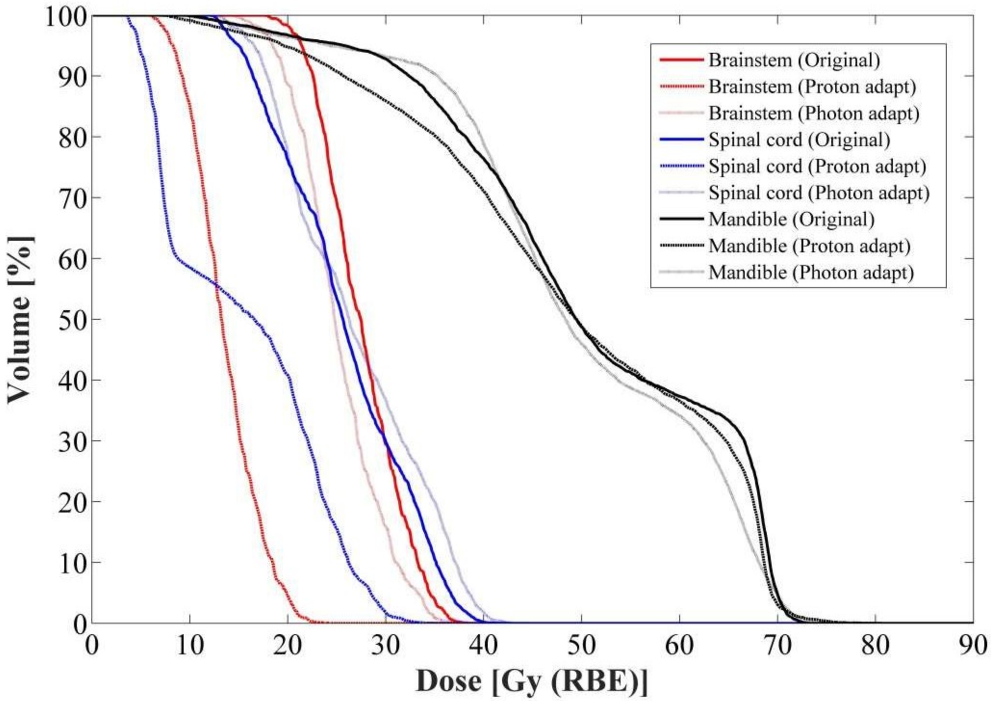


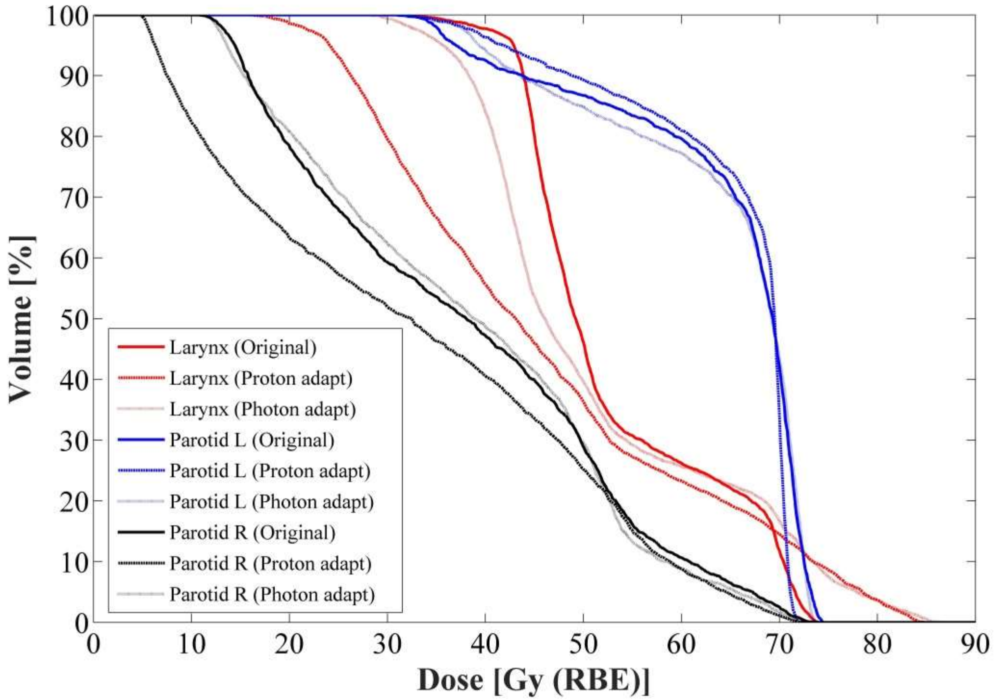


Adaptive RT

Original plan = 70 Gy
Boost to 84 Gy

OAR	NTCP (%)		
	Original plan	Adapted photon plan	Adapted proton plan
Brainstem	0	0	0
Spinal cord	0	0	0
Mandible	12	8	11
Larynx	**72**	**73**	**56**
Parotid L	97	97	97
Parotid R	**52**	**53**	**42**





Conclusions

- Functional imaging has the potential to provide a paradigm shift in treatment planning and optimisation in cancer therapy that extends well beyond target definition.

- Pre-treatment investigations, possibly combined with predictive molecular information on the intrinsic features of each patient, provide initial information on the dose levels needed to be included in the ***personalised treatment plan*** and the likely therapeutic approaches.

- Subsequent examinations early during the treatment provide information on tumour responsiveness to be used to determine the need for ***personalised treatment adaptation***.

➡ ***Individualised radiotherapy based on tumour features and treatment response is in our grasp***

Acknowledgements

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Adaptive and innovative Radiation Treatment FOR improving Cancer patients treatment outcomE

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- Wouter van Elmpt

MAASTRO

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