Investigating strategies to minimize normal tissue complications in head and neck patients treated with protons

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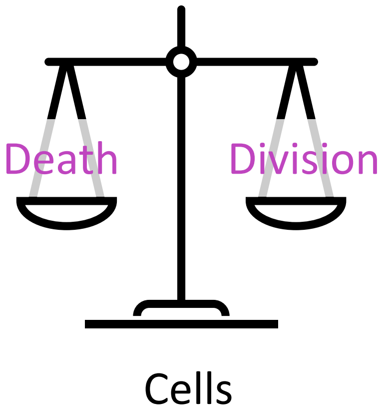
INTRODUCTION - CANCER



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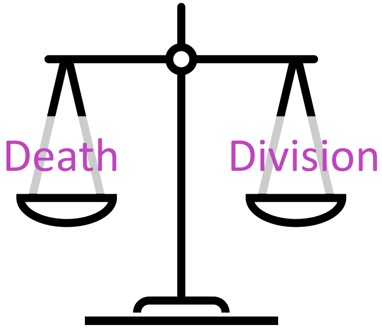
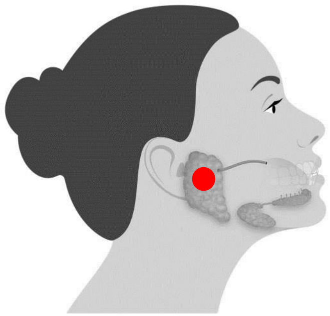


Cells



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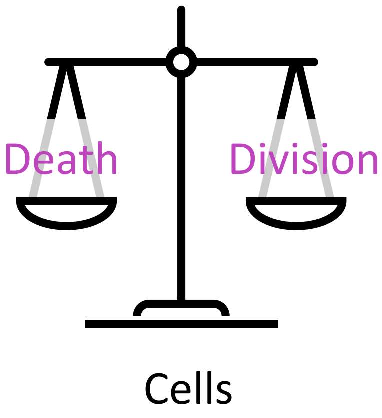
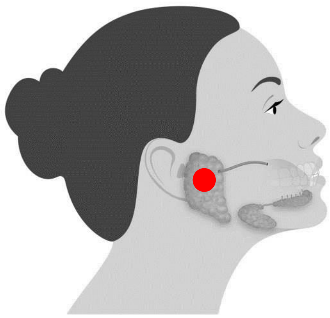
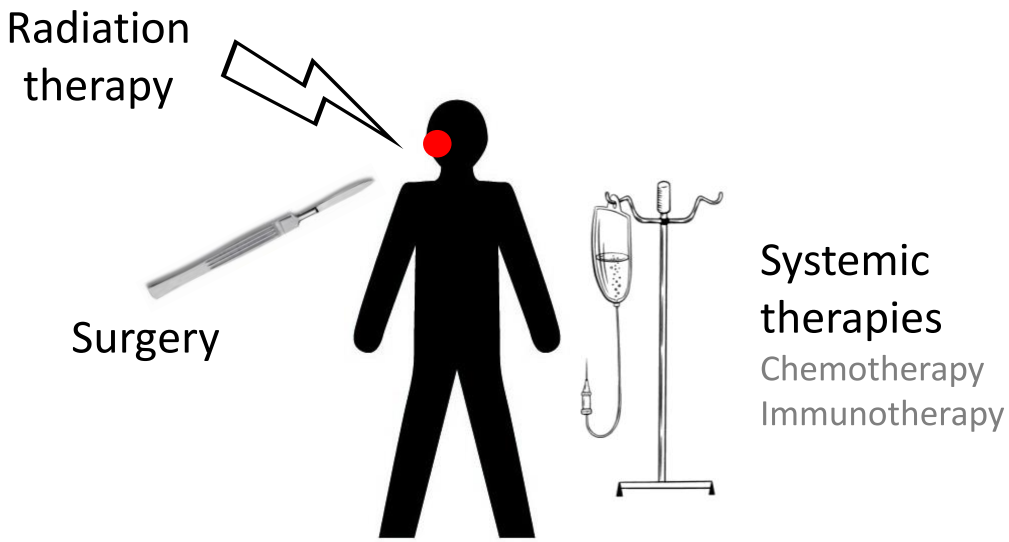
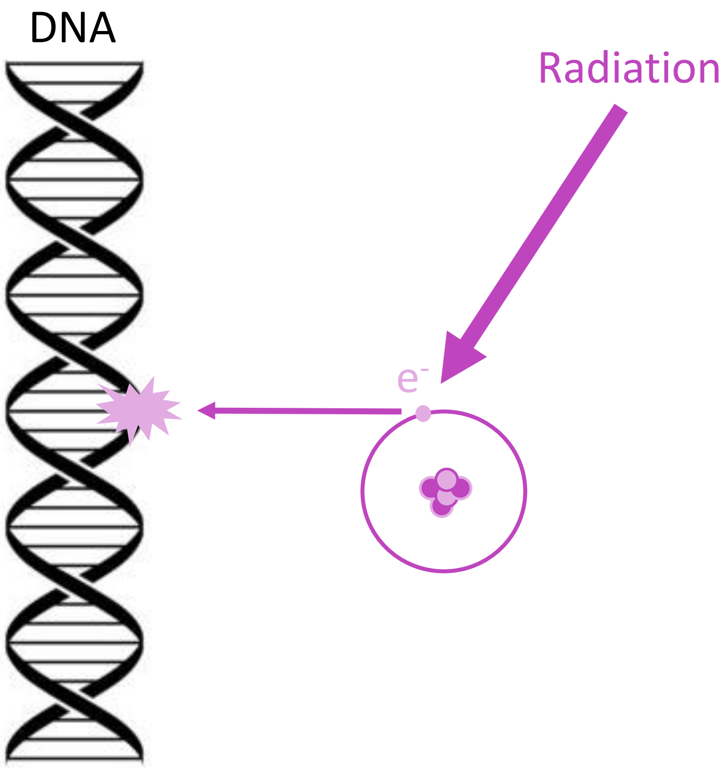
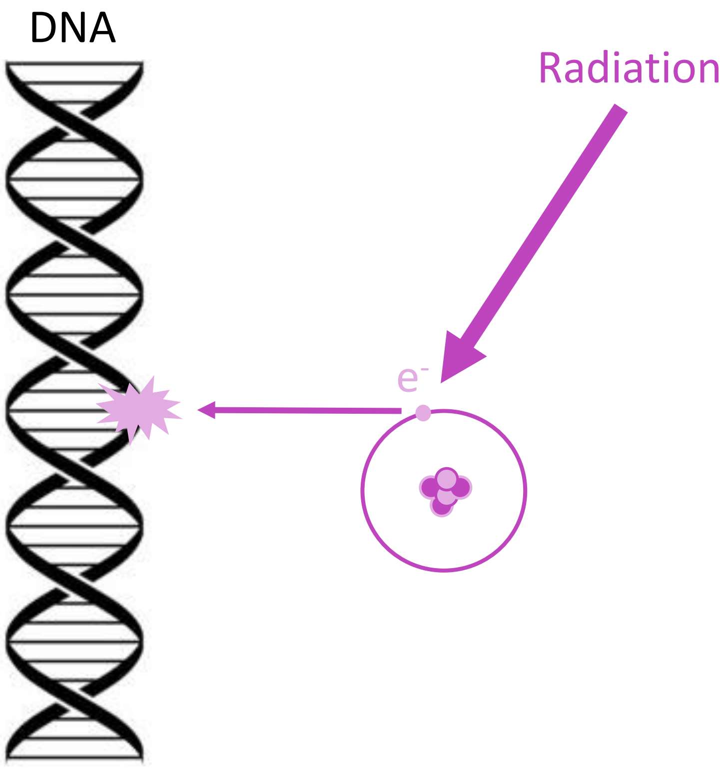


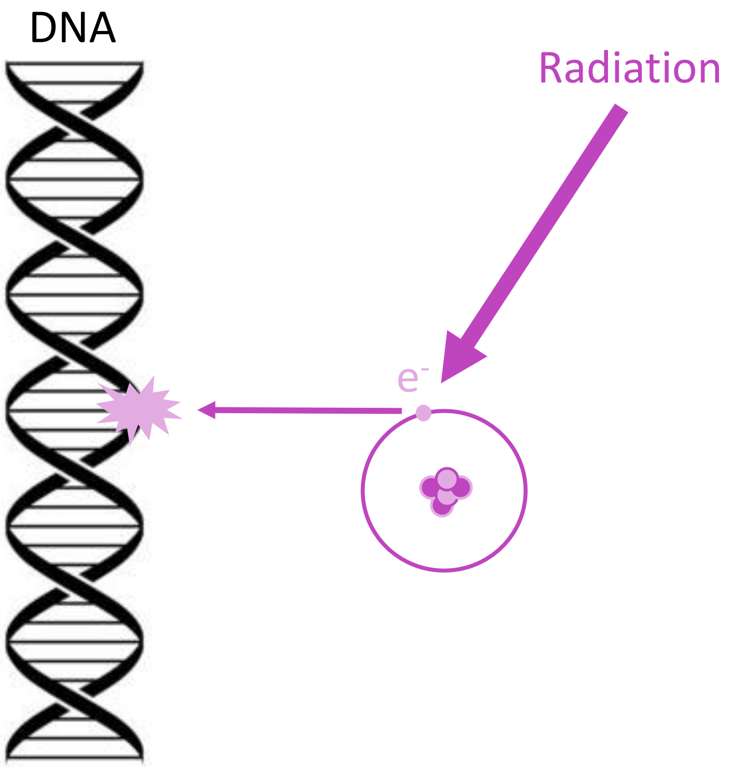





DNA
Radiation
e⁻



Advantages of radiotherapy	Disadvantages of radiotherapy
• Non-invasive • Highly effective for most cancers • Painless	• Lower effectiveness for large tumors • Damage to surrounding healthy tissues (side effects)



Physical dose $D = \frac{dE}{dm}$ [Gy=J/kg]

Linear energy transfer $LET = \frac{dE}{dx}$ [keV/µm]

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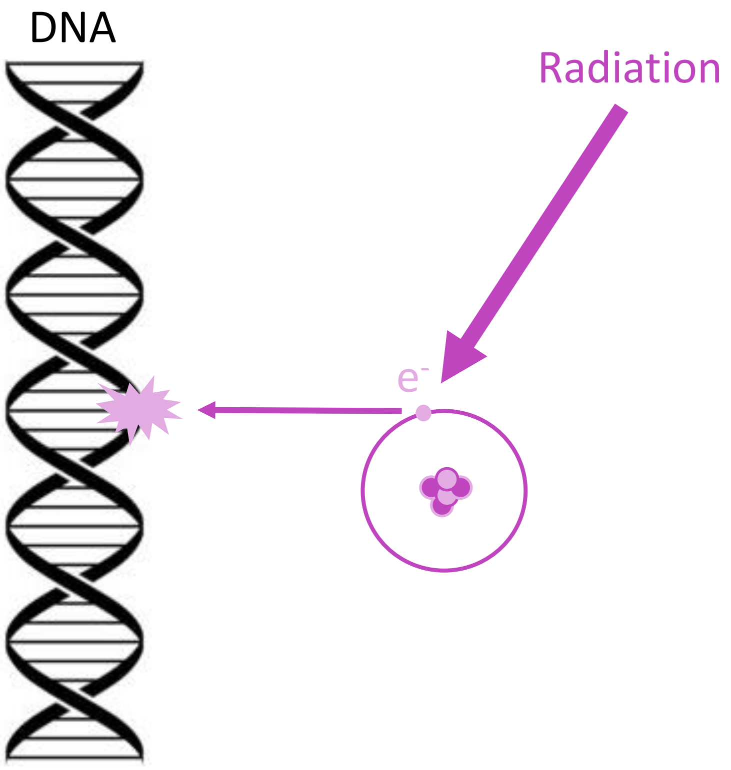

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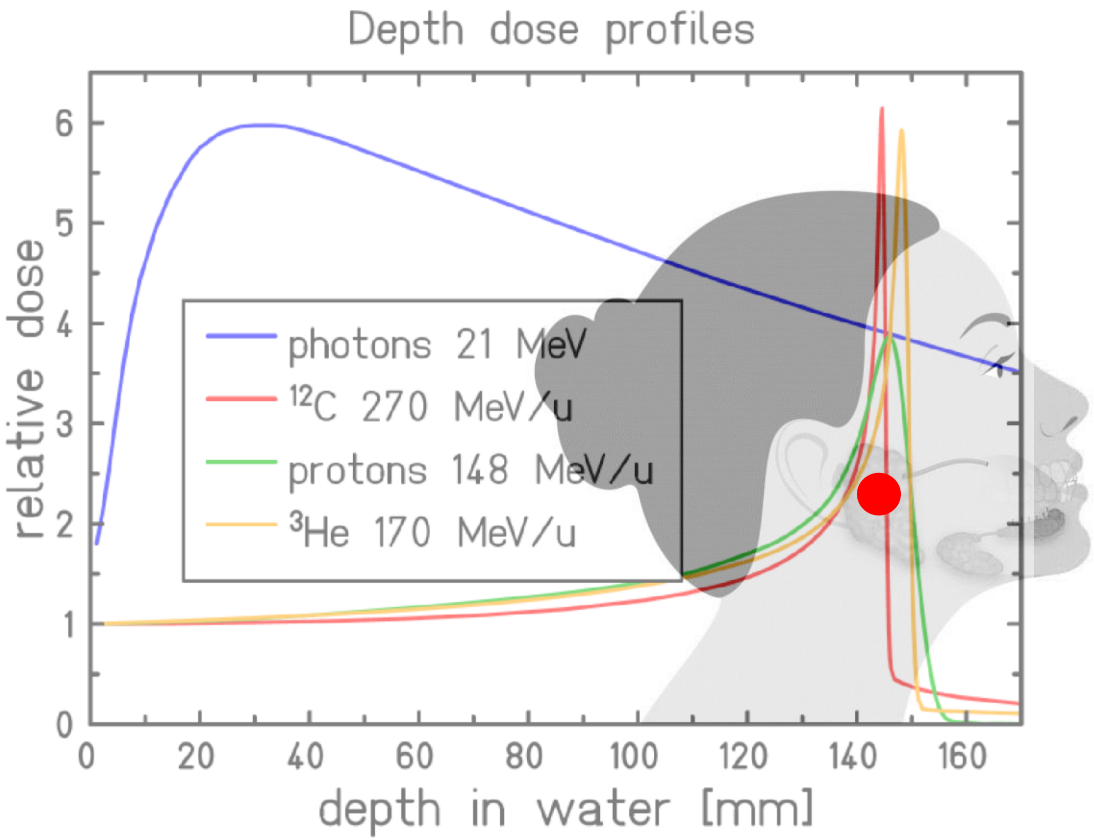

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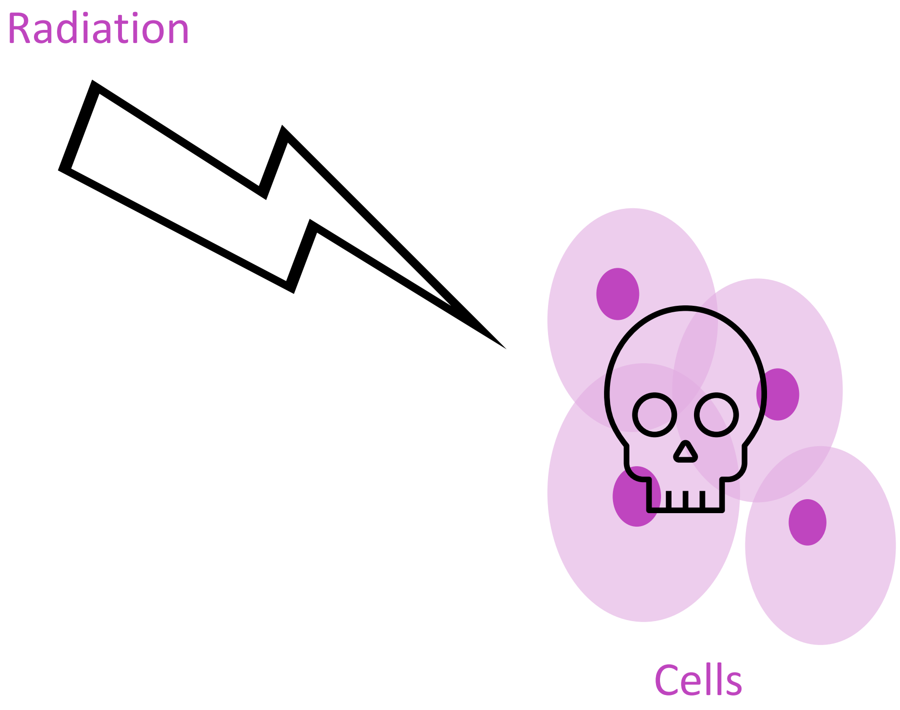
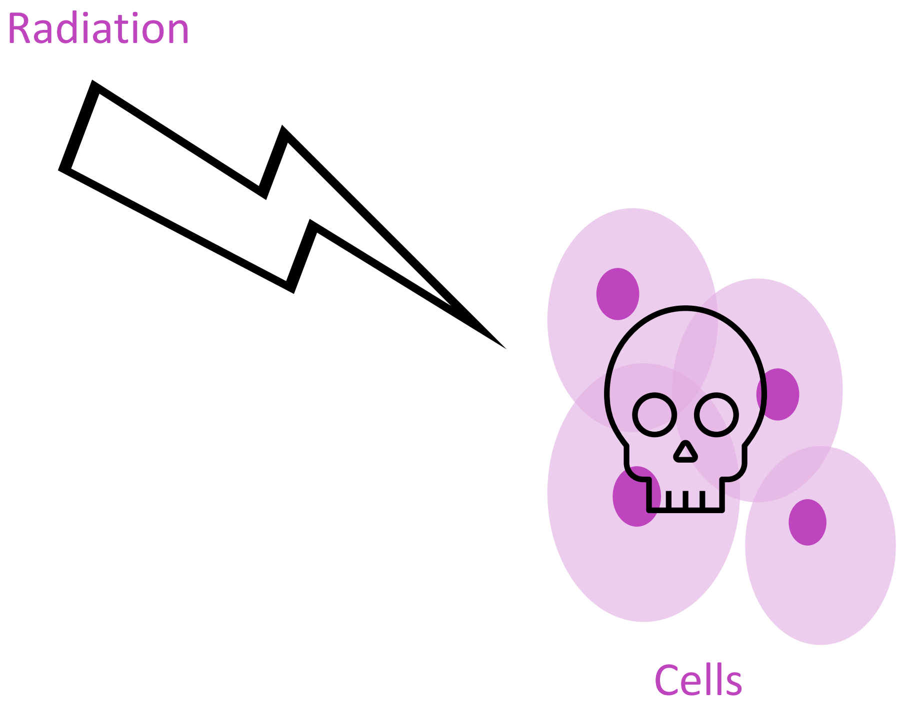
M. Krämer and al., Helium ions for radiotherapy? Physical and biological verifications of a novel treatment modality : Medical Physics, 43(4) :1995–2004, Mar. 2016. ISSN 00942405


Radiation
Cells

Linear quadratic model :

$$\text{Survival fraction} = e^{-\alpha D-\beta D^2}$$



DEFINITIONS - SURVIVAL

Linear quadratic model :

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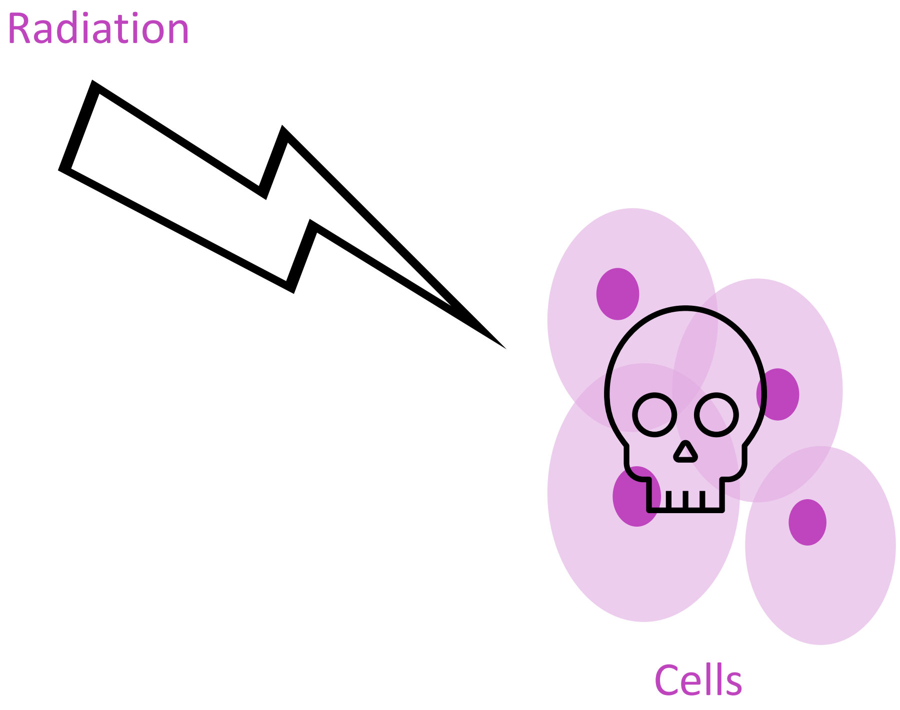
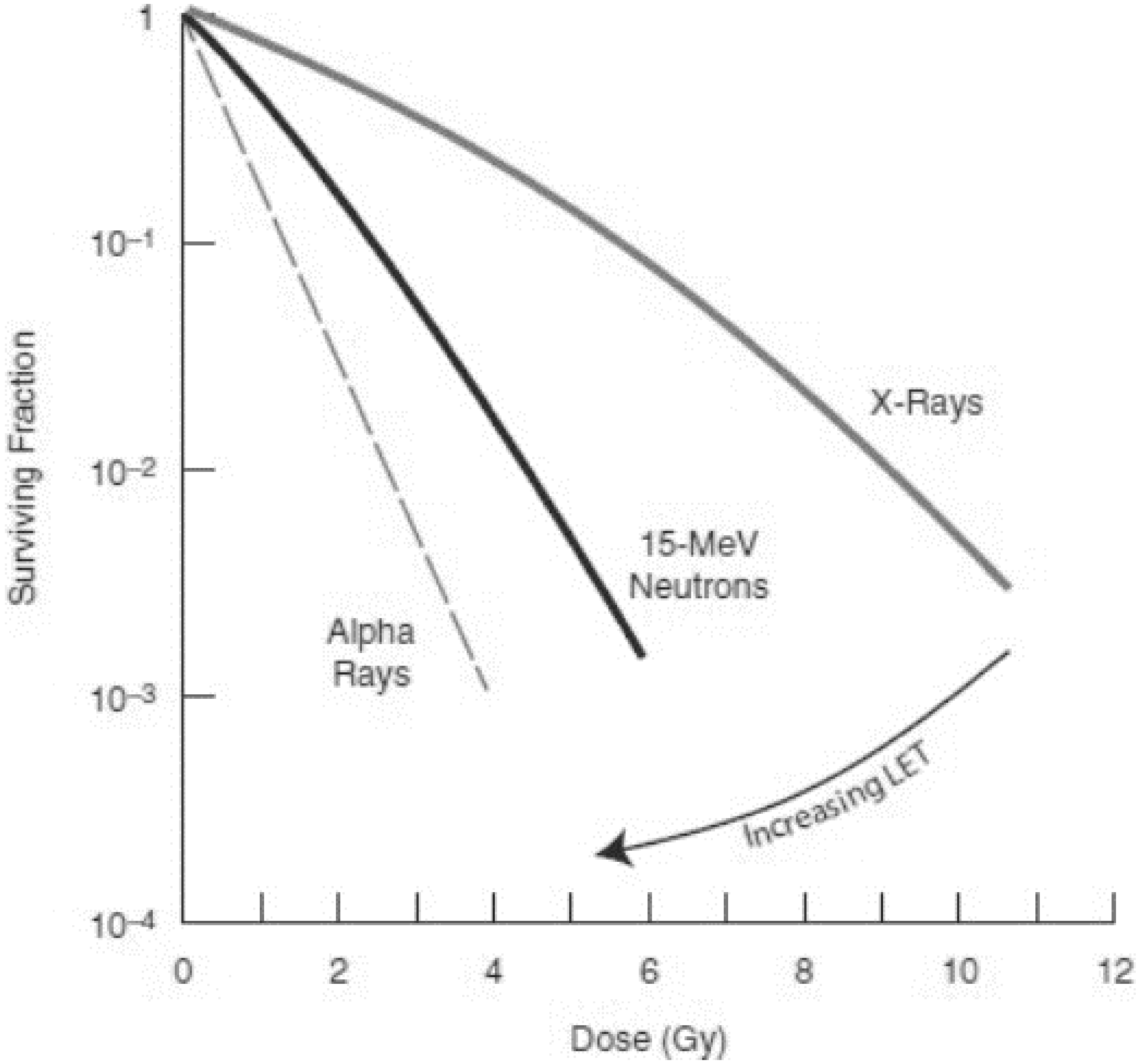
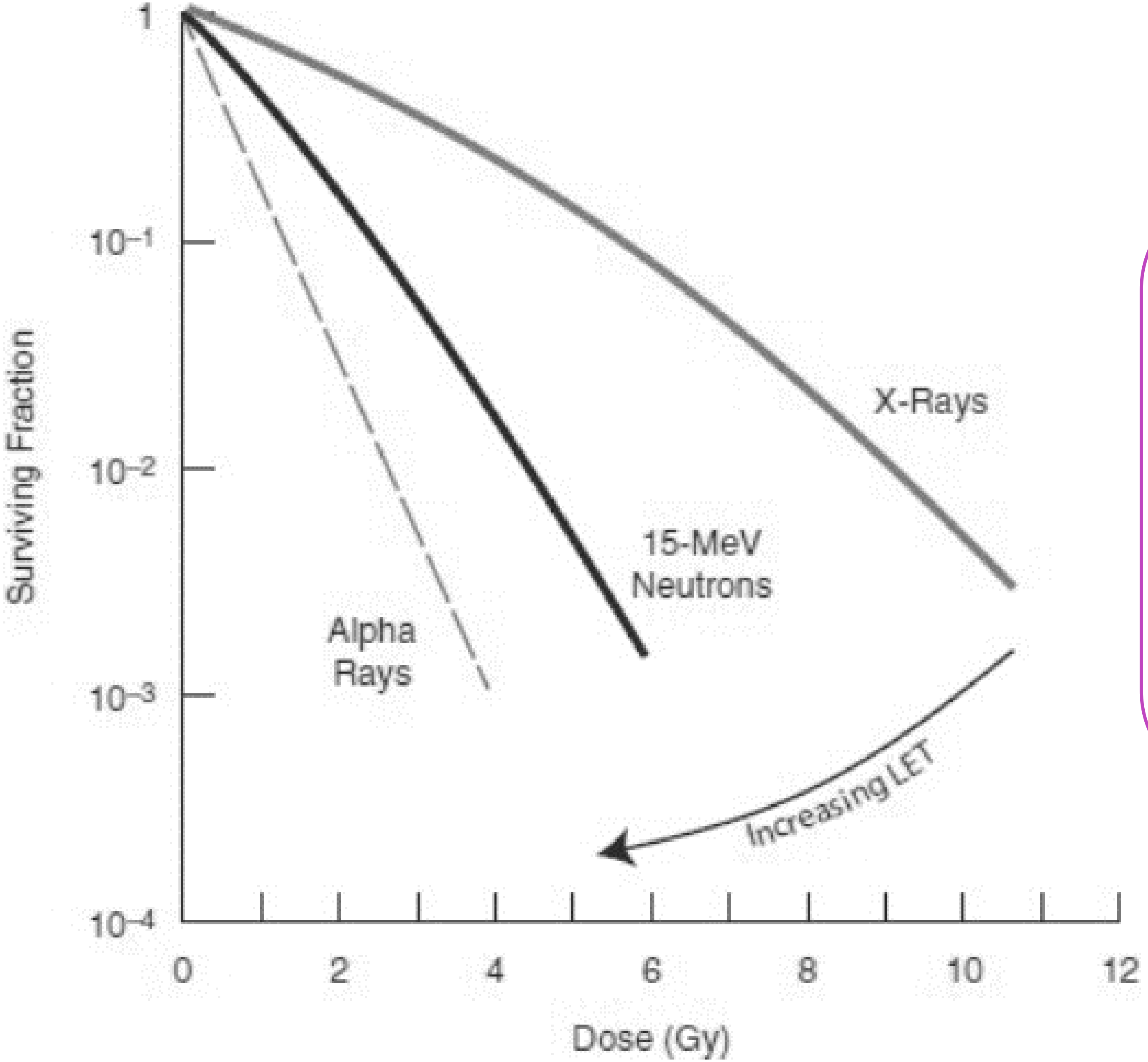




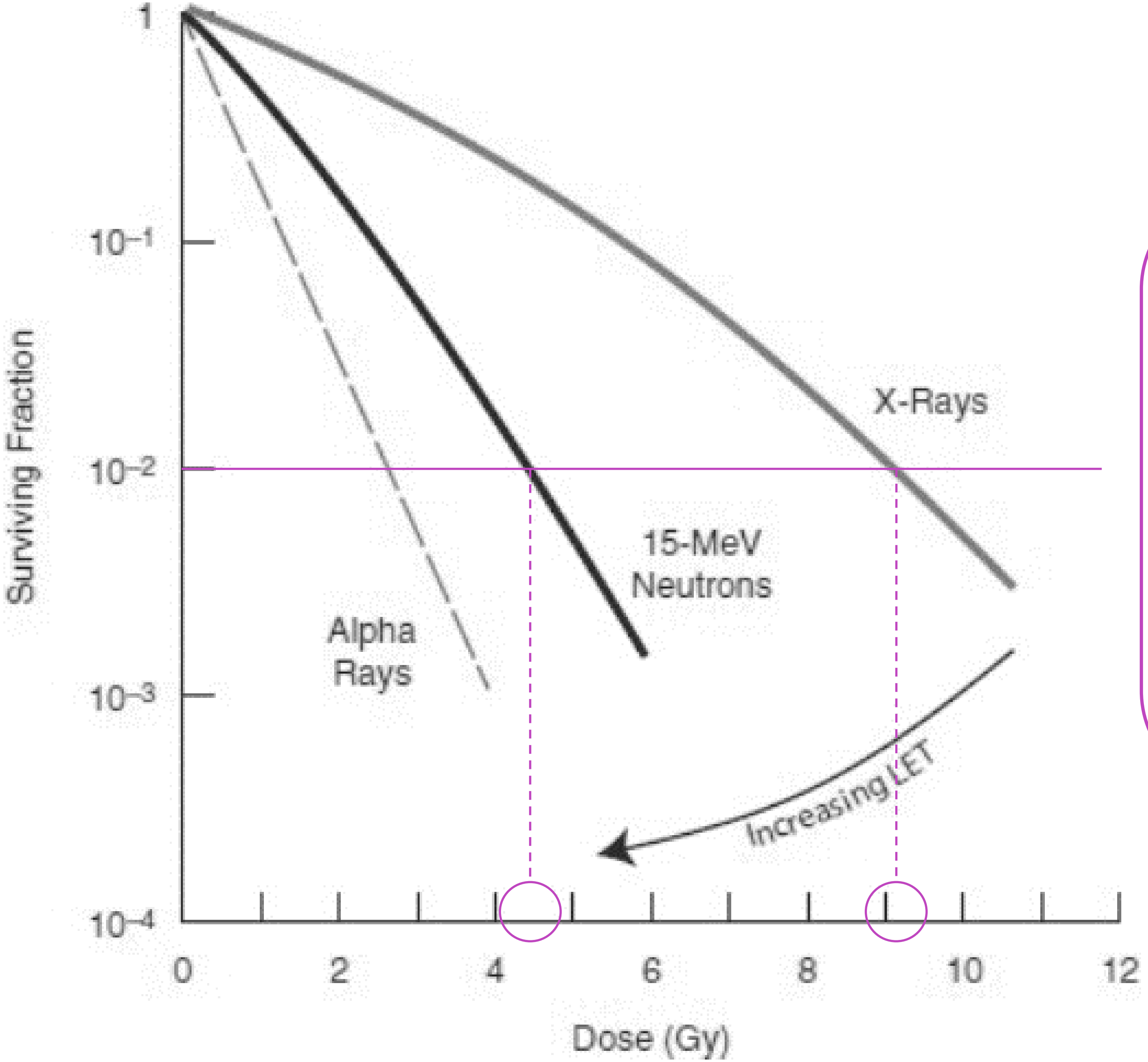
DEFINITIONS - SURVIVAL & RBE



RELATIVE BIOLOGICAL EFFECTIVENESS (RBE)

- Ability of a radiation to destroy cells
- Depends on the radiation type, the energy and dose

DEFINITIONS - SURVIVAL & RBE

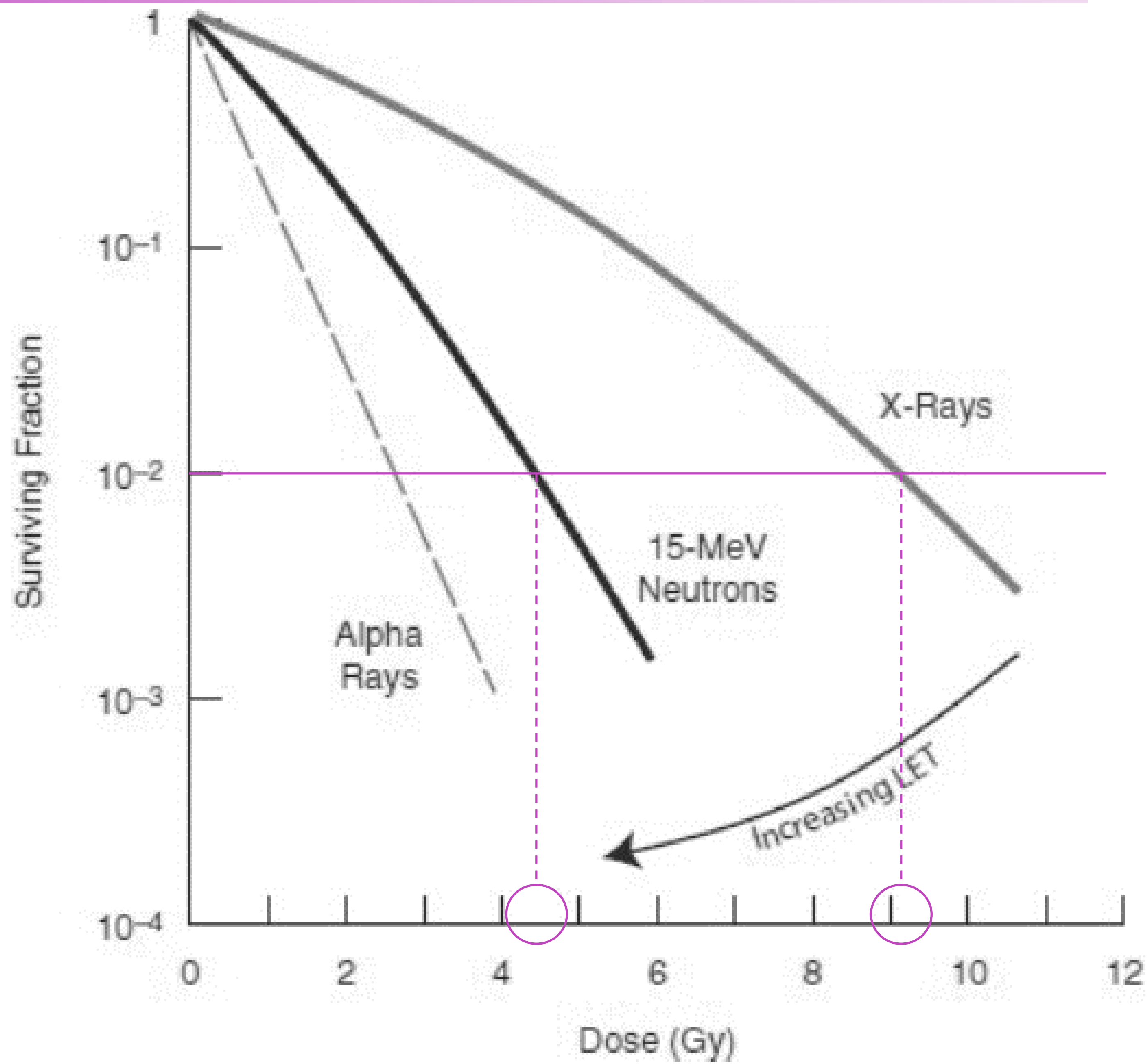


RELATIVE BIOLOGICAL EFFECTIVENESS (RBE)

- Ability of a radiation to destroy cells
- Depends on the radiation type, the energy and dose

$$\mathbf{RBE_{Survival}} = \frac{\mathbf{Dose_{Xrays}}}{\mathbf{Dose}}$$

Neutron RBE = 2



BIOLOGICAL DOSE

$$\text{Biological dose} = \text{RBE} \times \text{Physical dose}$$

DEFINITIONS - RBE

CONVENTION : fixed RBE of 1.1 for protons

REALITY : variable RBE, higher than 1.1 out of field for protons

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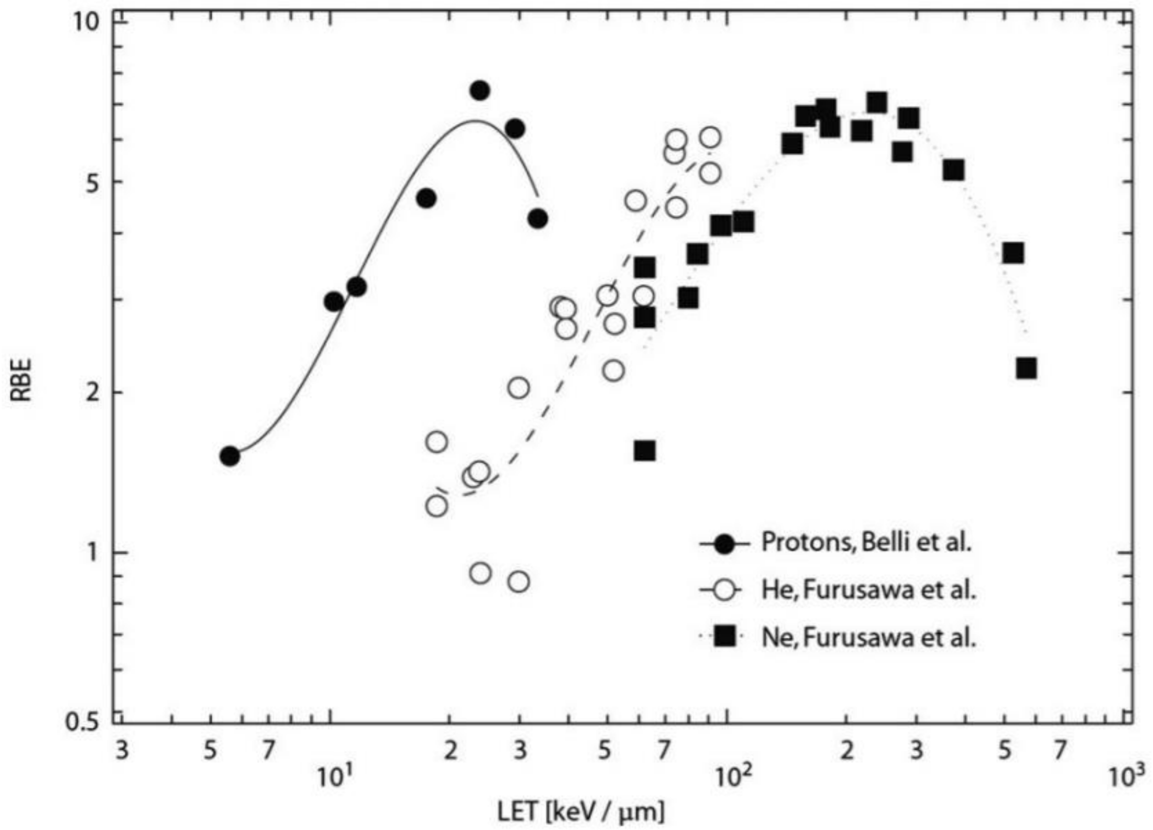
REALITY : variable RBE, higher than 1.1 out of field for protons

RBE depends on dose, LET, biological parameters, radiation…



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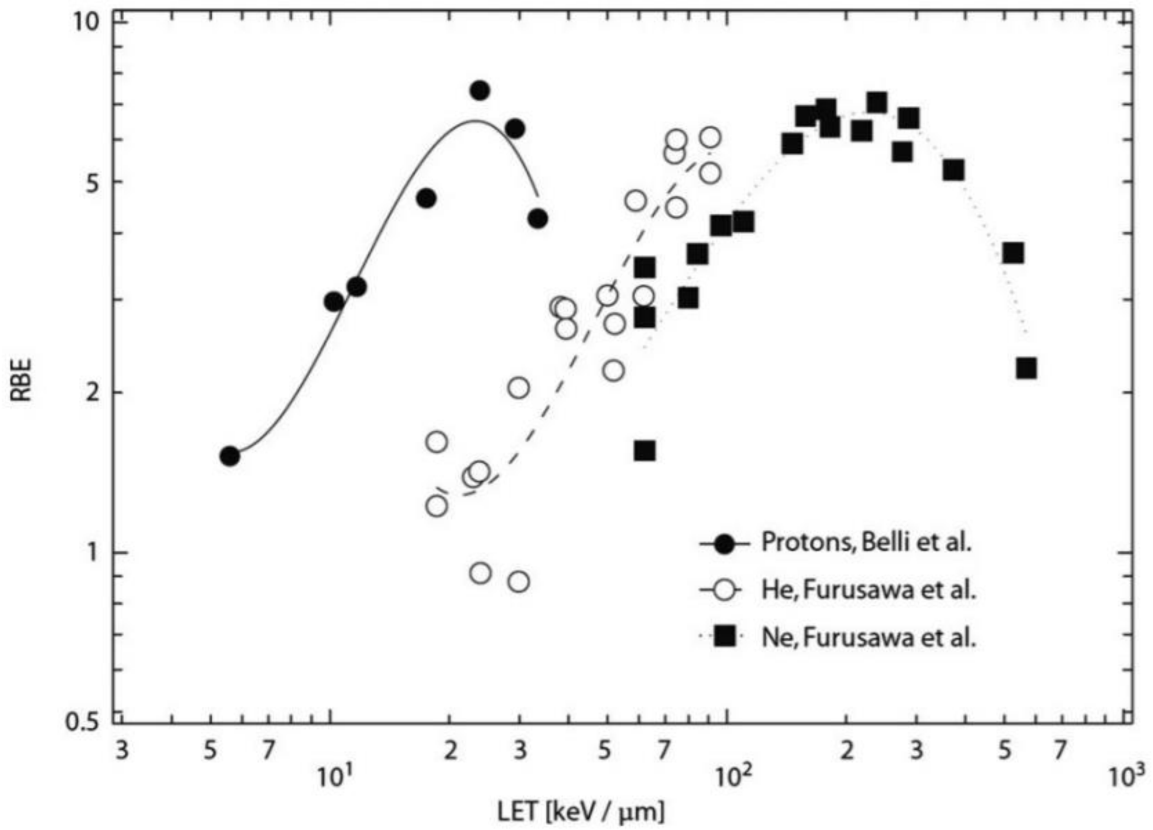

What RBE models can be used ?

McNamara model :

Phenomenological model that predicts proton RBE

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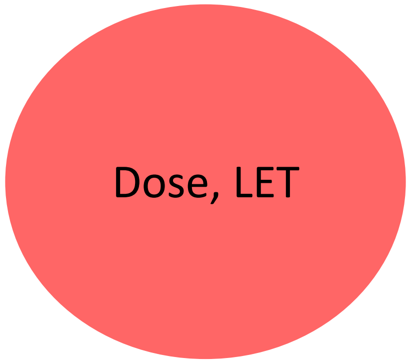
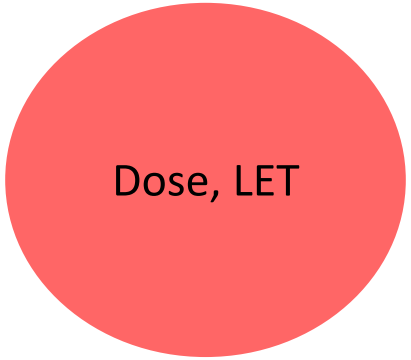


TUMOR

DEFINITIONS - RBE

McNamara model :

Phenomenological model that predicts proton RBE



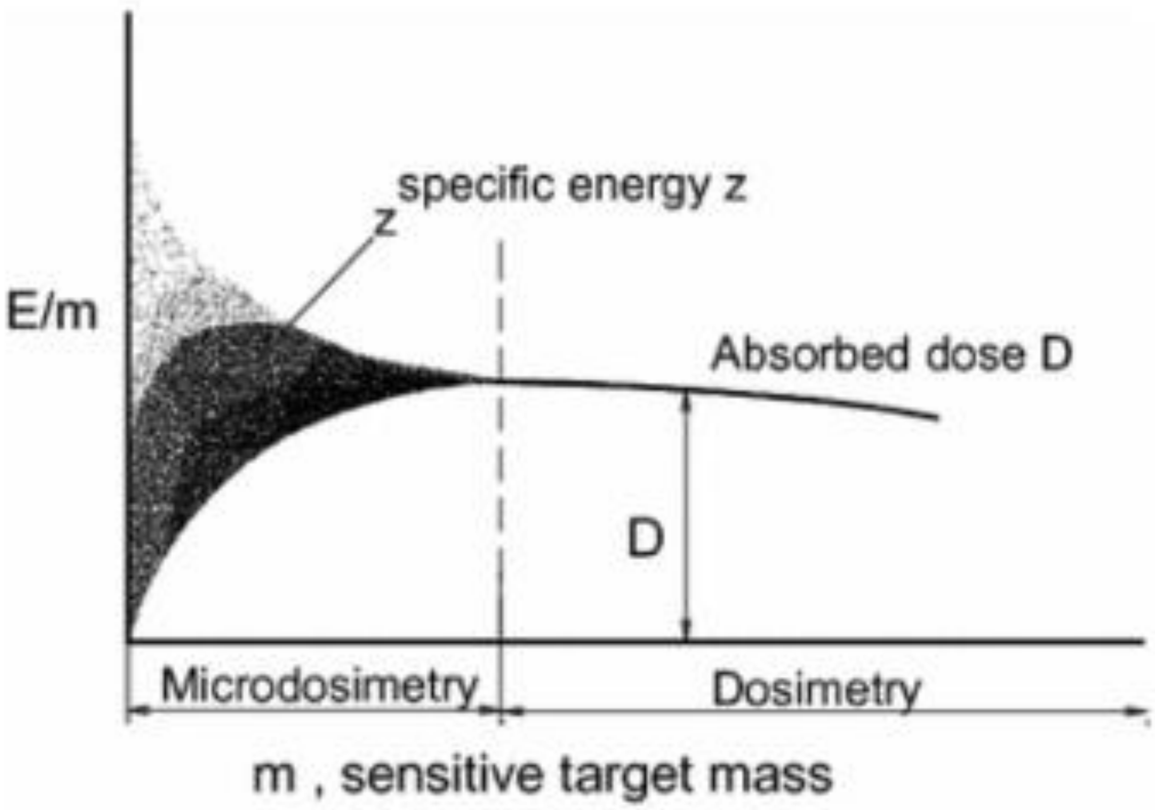
TUMOR

Advantages	Disadvantages
• Easy and fast to compute • Depends on physical dose, LET and α/β ratio	• Unreliable out of field because LET is calculated from protons and not other secondary particles • Based on *in vitro* data

Microdosimetry :

Specific energy $z = \frac{\epsilon}{m}$

Lineal energy $y = \frac{\epsilon_l}{\bar{l}}$



ε	Energy deposited
m	Volume
ε_l	Energy of a single radiation
$\bar{l}$	Mean chord length of the volume

Stochastic Microdosimetric Kinetic Model (SMKM) :

Microdosimetric model that predicts cell survival

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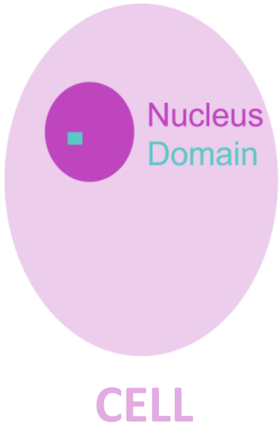

Microdosimetric model that predicts cell survival

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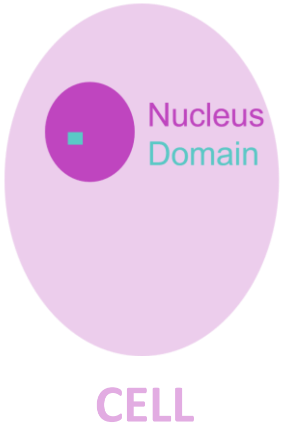


Microdosimetric model that predicts cell survival

Specific energy $z = \frac{\epsilon}{m}$

Advantages	Disadvantages
• Based on microdosimetry so more accurate • Depends on physical dose, specific energies absorbed by the nucleus and subnuclear domain • Depends on α and β	• Based on microdosimetry so longer to compute • Based on *in vitro* data

OBJECTIVES

Higher RBE → Higher biological dose

$$Biological\ dose = RBE \times Physical\ dose$$

OBJECTIVES

Higher RBE → Higher biological dose → Side effects

$$Biological\ dose = RBE \times Physical\ dose$$

Oral Mucositis : inflammation and ulcers in the oral cavity

For **Head and Neck** patients treated with **proton therapy** :
30% to 60% risk of developing oral mucositis

OBJECTIVES

Higher RBE → Higher biological dose → Side effects

$$Biological\ dose = RBE \times Physical\ dose$$

Oral Mucositis : inflammation and ulcers in the oral cavity

For **Head and Neck** patients treated with **proton therapy** :
30% to 60% risk of developing oral mucositis

What are the physical processes that lead to the development of oral mucositis in head and neck patients treated with protons ?
How can they be used to optimize the treatment plans and reduce the side effects ?

- **Eclipse** : Clinical treatment planning software, contains the geometry of the treatment, the dose, the CT scans
- **TOPAS** : Toolkit based on Geant4, used for Monte Carlo simulations of radiation-matter interactions, dedicated to medical physicists, can create the geometry from the CT scans of the patients
- **Machine learning** : Classification algorithm used to make predictions and study the correlation between the parameters and the occurrence of side effects, decision based on Random Forest

MATERIAL & METHODS

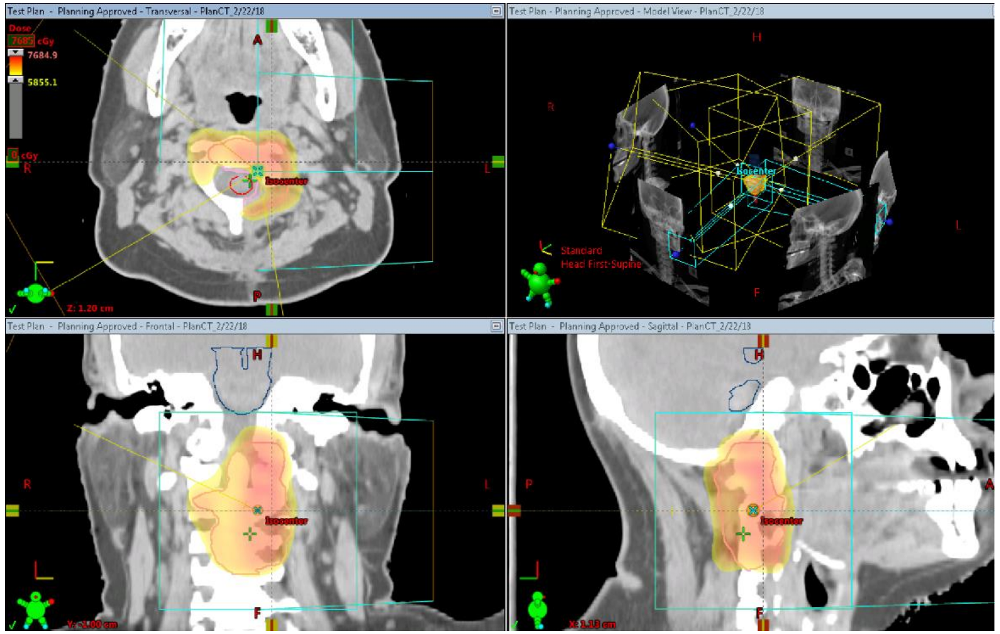
PATIENTS

Eclipse

CT Scan, dose, organs contour

Eclipse™

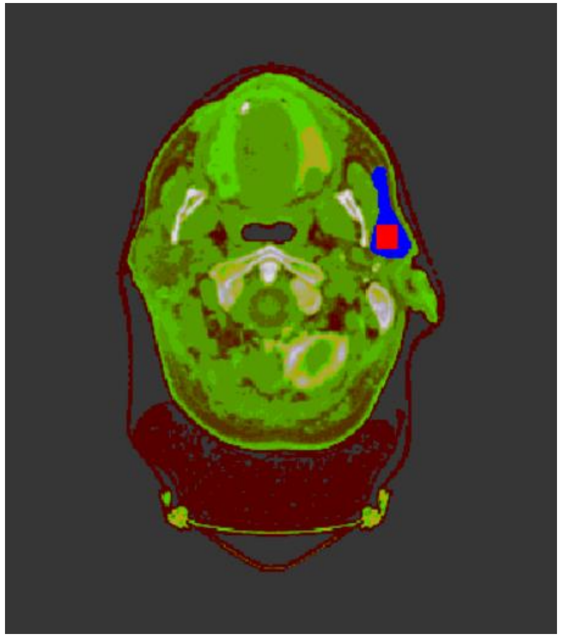
Treatment planning software

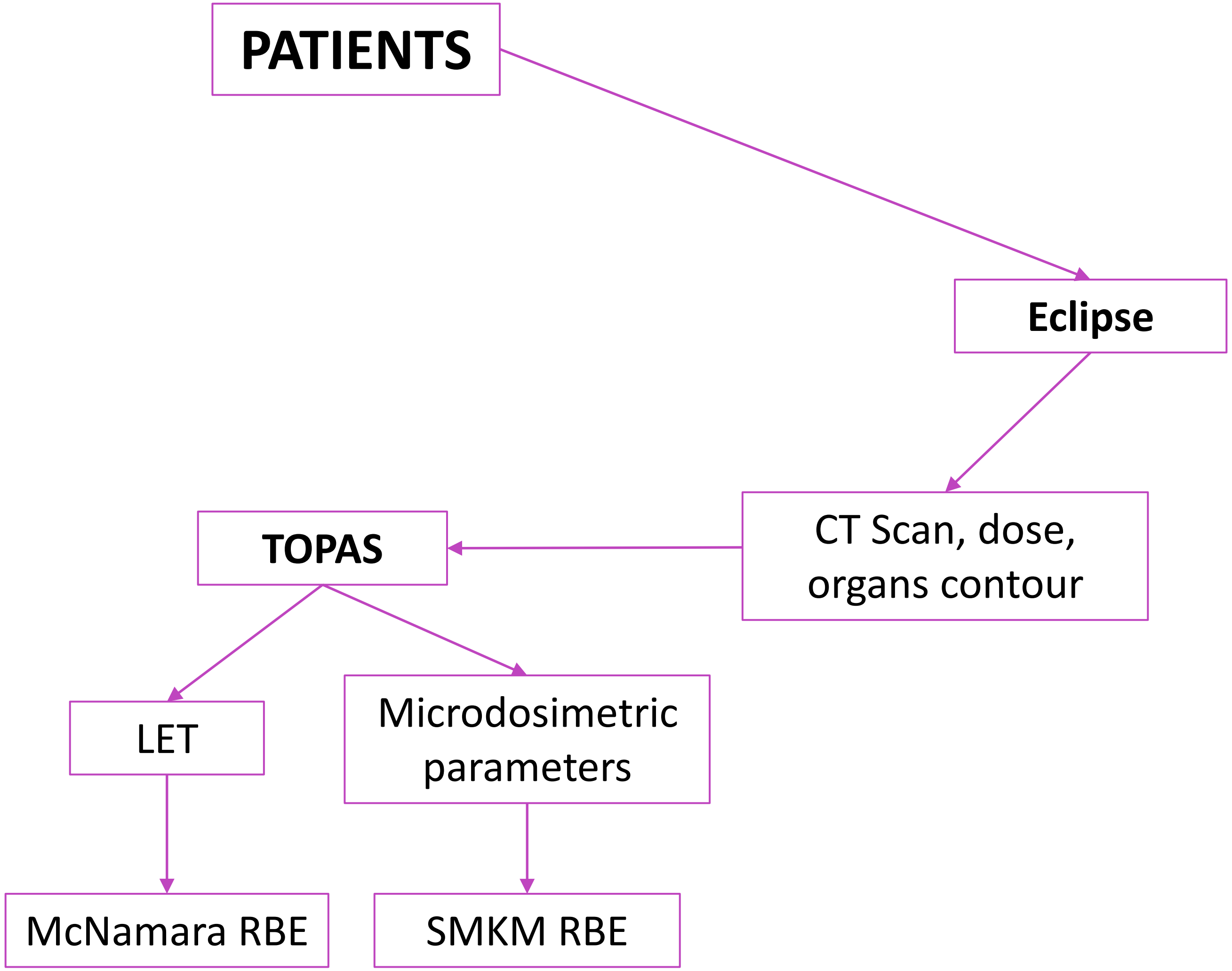


Contribution : 3D treatment planning system – Varian Eclipse for proton therapy planning; N.Sahoo, F.Poenisch, X.Zhang, Y.Li, M.Lii, A.Gautam,R.Wu, M.Gilin, X.Zhu; Physics,Medecine

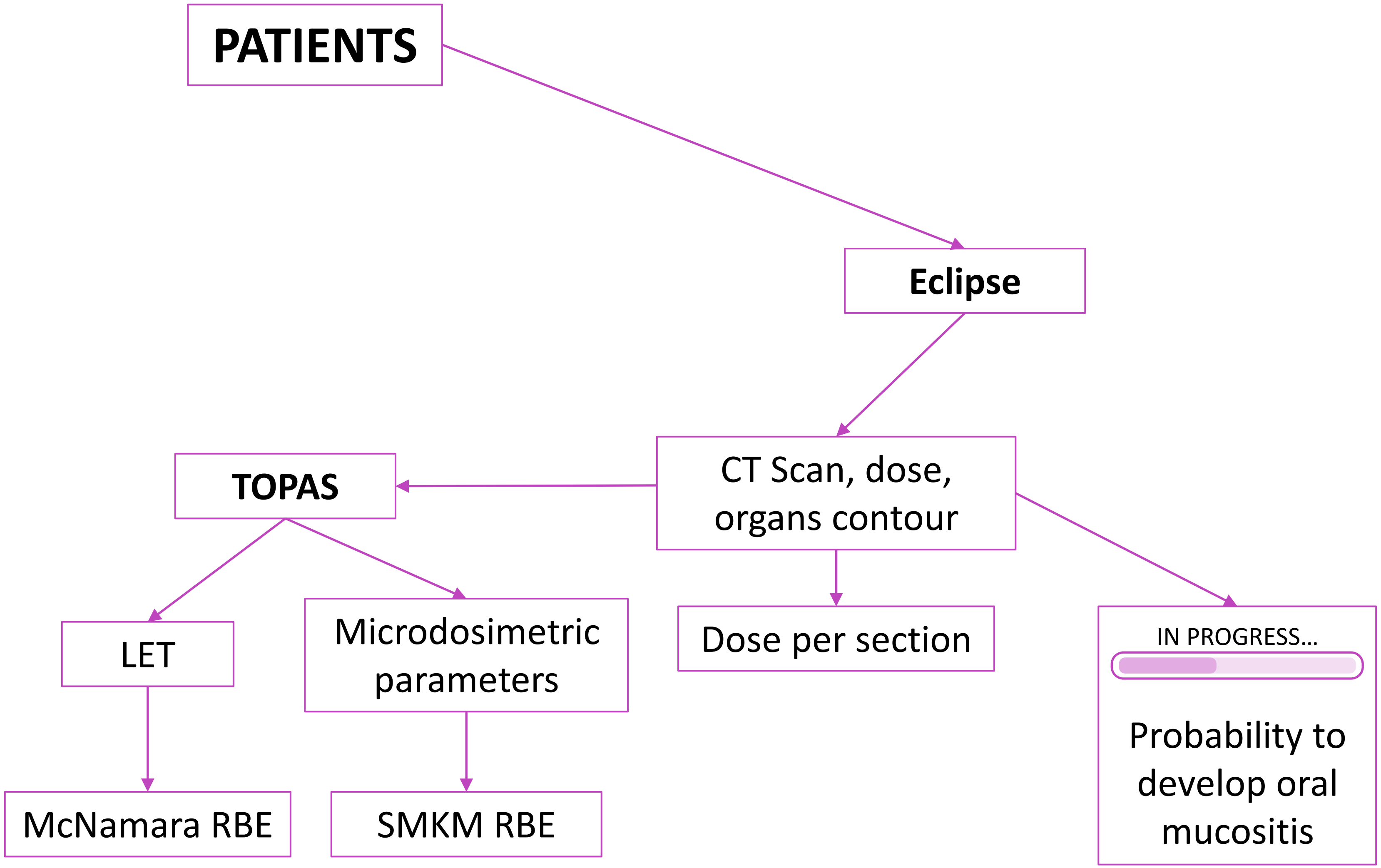
MATERIAL & METHODS

- Monte Carlo simulations
- Based on Geant4





MATERIAL & METHODS



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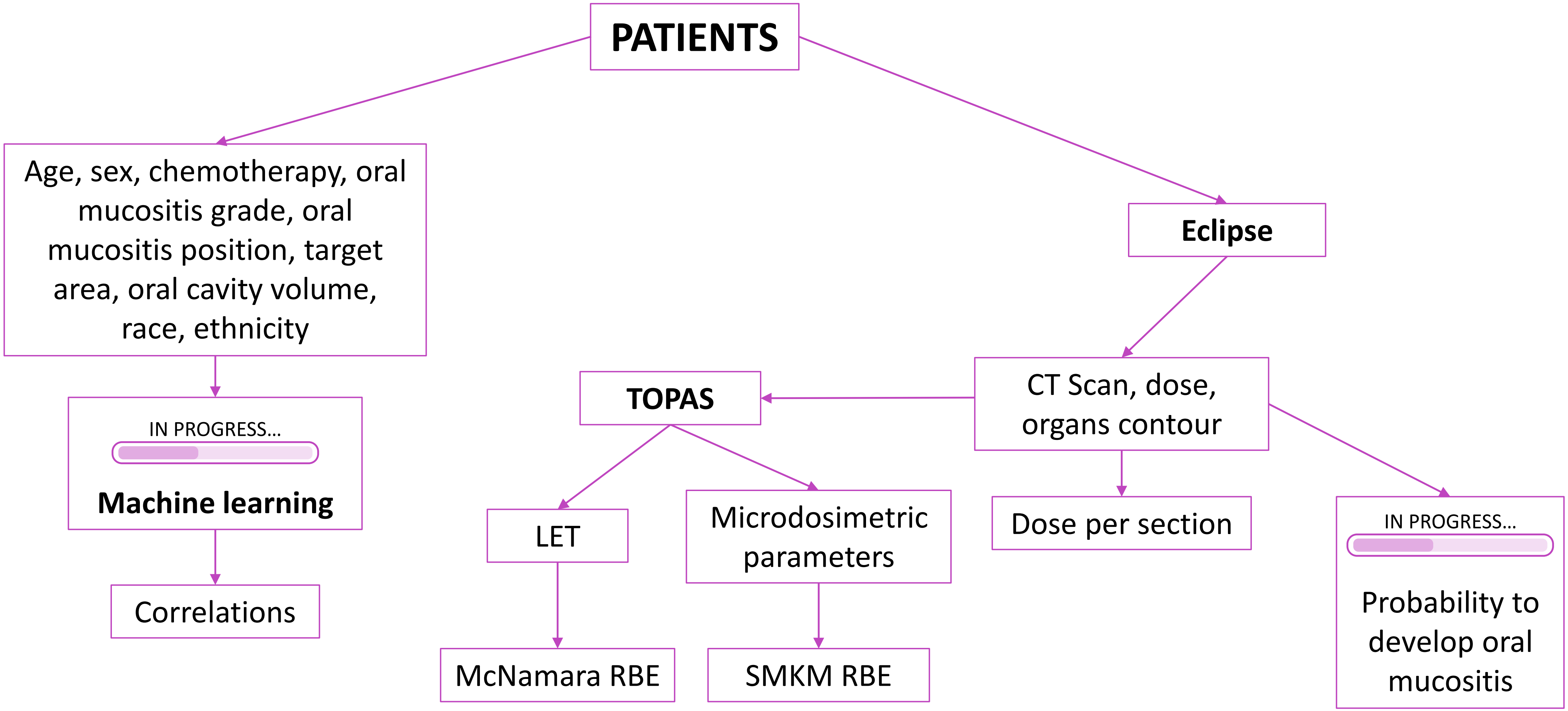
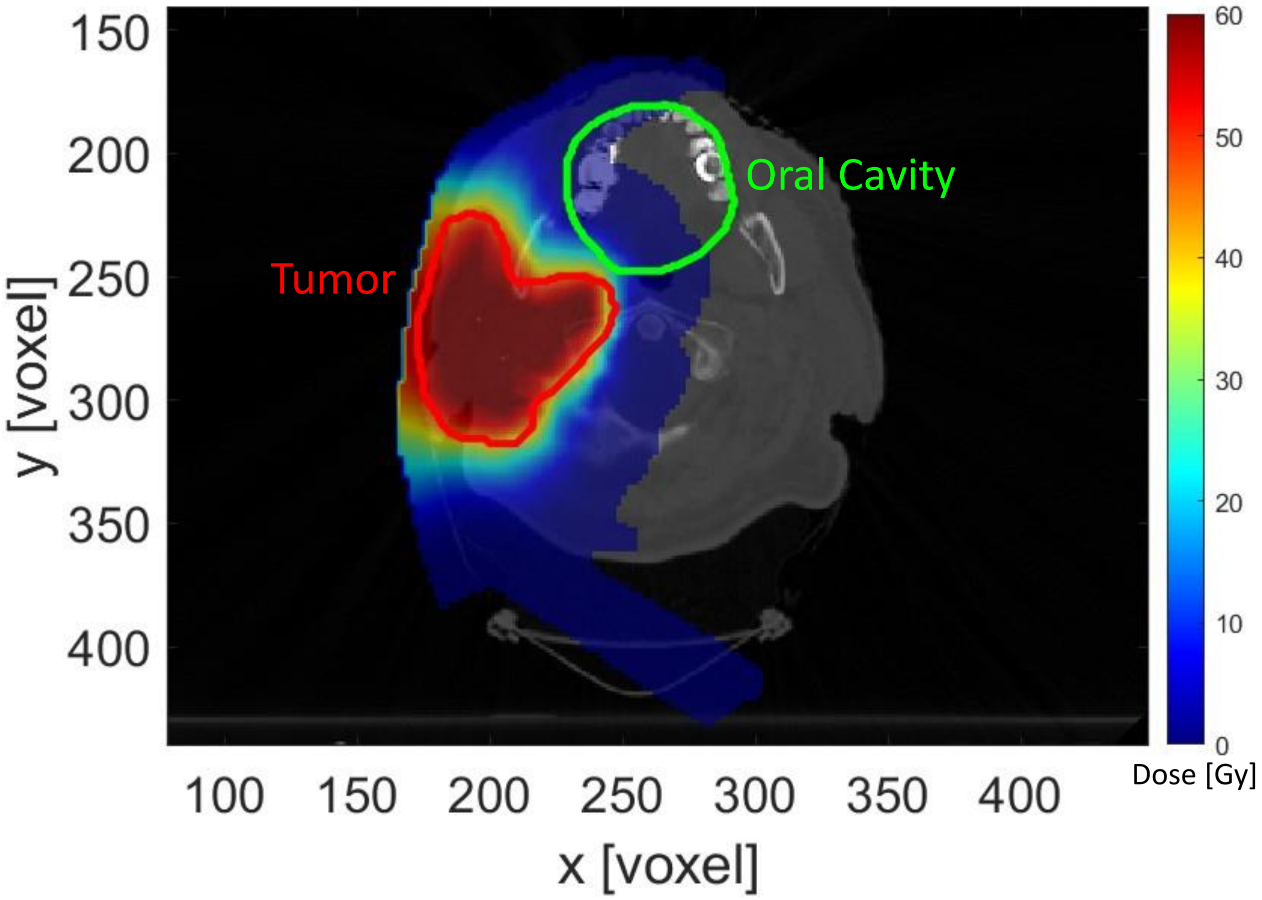
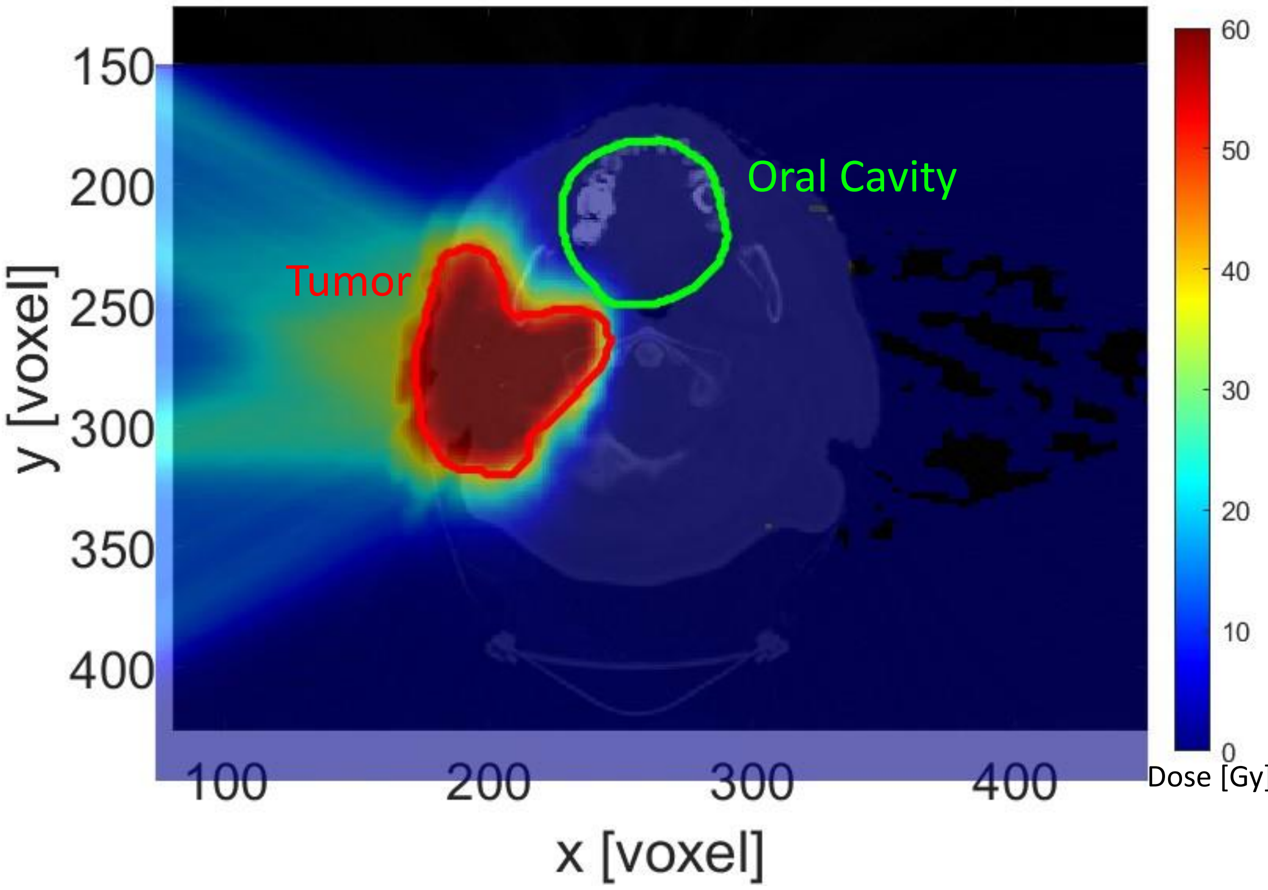


Eclipse → CT Scan, dose, organs contour → TOPAS

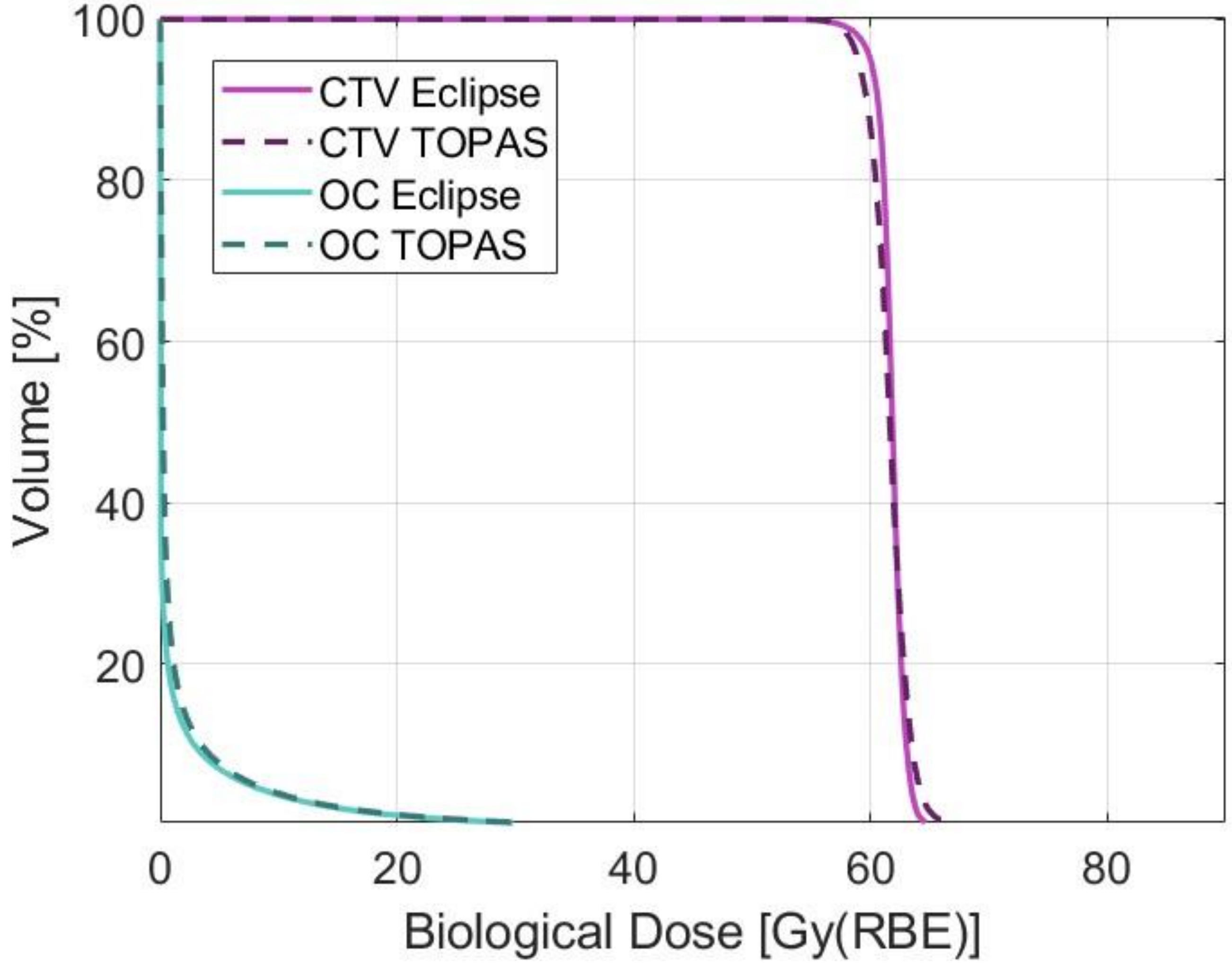
Dose extracted from Eclipse

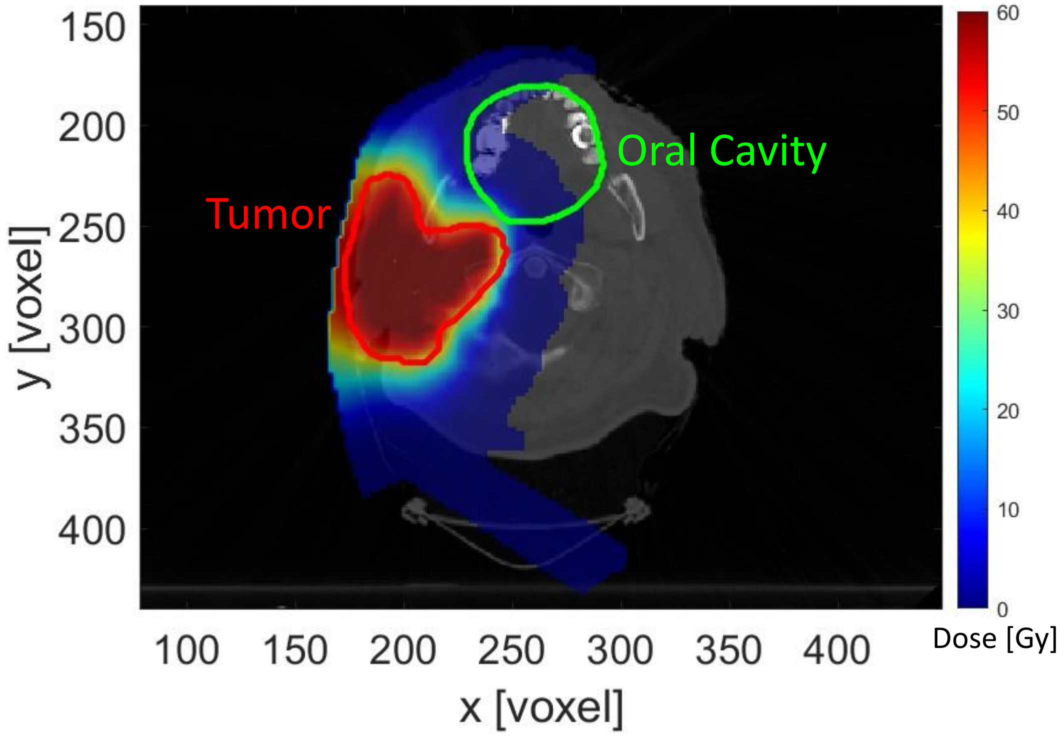


Dose simulated with TOPAS



Dose-Volume Histogram DVH
with the dose extracted from Eclipse and simulated by TOPAS,
for the tumor (CTV) and oral cavity (OC)





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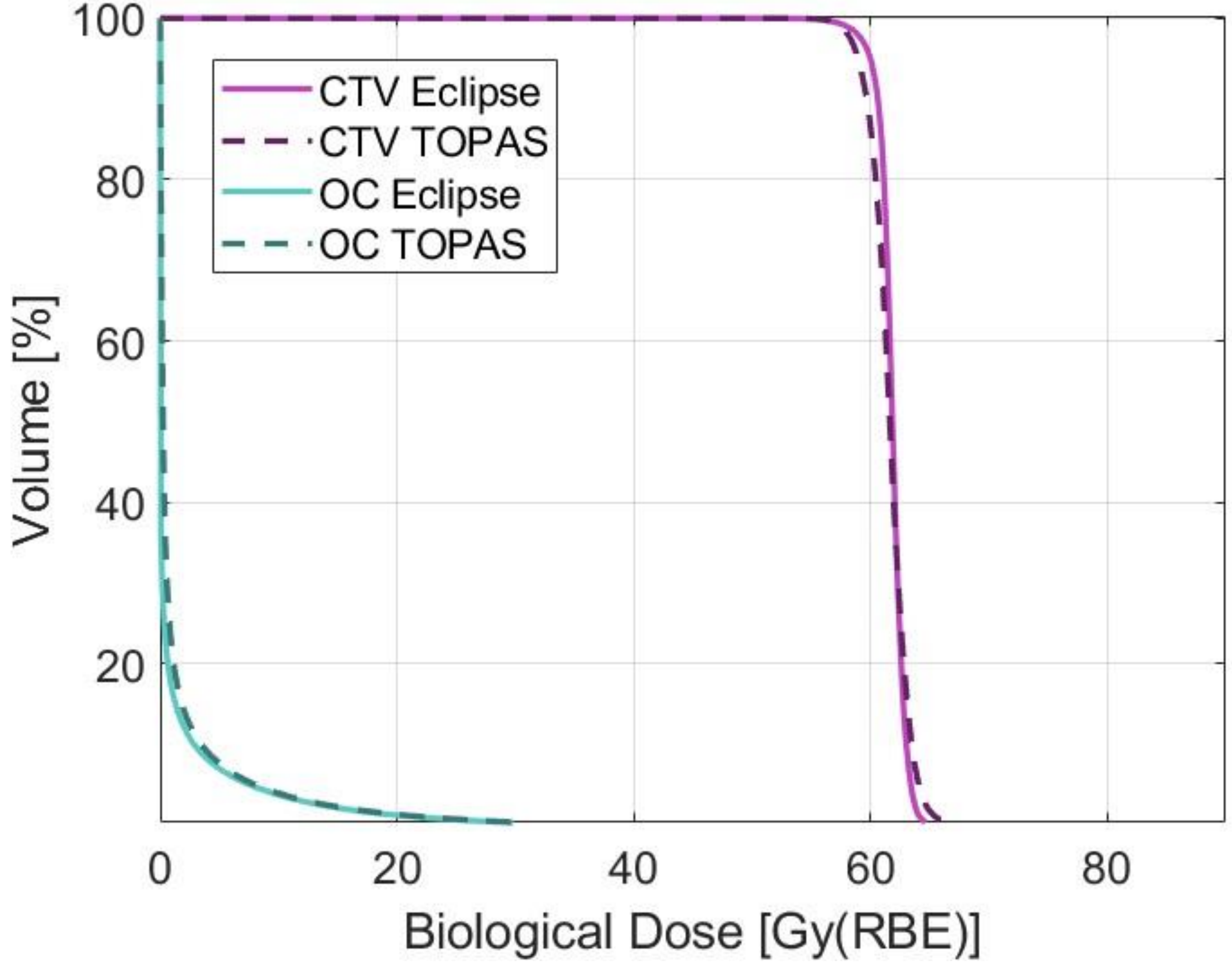
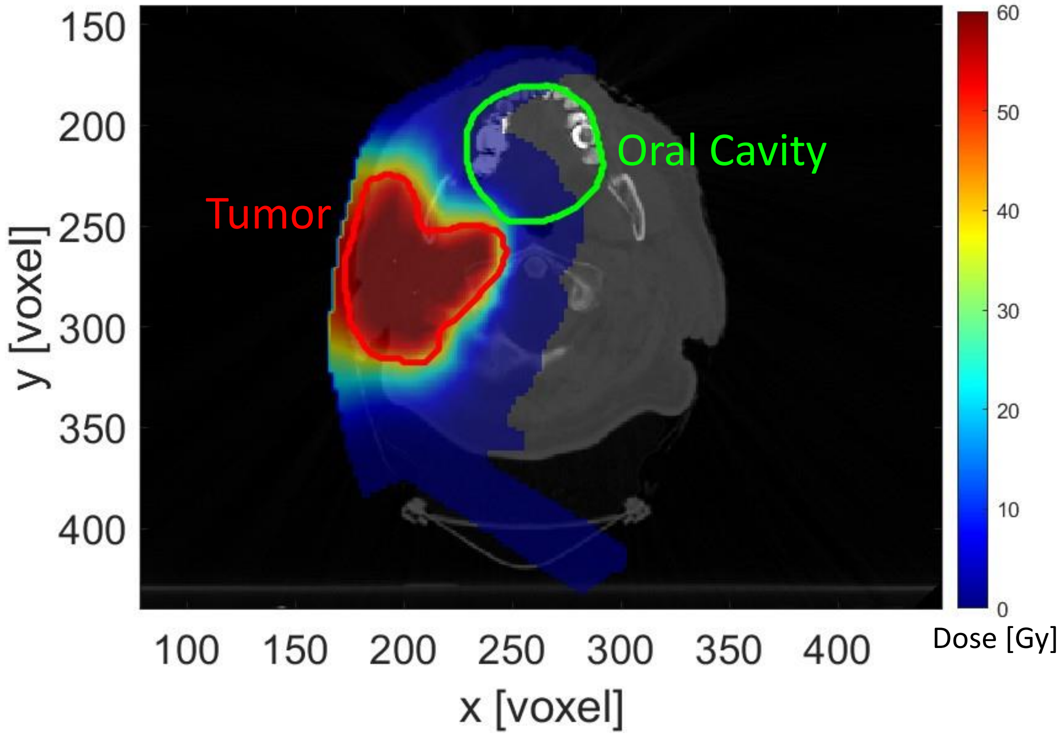
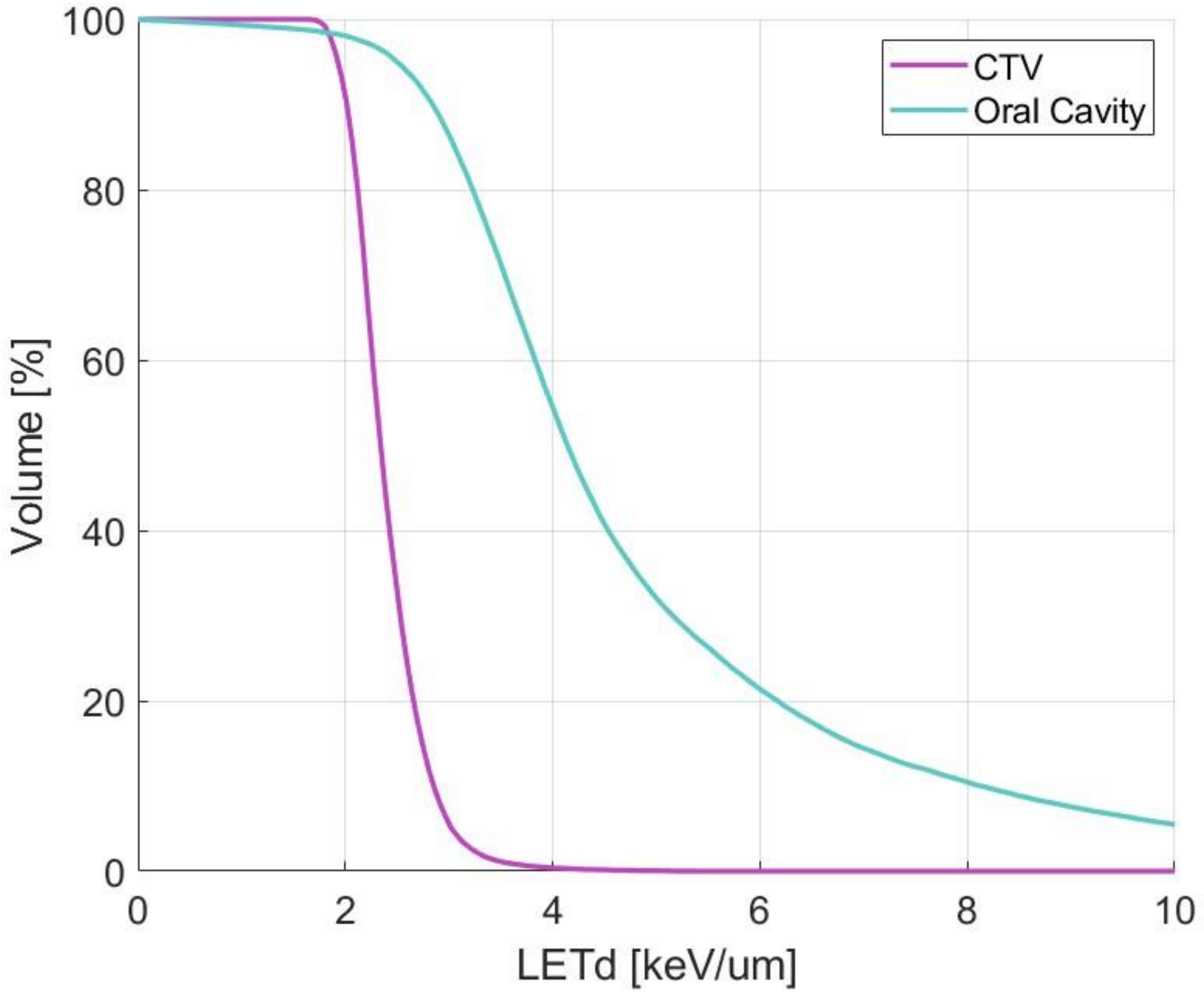
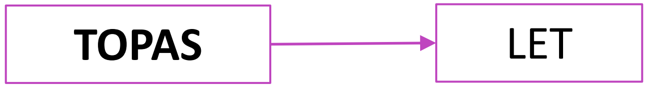


- TOPAS is based on Monte Carlo and Eclipse is analytical
- **Small difference in values but the trend is similar enough to trust the future simulations**



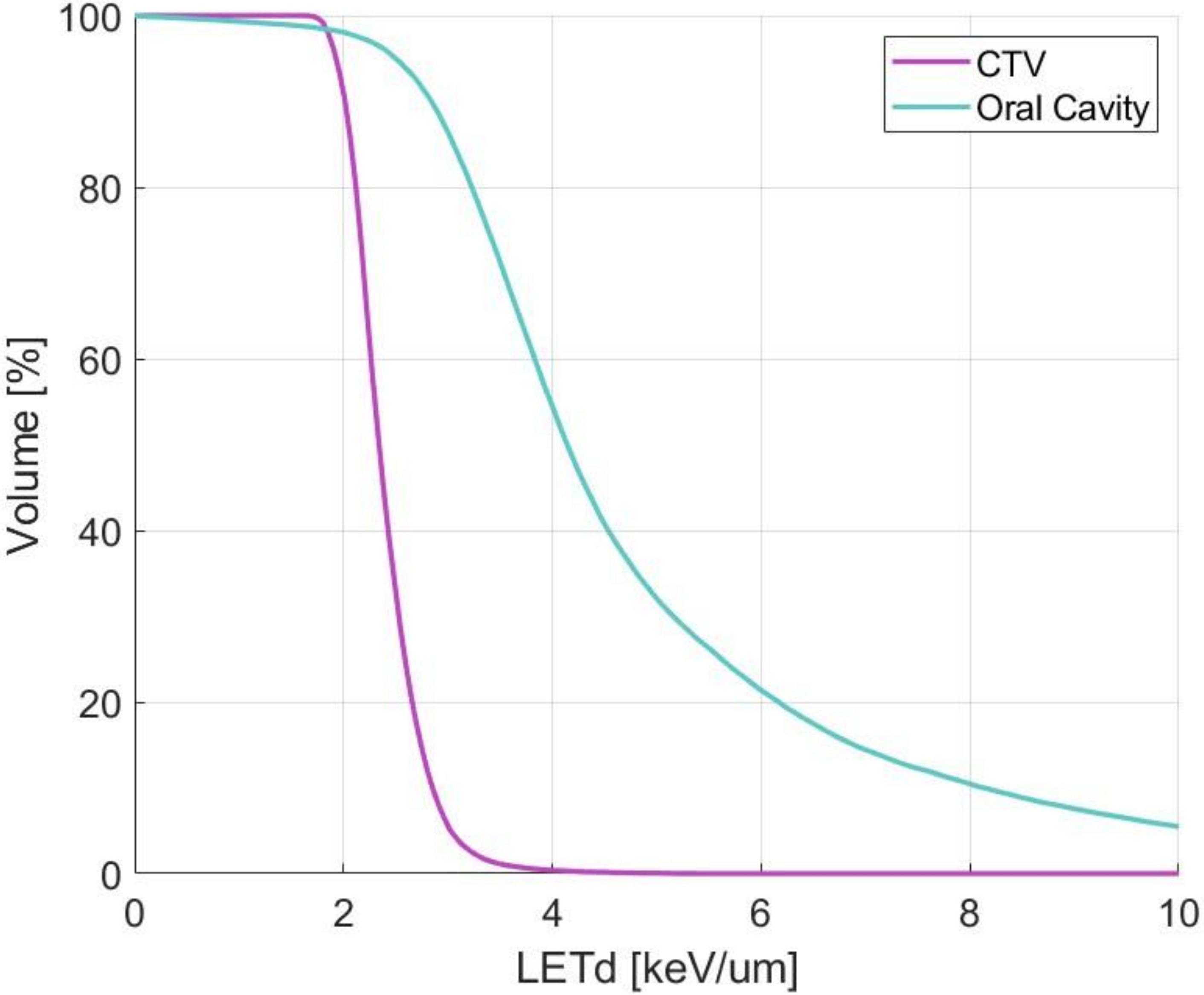
RESULTS - LET

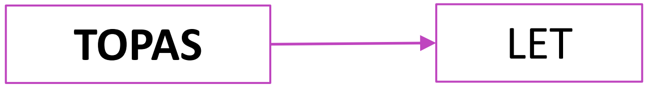




LET-Volume Histogram LET-VH
simulated by TOPAS, for the tumor (CTV) and oral cavity

RESULTS - LET





LET-Volume Histogram LET-VH
simulated by TOPAS, for the tumor (CTV) and oral cavity

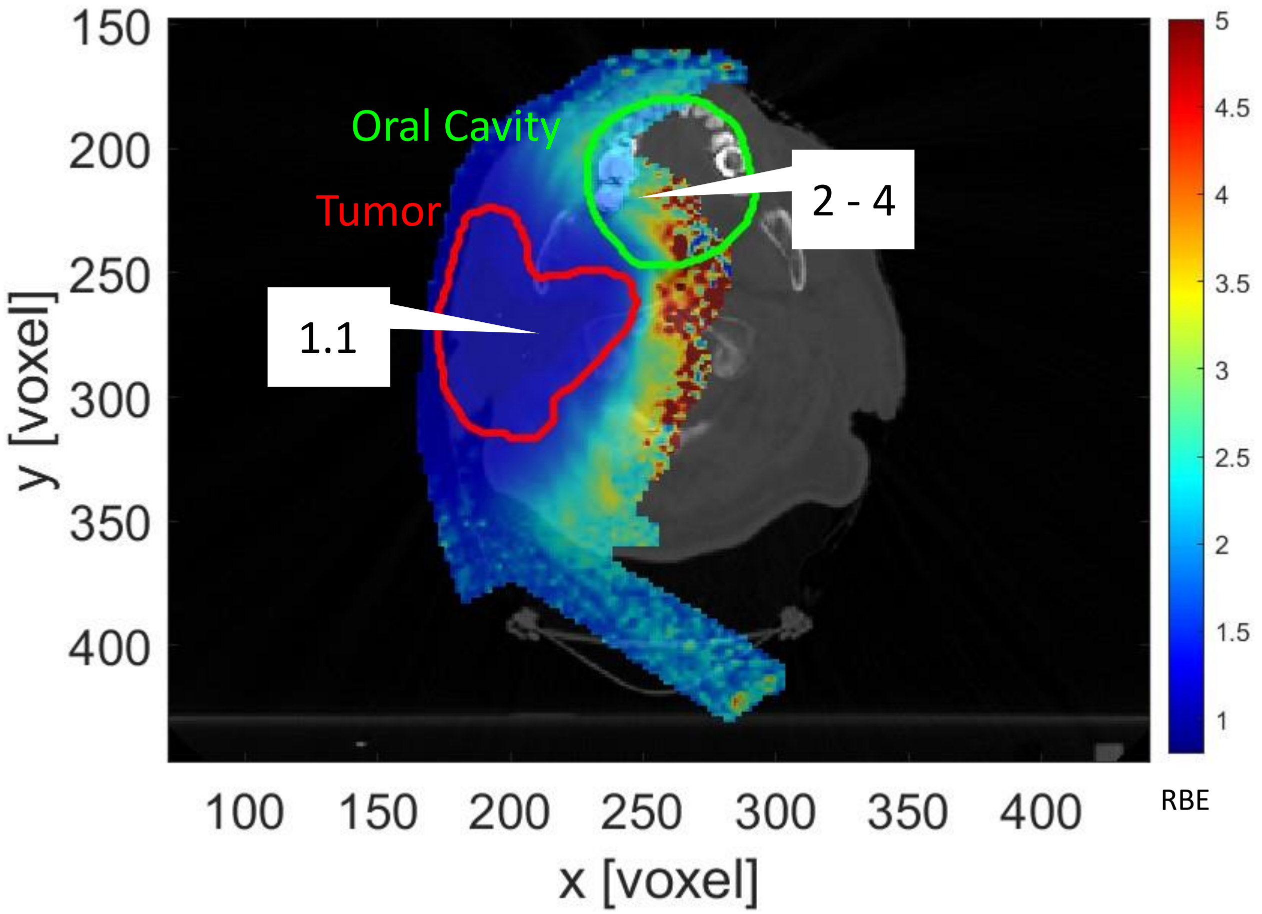
- Needed to calculate the RBE
- Increase out of field due to the creation of secondary particles

Low-energy secondary particles have high LET

RESULTS - RBE

TOPAS → LET → McNamara RBE

McNamara RBE map

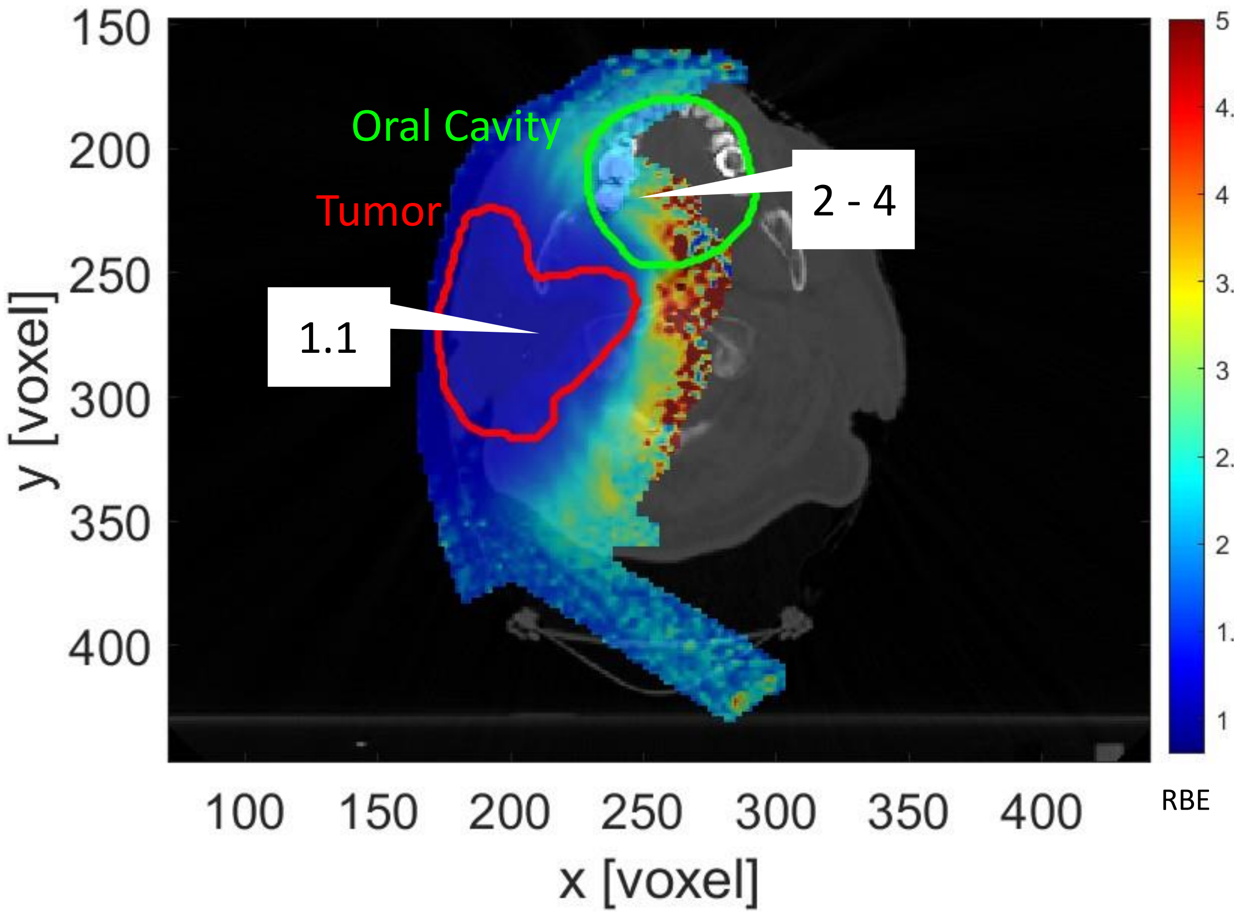


RESULTS - RBE

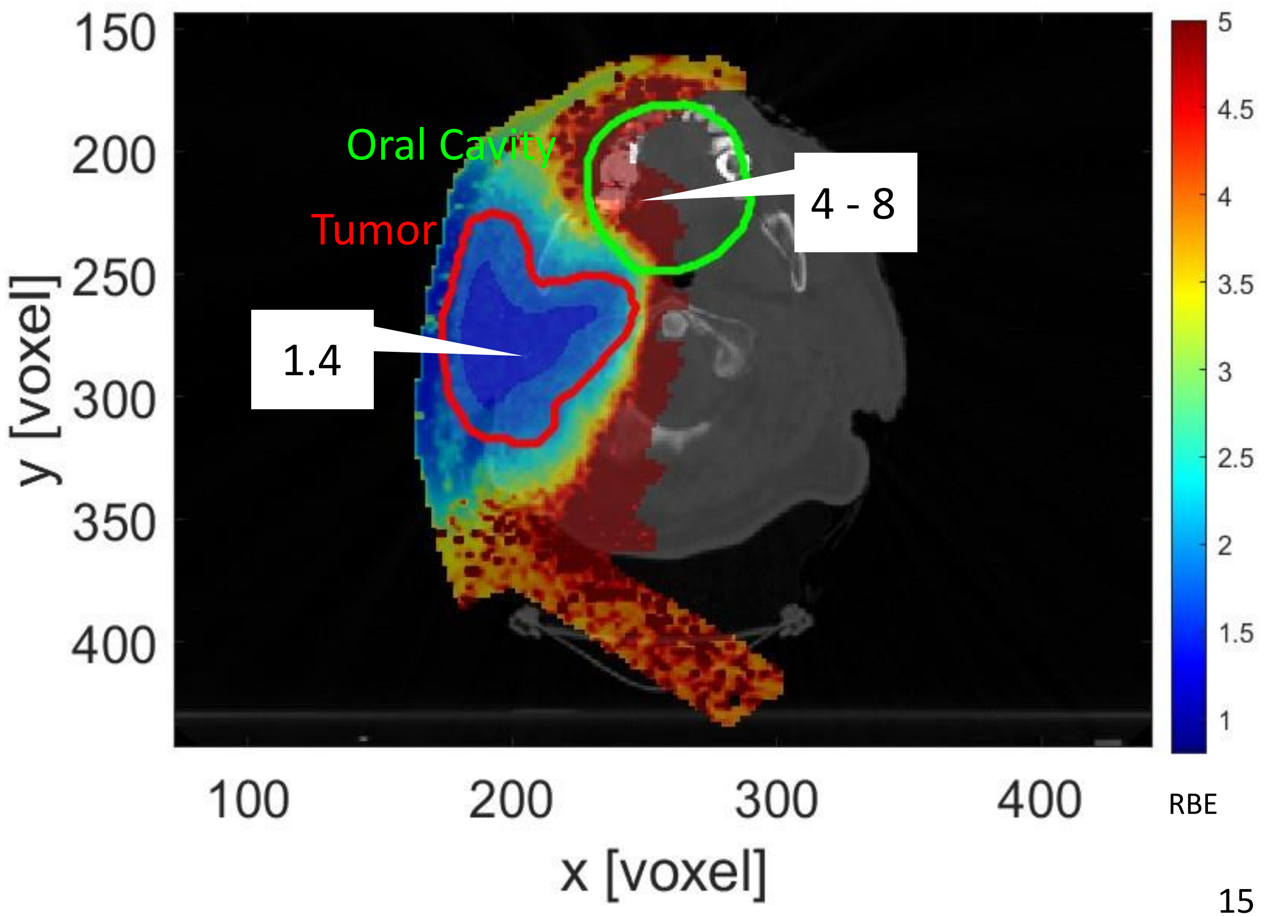
TOPAS → LET → McNamara RBE

TOPAS → Microdosimetric parameters → SMKM RBE

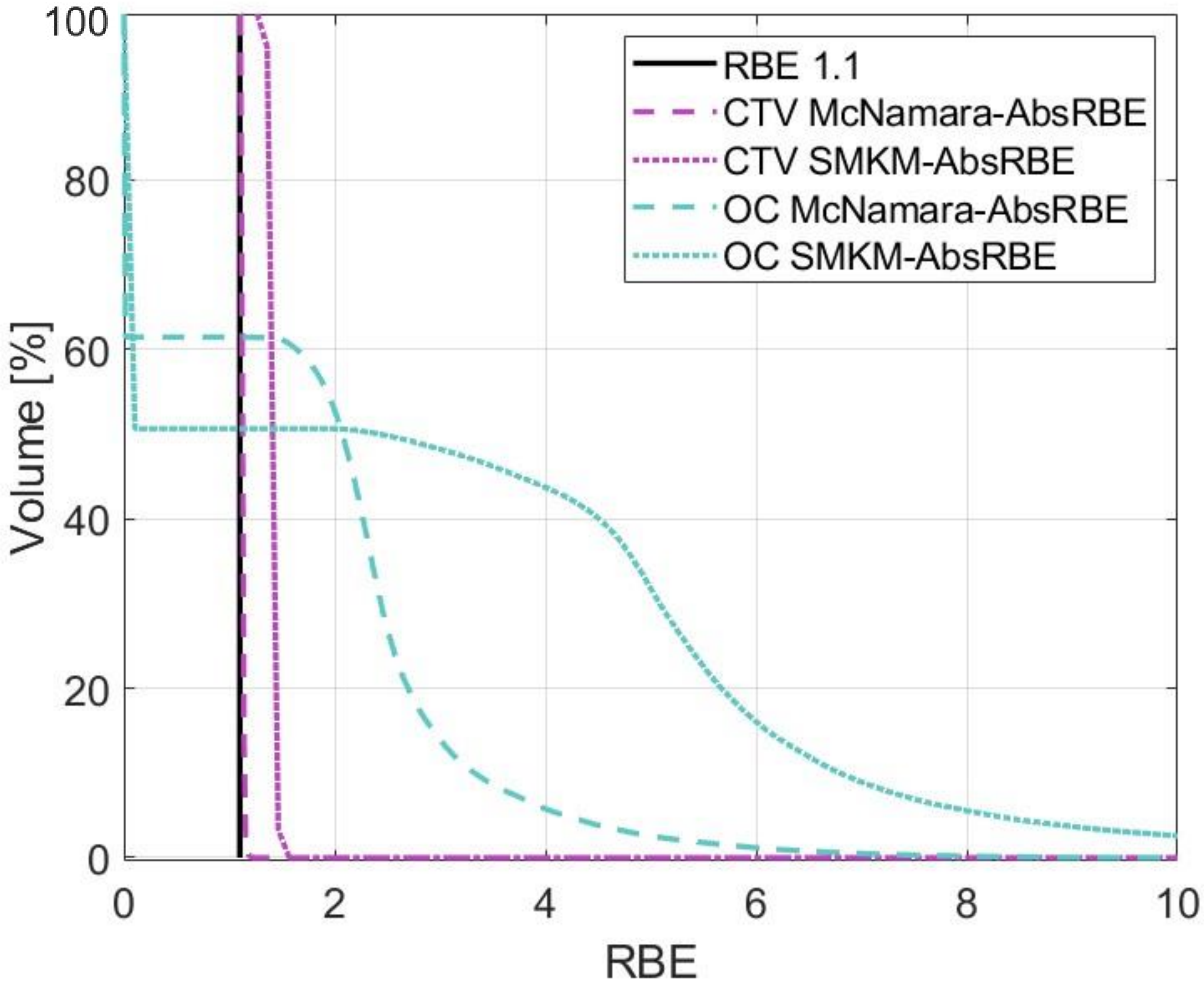
McNamara RBE map



SMKM RBE map

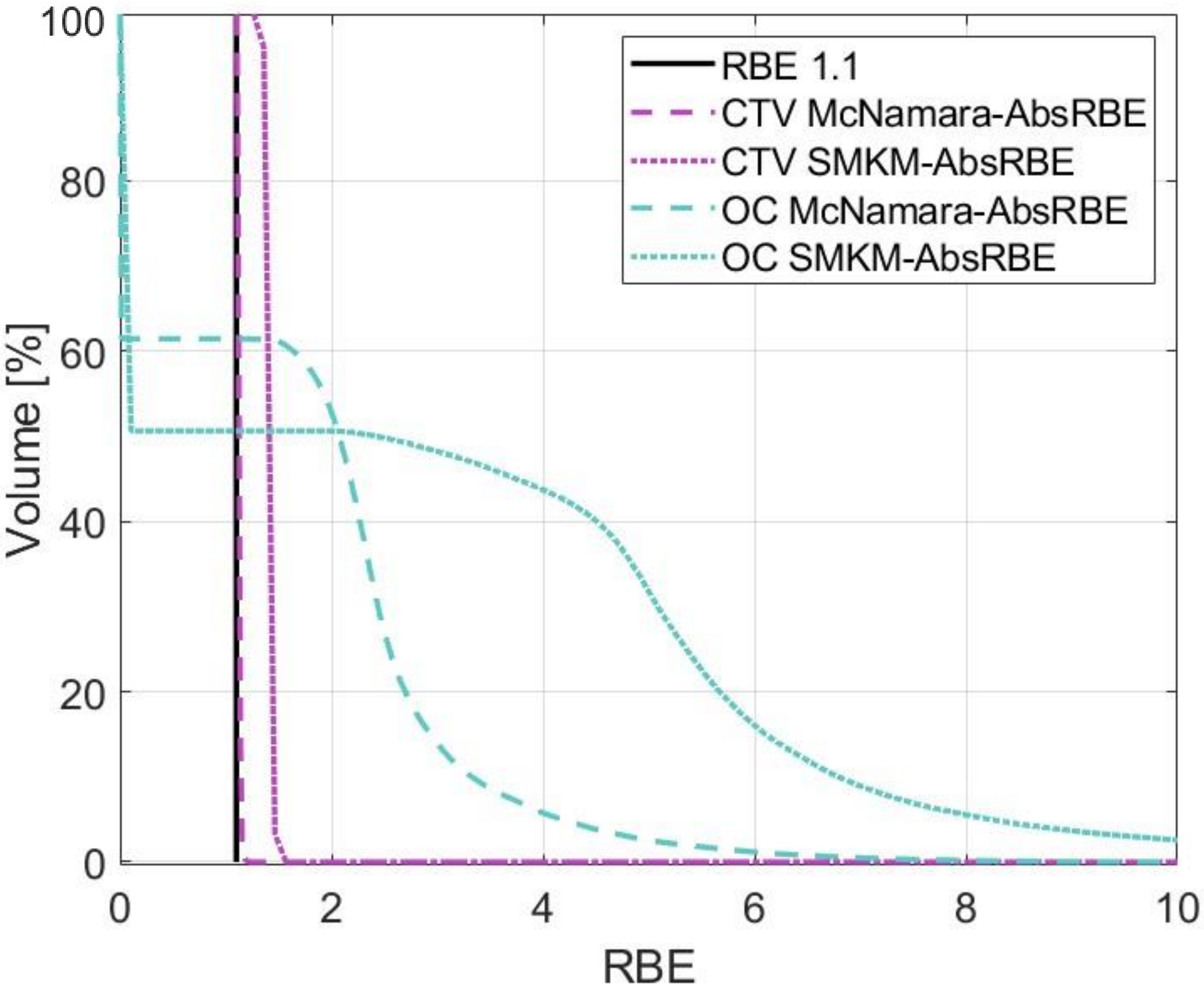


RESULTS - RBE



RBE-Volume Histogram RBE-VH
calculated with McNamara and SMKM,
in the tumor (CTV) and the oral cavity (OC)

RESULTS - RBE

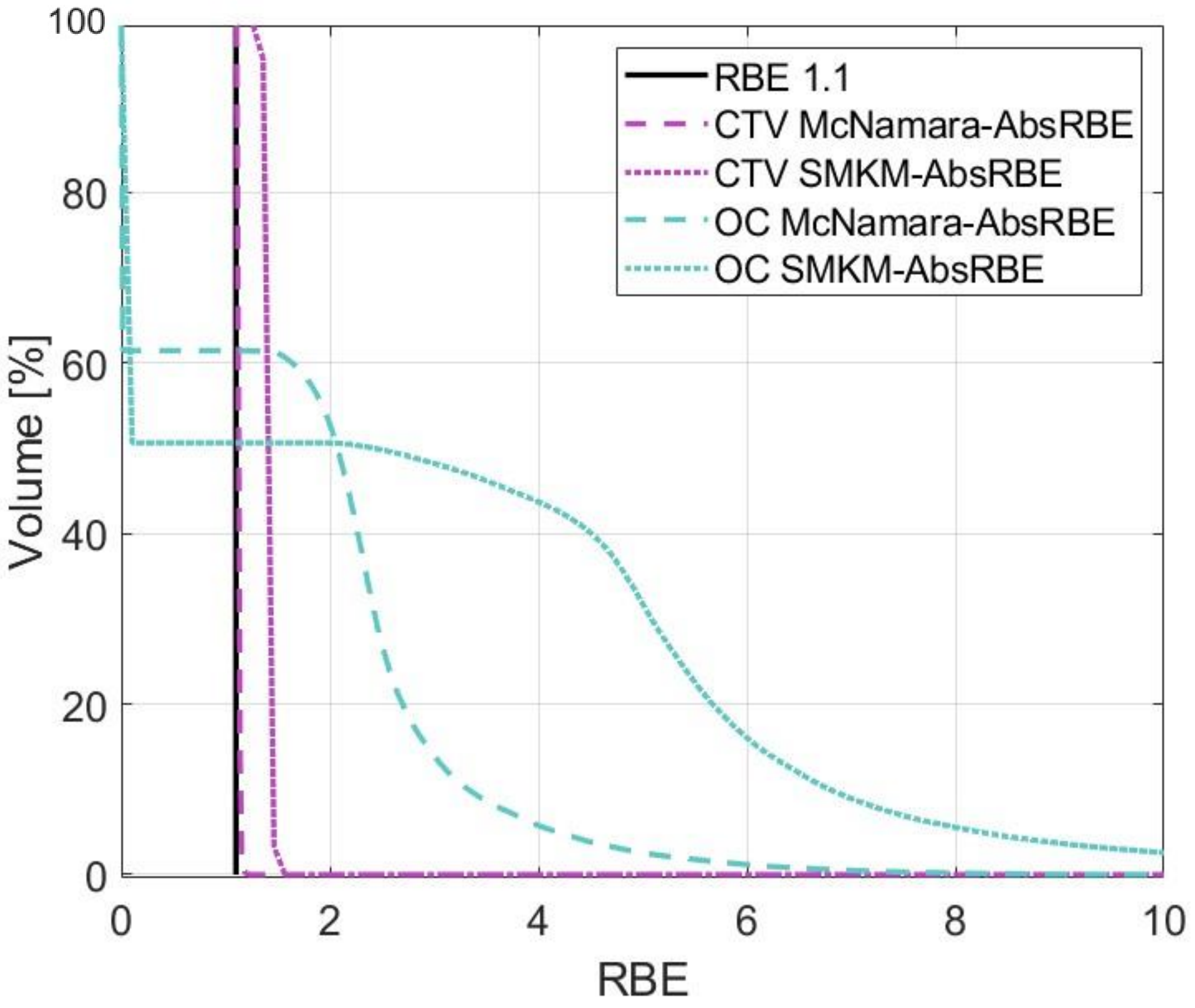


RBE-Volume Histogram RBE-VH
calculated with McNamara and SMKM,
in the tumor (CTV) and the oral cavity (OC)

- Higher values of RBE with SMKM than with McNamara
- **Higher RBE leads to a higher dose deposited in the organs**

- But which model is correct and what is the real RBE in the oral cavity ?

RBE-VH calculated with McNamara and SMKM, in the tumor (CTV) and the oral cavity (OC), in absolute values



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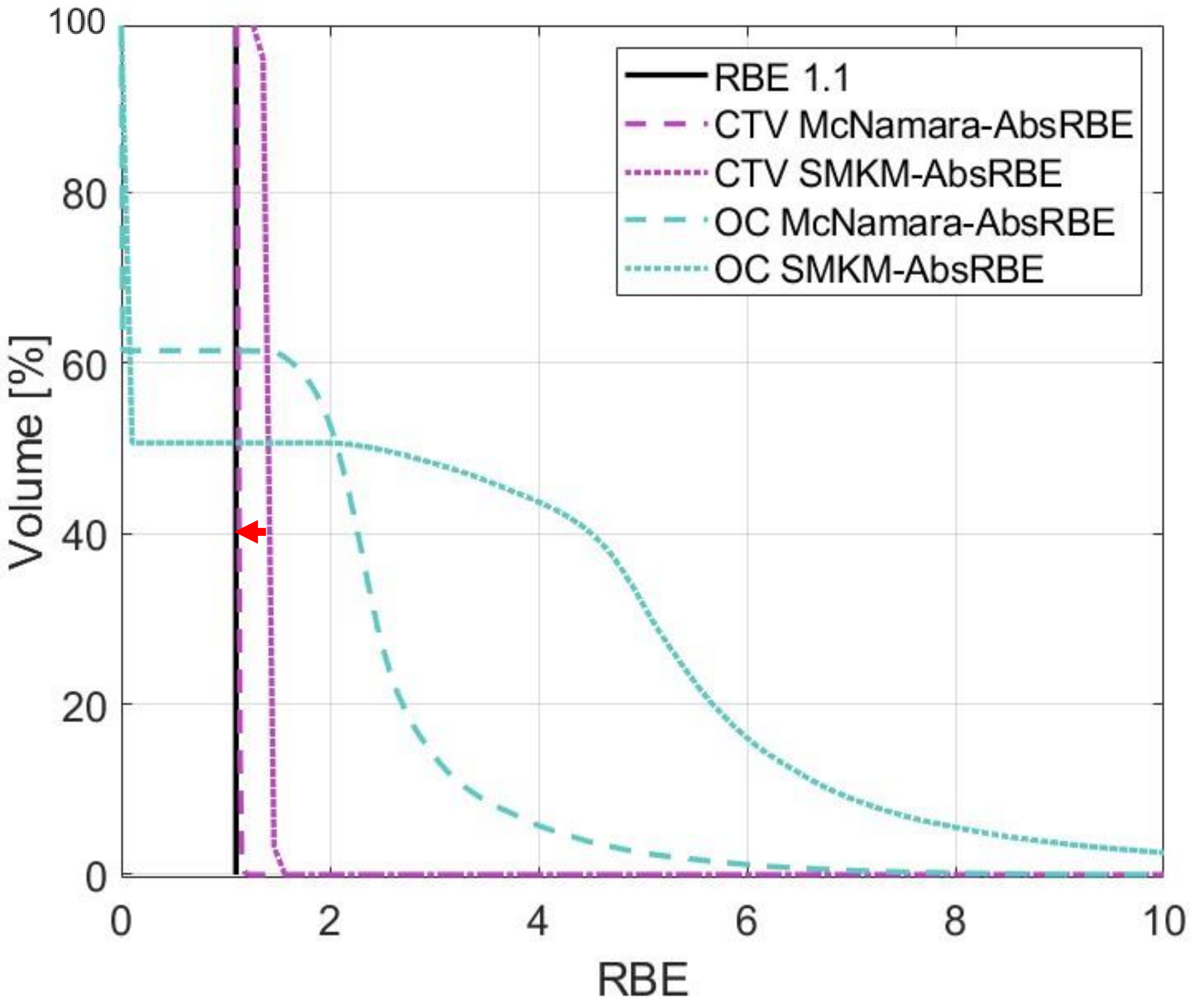
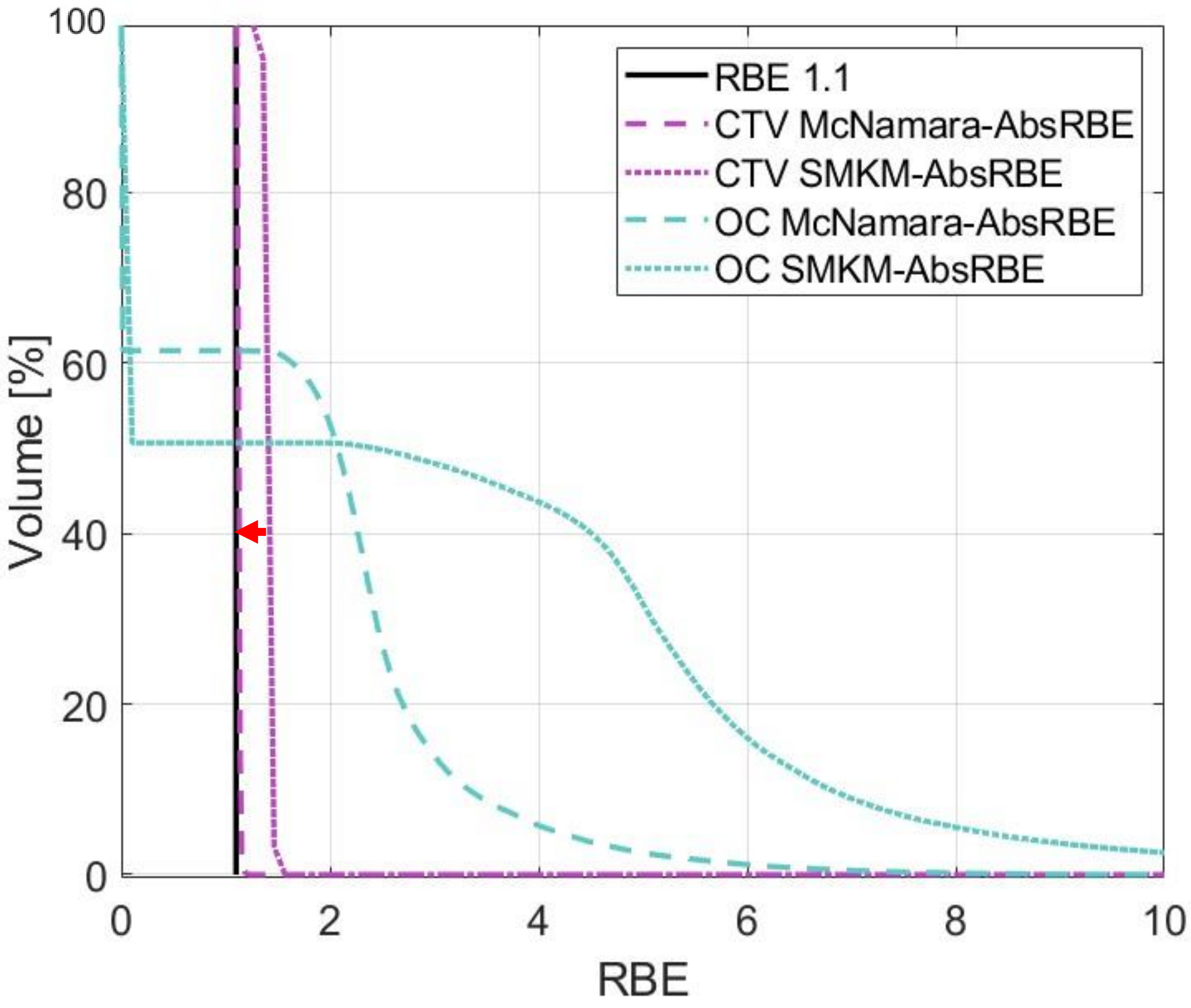
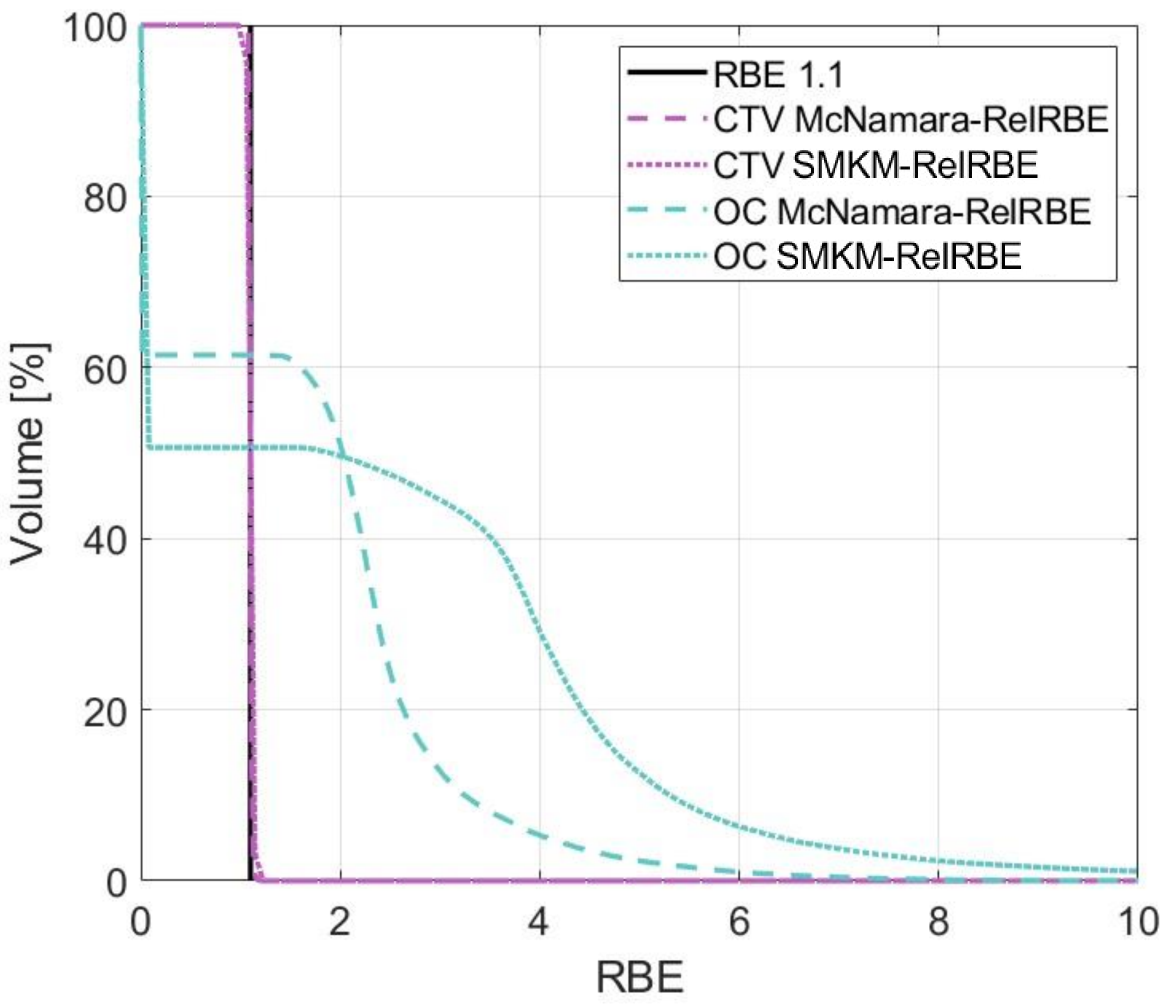


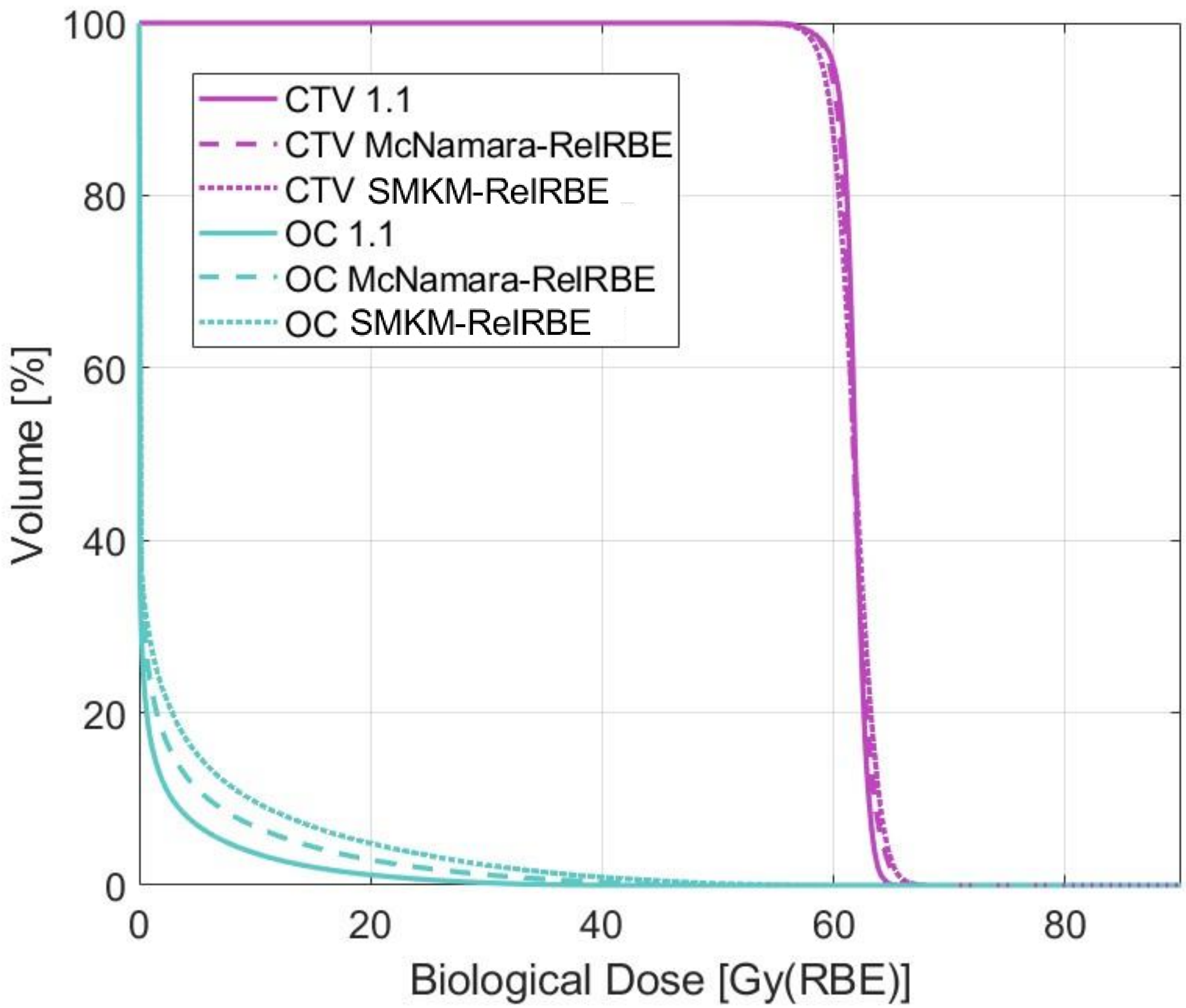
RBE-VH calculated with McNamara and SMKM, in the tumor (CTV) and the oral cavity (OC), in absolute values



RBE-VH calculated with McNamara and SMKM, in the tumor (CTV) and the oral cavity (OC), in relative values



RESULTS – BIOLOGICAL DOSE



DVH for the 3 RBE models, in the tumor (CTV) and the oral cavity (OC), in relative values

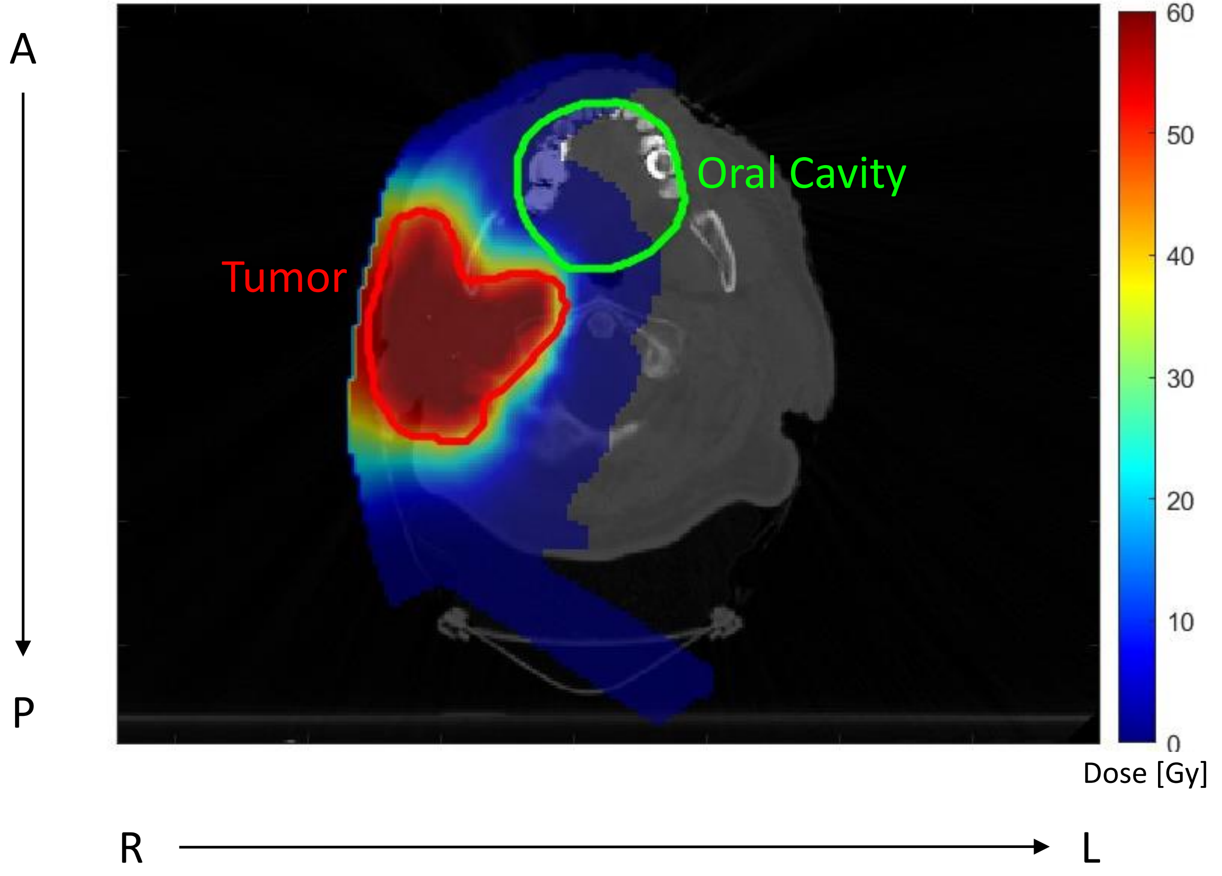
- **Dose increases in oral cavity with variable RBE**
- RBE of 1.1 might be correct for the tumor but not the oral cavity

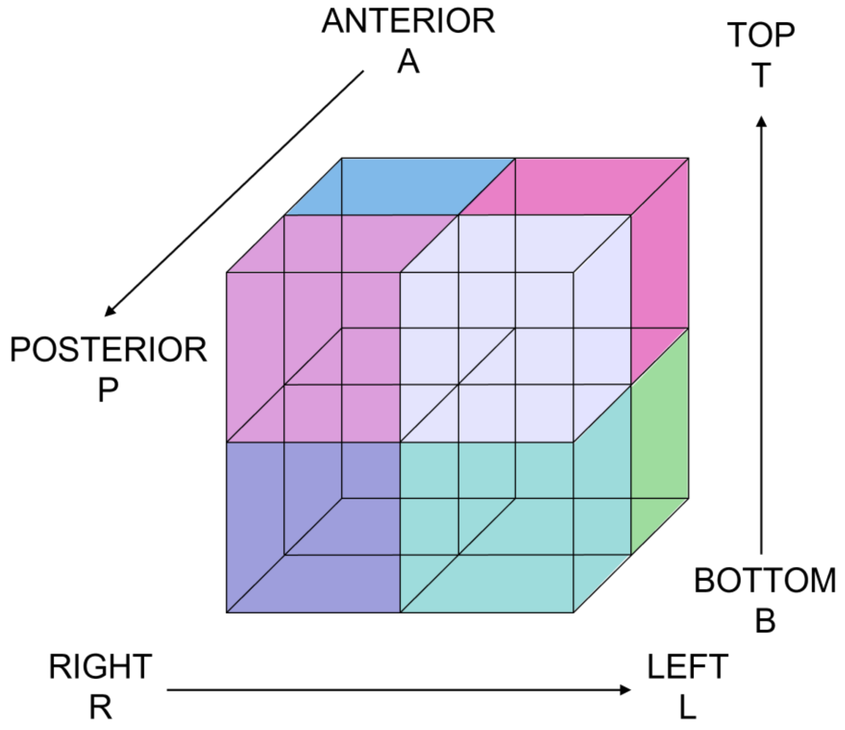
- However, this is an average dose for the whole organ, what is the dose is a smaller volume ?

RESULTS – LOCALIZED DOSE

Report :
R side : mild grade 1 mucositis

Eclipse → CT Scan, dose, organs contour → Dose per section





RESULTS – LOCALIZED DOSE

Equivalent Uniform Dose $$EUD = \left(\sum_i v_i D_i^{\frac{1}{n}} \right)^n$$

v_i	Relative volume
D_i	Dose given to the volume
n	Volume effect

RESULTS – LOCALIZED DOSE

Equivalent Uniform Dose

$$EUD = \left(\sum_i v_i D_i^{\frac{1}{n}}\right)^n$$

v_i Relative volume

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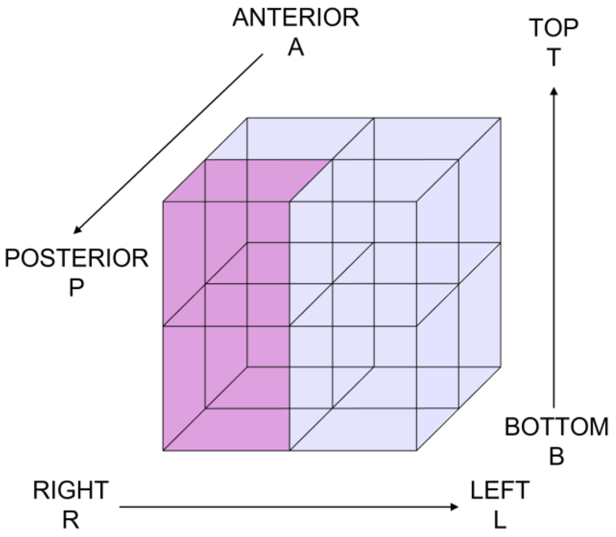

Table of EUD [Gy] values for the sectors of interest with the 3 RBE models

	EUD [Gy] (RBE 1.1)	**EUD [Gy] (Relative RBE McNamara)**	**EUD [Gy] (Relative RBE SMKM)**
TRP	4.77	7.80 ± 0.16	10.58 ± 0.21
BRP	13.89	19.22 ± 0.38	22.76 ± 0.46

RESULTS – LOCALIZED DOSE

Equivalent Uniform Dose $$EUD = \left(\sum_i v_i D_i^{\frac{1}{n}} \right)^n$$

v_i Relative volume

D_i Dose given to the volume

n Volume effect

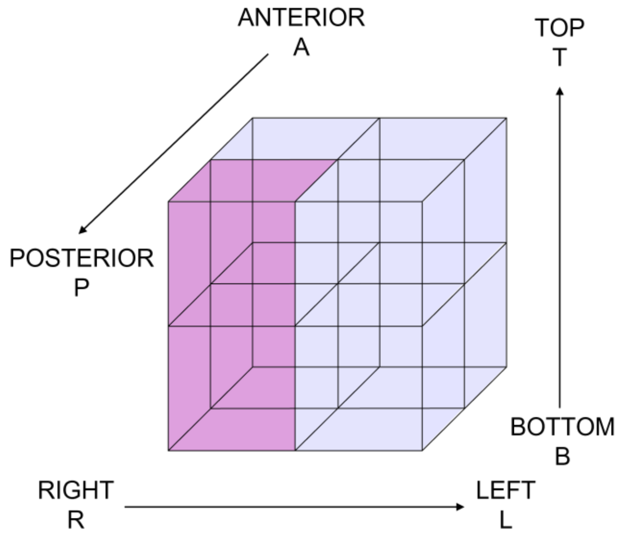

Table of EUD [Gy] values for the sectors of interest with the 3 RBE models

	EUD [Gy] (RBE 1.1)	EUD [Gy] (Relative RBE McNamara)	EUD [Gy] (Relative RBE SMKM)
TRP	4.77	7.80 ± 0.16	10.58 ± 0.21
BRP	13.89	19.22 ± 0.38	22.76 ± 0.46

Factor of 1.4 to 2.2 between EUD (RBE 1.1) and EUD (variable RBE)
Delivered biological dose underestimated with the fixed RBE convention

CONCLUSION

- Constant RBE in normal tissues is incorrect
- Underestimation of the dose deposited in the normal tissues when considering a constant RBE
- Assessing correct RBE requires pre-clinical and clinical data (*in vivo*)

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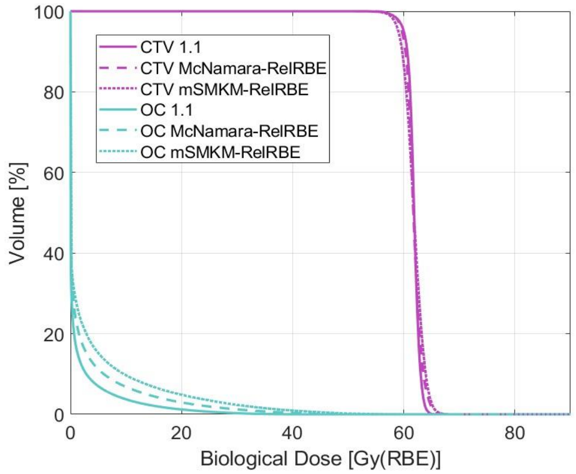
PERSPECTIVES

- Repeat the same analysis on more patients
- Construct a probability model to develop oral mucositis with proton therapy
- Compare with existing model for photon therapy
- Use machine learning to find correlations between the parameters and determine which one influence the most the occurrence and severity of oral mucositis

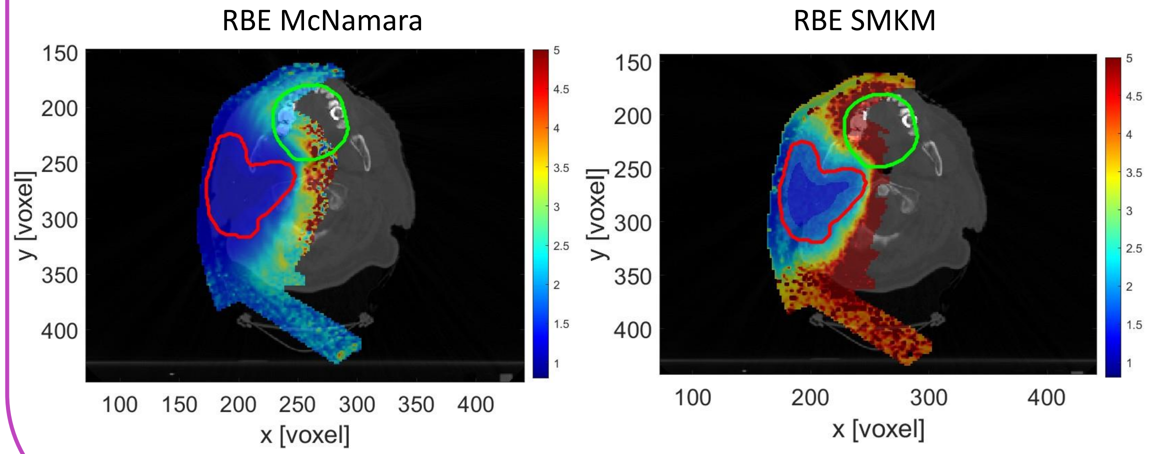
SUMMARY

ANALYTICAL AND MONTE CARLO DATA

HIGHER DOSE DELIVERED TO THE ORAL CAVITY



VARIABLE RBE : HIGHER VALUES IN HEALTHY TISSUES



REFERENCES

[1] Aimee L McNamara, Jan Schuemann, and Harald Paganetti. A phenomenological relative biological effectiveness (rbe) model for proton therapy based on all published in vitro cell survival data. Physics in Medicine & Biology, 60(21):8399, oct 2015

[2] T Inaniwa and N Kanematsu. Adaptation of stochastic microdosimetric kinetic model for charged-particle therapy treatment planning. Physics in Medicine & Biology, 63(9):095011, may 2018

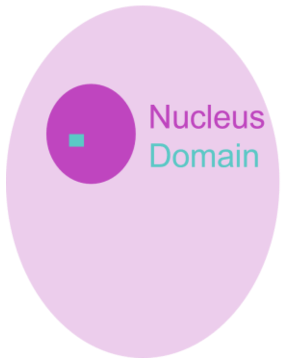
McNamara RBE :

$$RBE = \frac{1}{2D_p}\left(\sqrt{\left(\frac{\alpha}{\beta}\right)^2_x + 4D_p\left(\frac{\alpha}{\beta}\right)_x\left(0{,}999064 + \frac{0{,}35605}{\left(\frac{\alpha}{\beta}\right)_x}LET_d\right) + 4D_p^2\left(1{,}1012 - 0{,}0038703\sqrt{\left(\frac{\alpha}{\beta}\right)_x}LET_d\right)^2} - \left(\frac{\alpha}{\beta}\right)_x\right)$$

Aimee L McNamara, Jan Schuemann, and Harald Paganetti. A phenomenological relative biological effectiveness (rbe) model for proton therapy based on all published in vitro cell survival data. Physics in Medicine & Biology, 60(21):8399, oct 2015

Stochastic Microdosimetric Kinetic Model (SMKM) :

$$S = \exp(-\alpha_{SMKM}D - \beta_{SMKM}D^2)\left(1 + D\left[-\beta_{SMKM} + \frac{1}{2}(\alpha_{SMKM} + 2\beta_{SMKM}D)^2\right]z_{n,D}\right)$$



With $\alpha_{SMKM} = \alpha_0 + z^*_{d,D}\beta_0$ and $\beta_{SMKM} = \beta_0\left(\frac{z^*_{d,D}}{z_{d,D}}\right)$

$$RBE = \frac{-\alpha_X + \sqrt{\alpha_X^2 - 4\beta_X S}}{2\beta_X D}$$

T Inaniwa and N Kanematsu. Adaptation of stochastic microdosimetric kinetic model for charged-particle therapy treatment planning. Physics in Medicine & Biology, 63(9):095011, may 2018

BACK UP - LIST OF PATIENTS

Total number of patients : 67

	Number of Patients	Fraction
No mucositis	36	54%
Grade 1	15	22%
Grade 2	9	13%
Grade 3	7	11%
Chemotherapy	25	37%
Men	44	66%
Women	19	28%
Unknown	4	6%

Target areas : Base skull, Base tongue, Buccal, Larynx, Mastoid, Nasal, Nasopharynx, Neck, Orbit, Oropharynx, Palate, Parotid, Salivary glands, Tongue, Tonsil

Normal Tissue Complication Probability

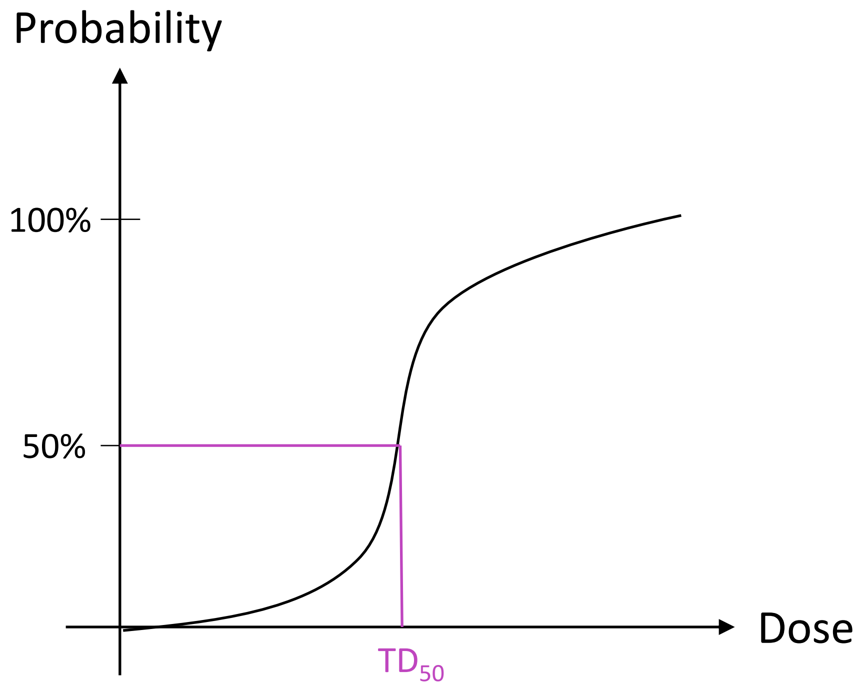
$$EUD = \left(\sum_i v_i D_i^{\frac{1}{n}}\right)^n$$

$$t = \frac{EUD - TD_{50}}{m \times TD_{50}}$$

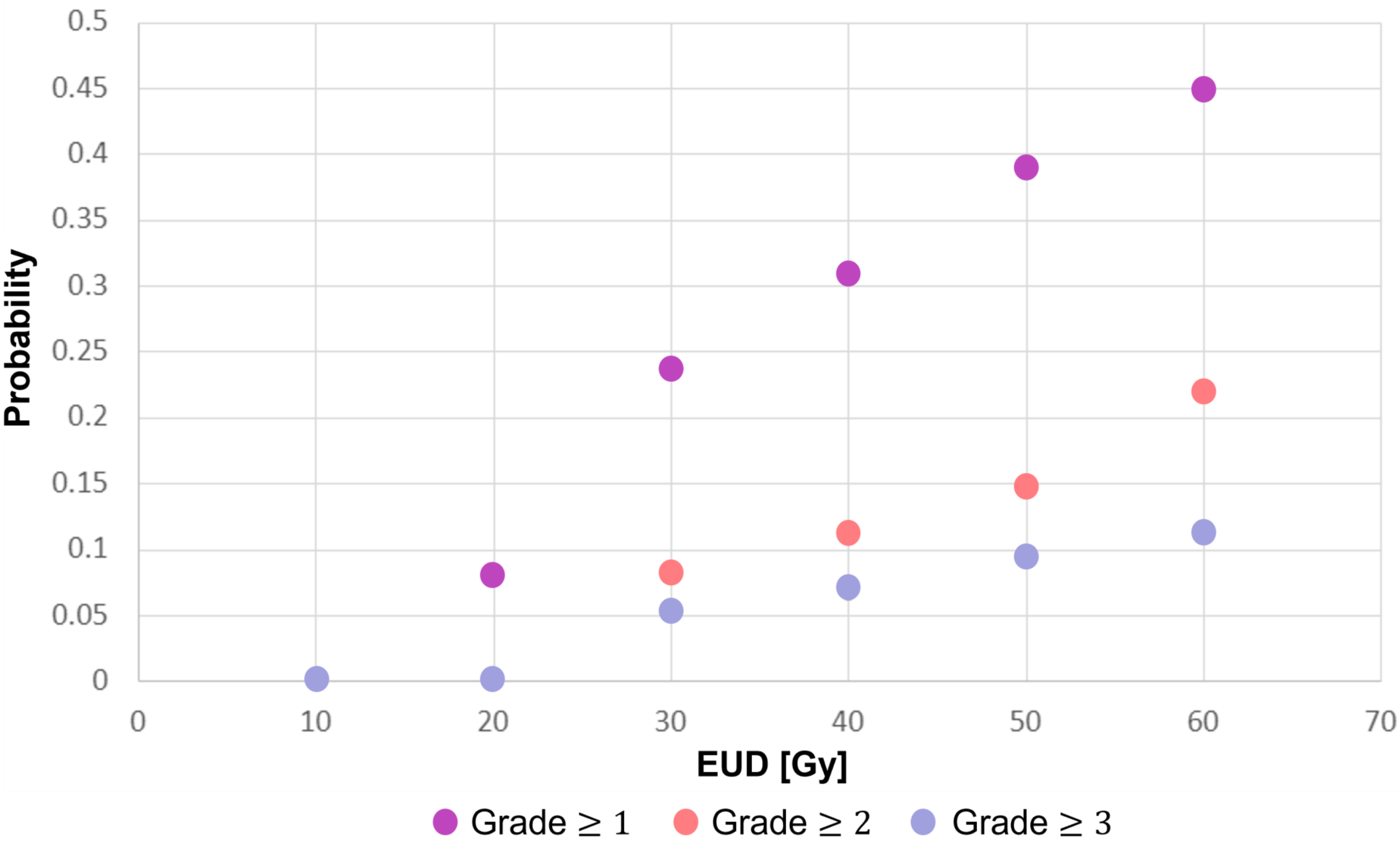
$$NTCP = \frac{1}{\sqrt{2\pi}} \int_{-\infty}^{t} e^{-\frac{x^2}{2}} dx$$

TD_{50} Dose tolerance associated with 50% complication risk

m Slope of the modeling at TD_{50}

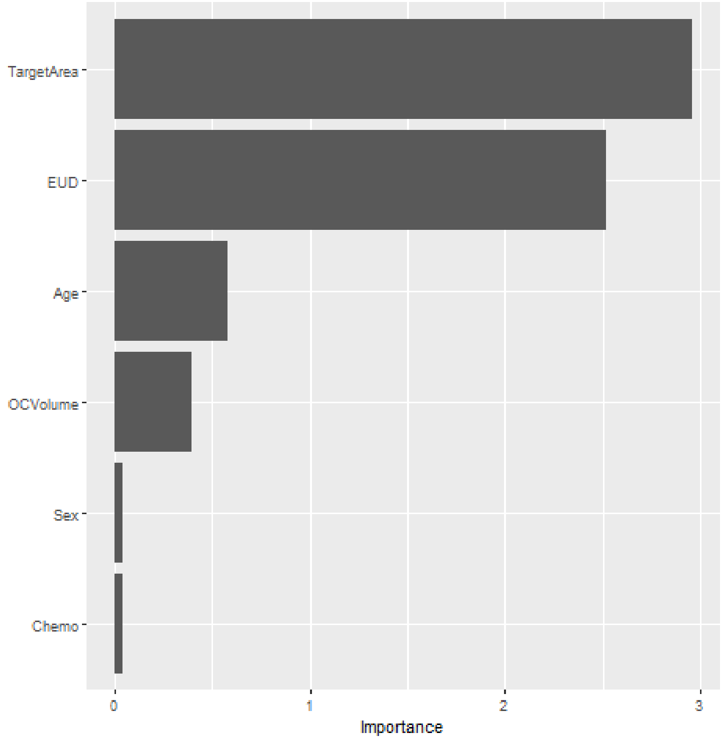


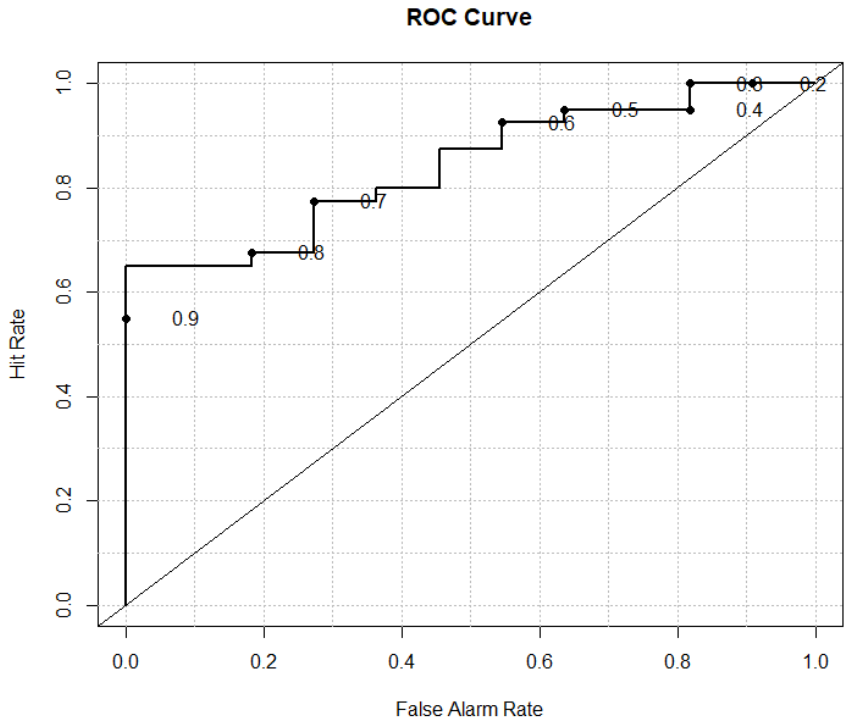
Normal Tissue Complication Probability



BACK UP - MACHINE LEARNING

- Train with Leave One Out method :
  - Train on the whole data set minus one row
  - Test on that single row
  - Repeat on the whole data set, each row is tested
- Classification based on Random Forest
- Get receiver operating characteristic (ROC) curve that gives the performance of the classification
- Get Variable Importance Plot (VIP) that gives the importance of each variable in the classification process





AUC = 0,82