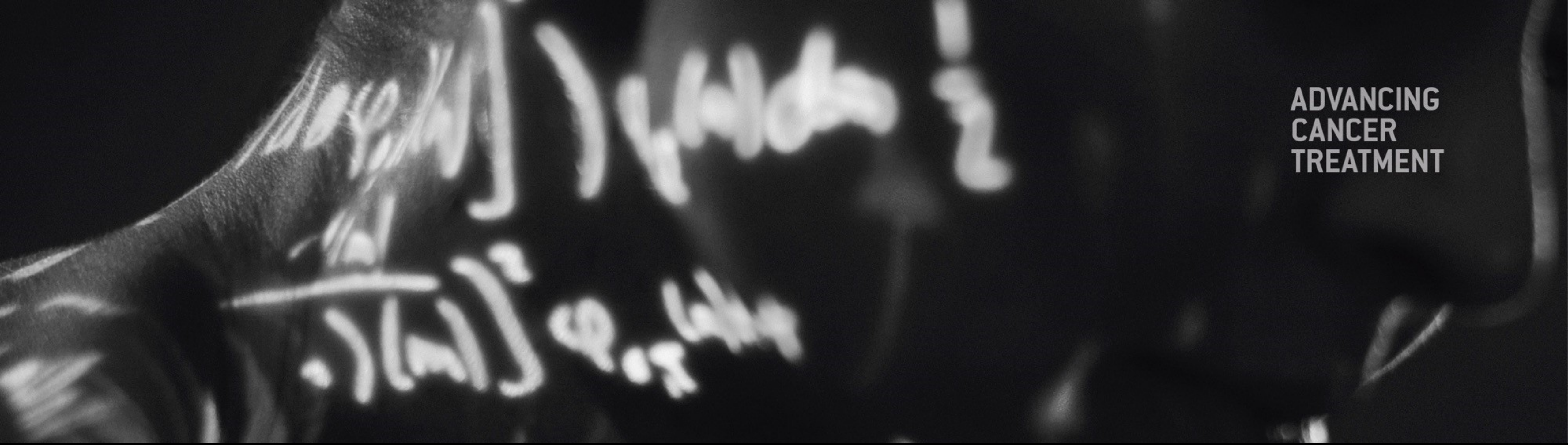

Track-end objectives in intensity modulated proton therapy to reduce linear energy transfer

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Disclosure

- Full-time employee as a Researcher at RaySearch Laboratories AB, Stockholm, Sweden
- Results mainly produced using a non-clinical research version of RayStation v9

Learning objectives

- To introduce proton track-end optimization as a tool to reduce…

  …linear energy transfer (LET) and relative biological effectiveness (RBE) in organs at risk (OARs)

  …normal tissue complication probabilities (NTCP)

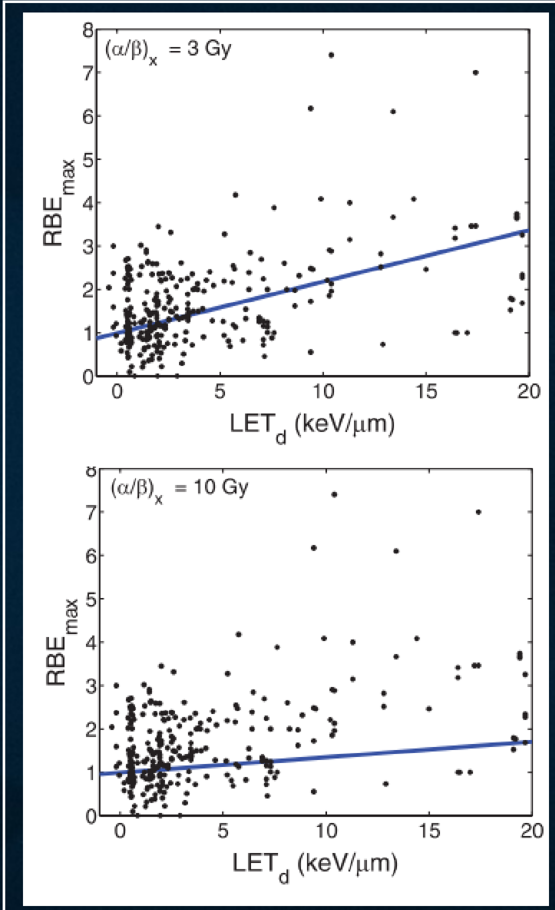
- To touch upon some comparisons with other optimization tools
  - LET optimization
  - Variable RBE optimization

Linear energy transfer (LET)

- LET is a macroscopic representation of the underlying microscopic energy deposition pattern
  - The unrestricted LET is the mean energy lost due to electronic interactions (*dE*) per unit track length (*dl*) [1]

- $\mathrm{LET} = \mathrm{LET}_{\infty} = \frac{\mathrm{dE}_{\infty}}{\mathrm{dl}} = \mathrm{S}_{\mathrm{el}}$

- Spectrum of LET in a voxel –> Averaging of LET per voxel
  - Dose-averaged unrestricted LET ($\mathrm{LET_d}$)
    - $\mathrm{LET_d}(x) = \frac{1}{\rho}\frac{\int_0^{\infty} \Phi_E(x) \cdot S_{el}^2(E)\, dE}{\int_0^{\infty} \Phi_E(x) \cdot S_{el}(E)\, dE}$



- *Increasing* RBE with *increasing* $\mathrm{LET_d}$
- Large uncertainties for *in vivo* RBE due to e.g...
  ...LET dependence
  ...patient specifics
  ...endpoint of interest
  ...tissue dependence
- Interest in indirect proton RBE optimization using...
  ...LET objectives
  ...objectives on where the proton stops

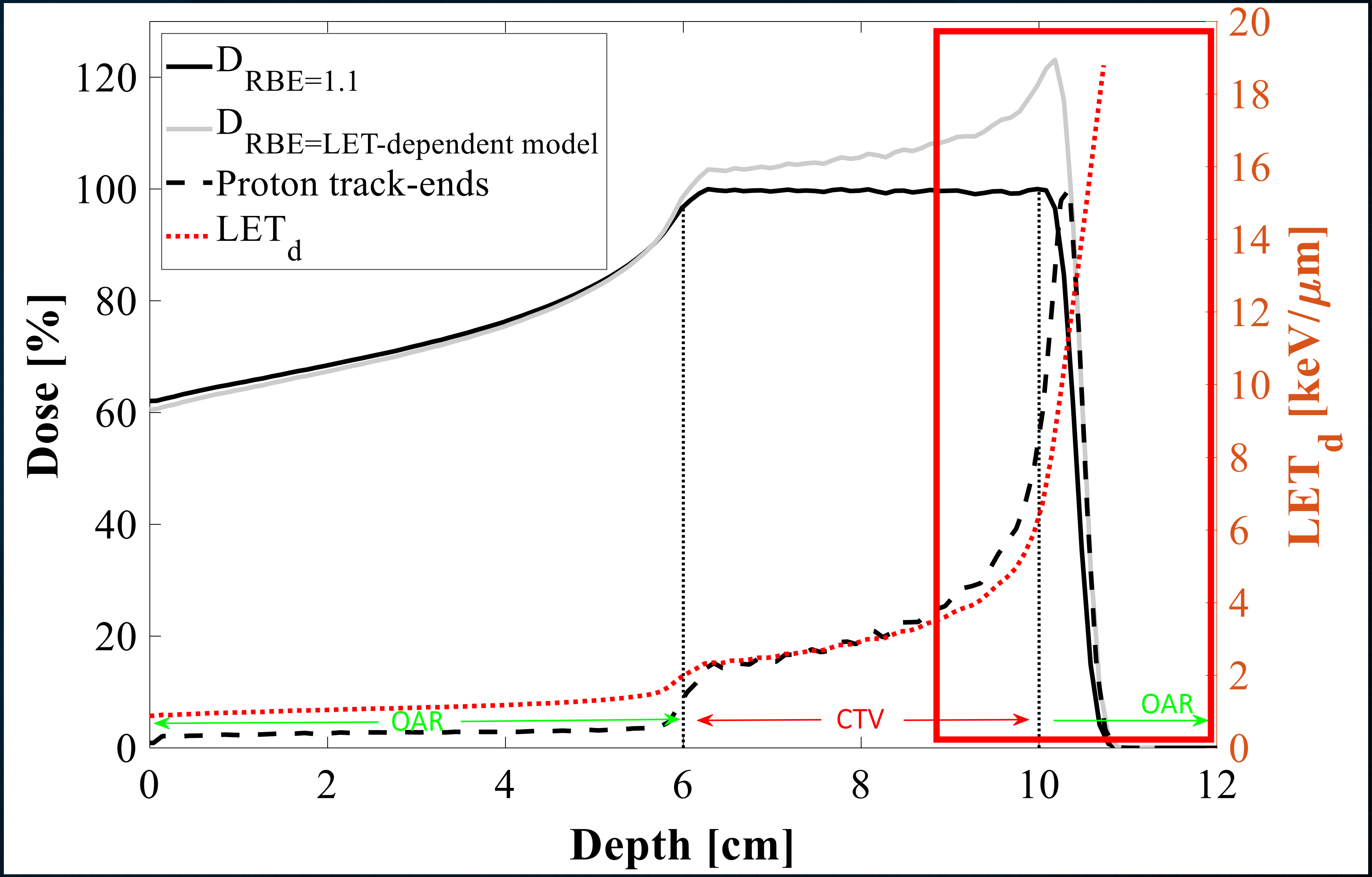
McNamara et al. *Phys. Med. Biol.* 2015 (data from Paganetti *Phys. Med Biol.* 2014)

[1] ICRU Report 85

RBE-weighted dose (D_{RBE}), LET_d and proton track-ends

- LET_d
  - Low & constant in entrance region
  - Higher & moderate increase in CTV
  - Rapid increase at distal edge
- LET-dependent RBE model
  - *Increased* D_{RBE} with *increasing* LET_d
  - Extended biological range
- Proton track-ends
  - Distribution where the proton stops
  - Peak correlates with *increased* D_{RBE}
- Proton range is defined as…

…the depth at which half the protons that undergo only electromagnetic interactions have stopped



Proton plan optimization

- D_{RBE} objectives assuming some RBE model
  - One RBE model for all ROI:s (RBE=1.1 clinical standard)
  - Multiple RBE models in various combinations [1]

- D_{RBE} objectives combined with objectives on RBE surrogates
  - LET based optimization [2] –> minimizing a general composite objective function $F = f_D + f_{LET}$
    - f_D – regular D_{RBE} based objective function
    - f_{LET} – some LET-based objective to reduce/increase LET in the volume of interest
    - As a high LET in a low dose voxel has small biological effect, LET objectives are typically…

      …weighted with dose ($\omega \cdot LET \cdot dose$, acting as a simplistic RBE model)

      …and/or only active above a certain dose threshold

[1] e.g. Sánchez-Parcerisa et al. *Med. Phys.* 2019, Unkelbach & Paganetti *Semin. Radiat. Oncol.* 2018, Ödén & Traneus AAPM 2020 e-Poster: PO-GeP-T-712
[2] e.g. An et al. 2017, Bai et al. 2019, Giantsoudi et al. 2013, Unkelbach et al. 2016

Proton track-end optimization

- Aims at shifting where the protons stop (named track-ends (TE) here)
  - ➢ *Reduce* # of proton track-ends in OARs to *reduce* LET, RBE & NTCP
  - ➢ *Increase* # of proton track-ends in tumor volumes to *increase* LET, RBE & TCP

- Minimizing the general composite objective function *F* [1]

$$F = f_D + f_{TE} = f_D + \lambda_{TE}^{OAR} \times H(TE^{OAR} - TE_{max}^{OAR}) \times \frac{[TE^{OAR} - TE_{max}^{OAR}]^2}{[TE_{max}^{OAR}]^2}$$

  - f_D – regular D_{RBE} based objective function
  - λ_{TE}^{OAR} – the relative weight of the TE objective for the OAR
  - TE^{OAR} – the ratio of proton TE:s stopping in the OAR to the total # of protons stopping in the patient
  - TE_{max}^{OAR} – the maximum allowable ratio of proton TE:s in the OAR to the total # of protons stopping in the patient
  - $H(x)$ – the Heaviside step function being equal to 1 if x >0, else equal to 0

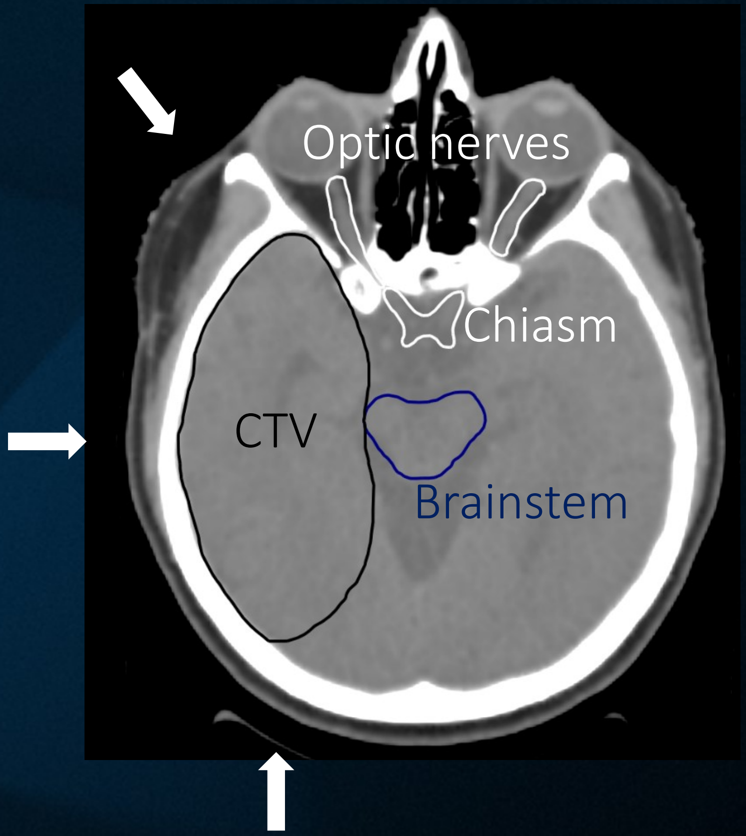
[1] Traneus & Ödén *IJROBP* 2019;103:747-757

Patient example case

- Intracranial case
  - Prescribed dose (PD) of 54 Gy (RBE) in 30 fractions

- 4 different proton plans using the same beam arrangement
  1) DOSEopt: $D_{RBE=1.1}$ objectives
  2) vRBEopt: $D_{RBE=Wedenberg}$ objectives
  3) LETopt: $D_{RBE=1.1}$ objectives + LET objectives for OARs
  4) TEopt: $D_{RBE=1.1}$ objectives + TE objectives for OARs

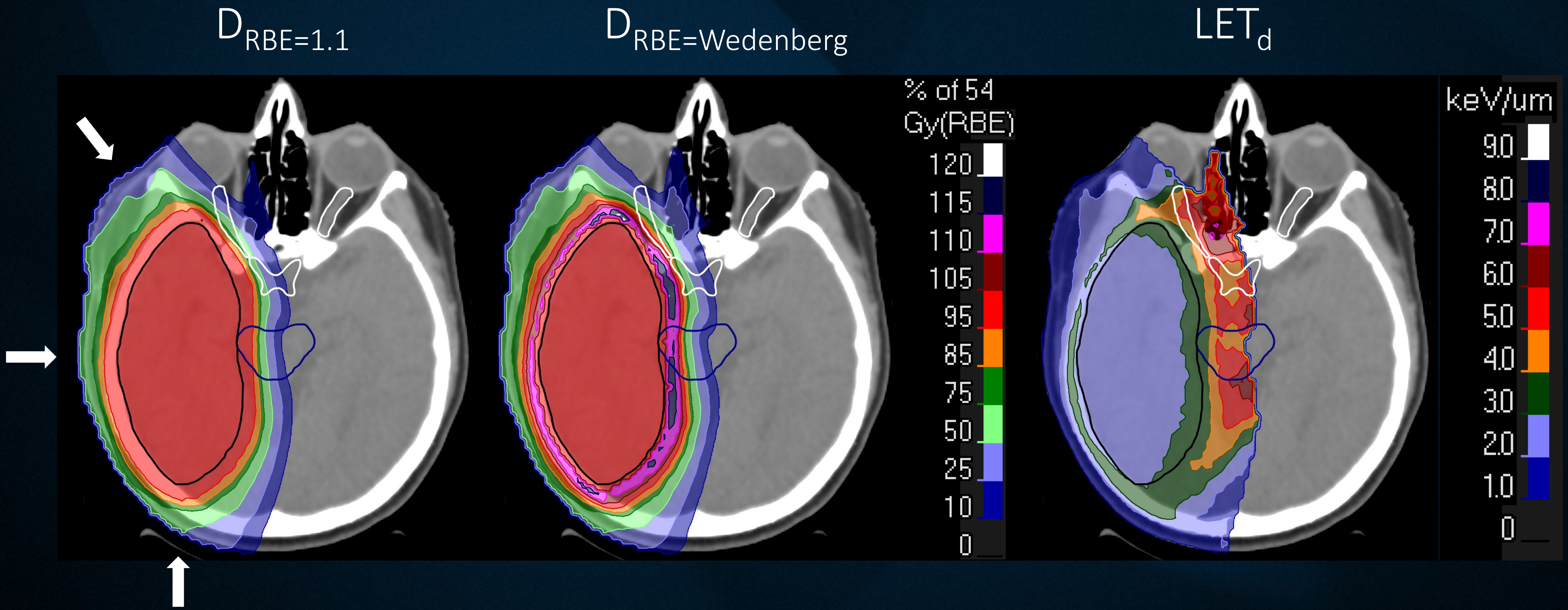
- Clinical goals
  - RBE = 1.1
  - Wedenberg RBE model [1]: α/β of 10 Gy for CTV and 2 Gy for OARs
    - Target: $D_{RBE,\ 98\%} \geq 95\%$ of PD
      $D_{RBE,\ 2\%} \leq 105\%$ of PD
    - Optical structures: $D_{RBE,\ 0.1\%} \leq 54$ Gy (RBE)
    - Brainstem: $D_{RBE,\ 0.1\ cm^3} \leq 60$ Gy (RBE)



[1] Wedenberg et al. *Acta Oncol.* 2013;52:580-588

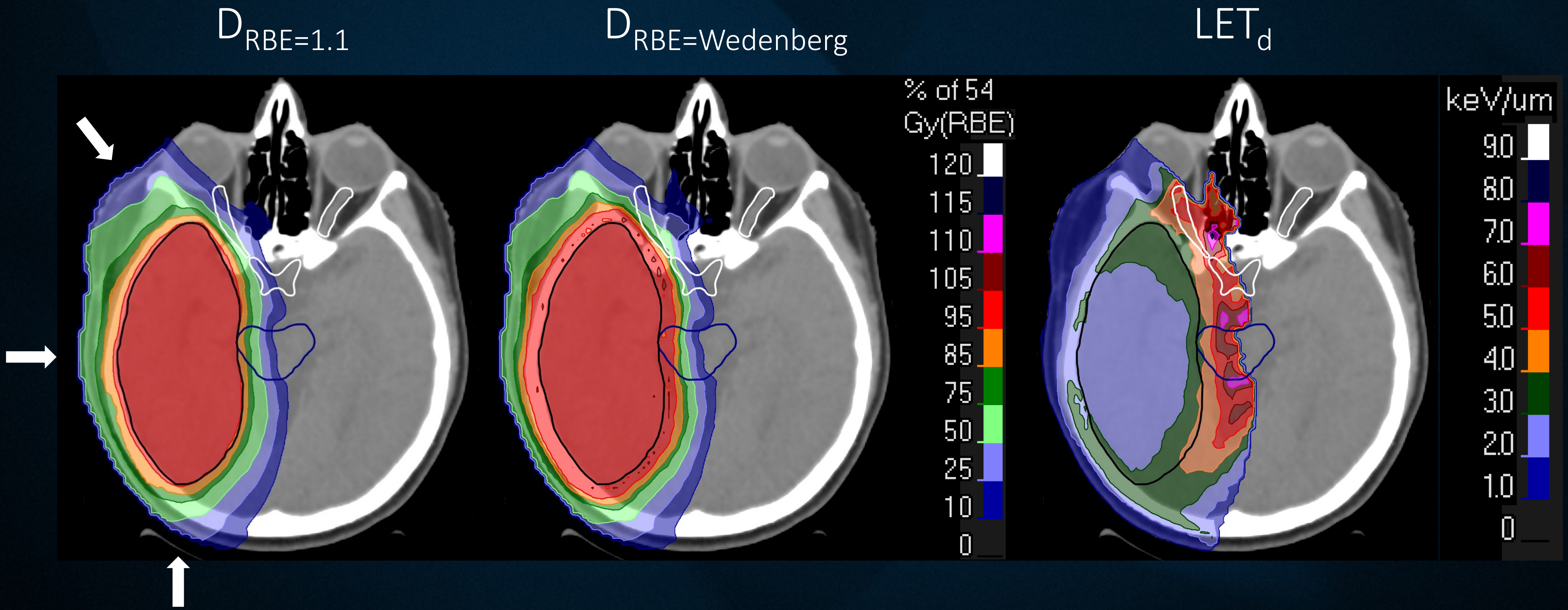
D_{RBE} & LET_d

Clinical goals / D_{mean}	DOSEopt
Min. target dose (RBE=1.1 / Wed)	YES / YES
OAR goals (RBE=1.1 / Wed)	YES / NO
D_{mean} for "Brain–CTV"	6.3 Gy



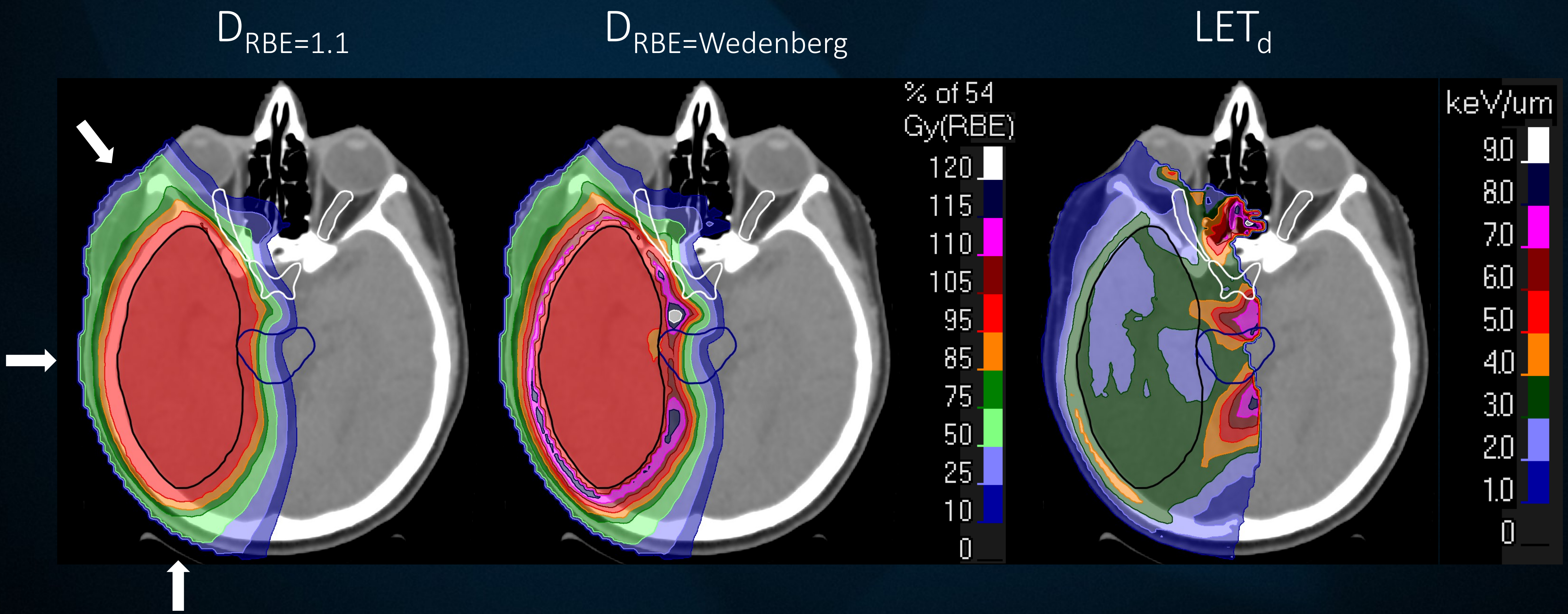
D_{RBE} & LET_d

Clinical goals / D_{mean}	DOSEopt	vRBEopt
Min. target dose (RBE=1.1 / Wed)	YES / YES	NO / YES
OAR goals (RBE=1.1 / Wed)	YES / NO	YES / YES
D_{mean} for "Brain–CTV"	6.3 Gy	-25%



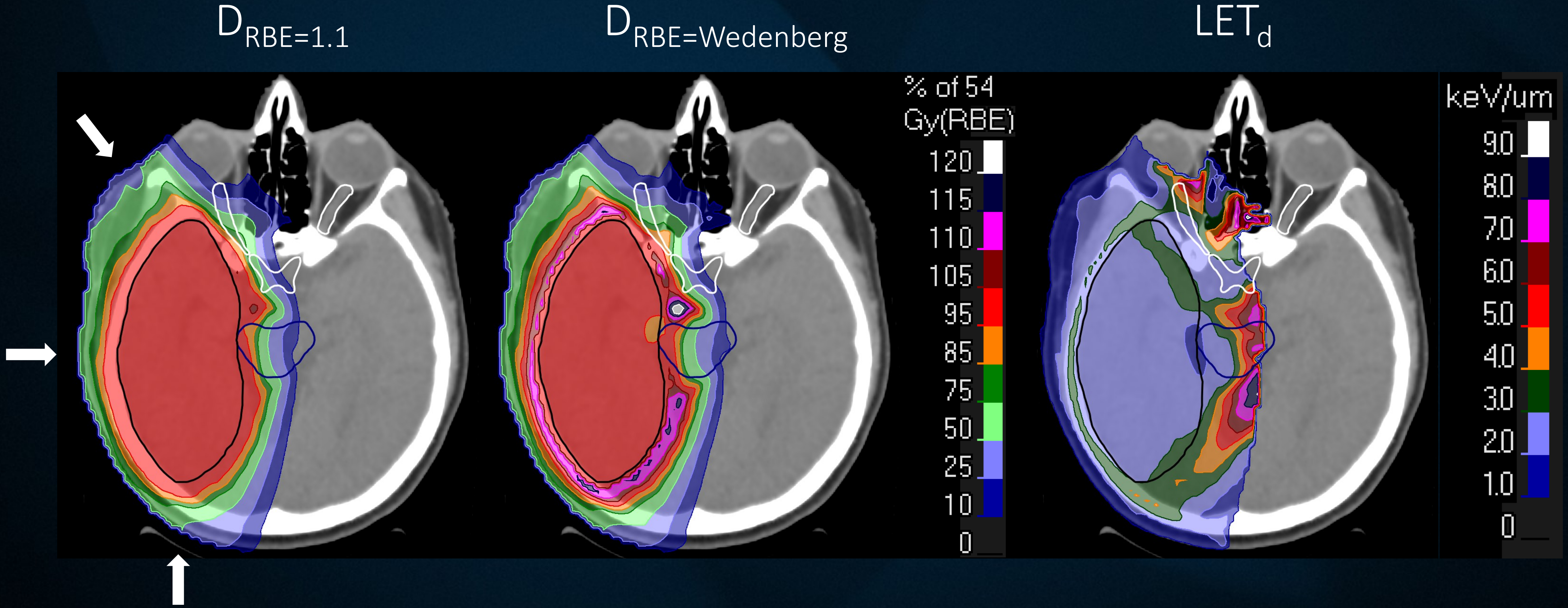
D_{RBE} & LET_d

Clinical goals / D_{mean}	DOSEopt	vRBEopt	TEopt
Min. target dose (RBE=1.1 / Wed)	YES / YES	NO / YES	YES / YES
OAR goals (RBE=1.1 / Wed)	YES / NO	YES / YES	YES / YES
D_{mean} for “Brain–CTV”	6.3 Gy	-25%	+4%

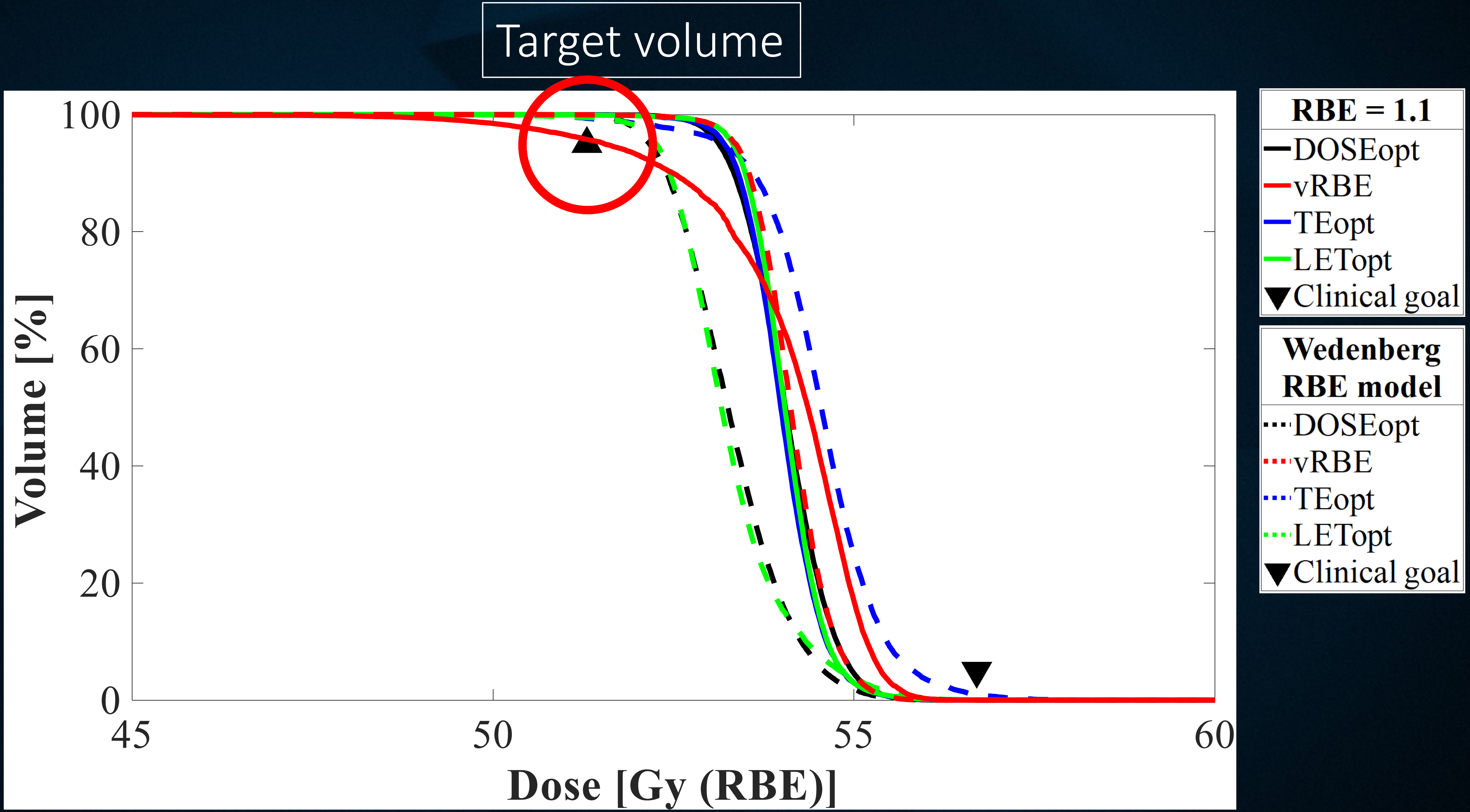


D_{RBE} & LET_d

Clinical goals / D_{mean}	DOSEopt	vRBEopt	TEopt	LETopt
Min. target dose (RBE=1.1 / Wed)	YES / YES	NO / YES	YES / YES	YES / YES
OAR goals (RBE=1.1 / Wed)	YES / NO	YES / YES	YES / YES	YES / YES
D_{mean} for "Brain–CTV"	6.3 Gy	-25%	+4%	+2%

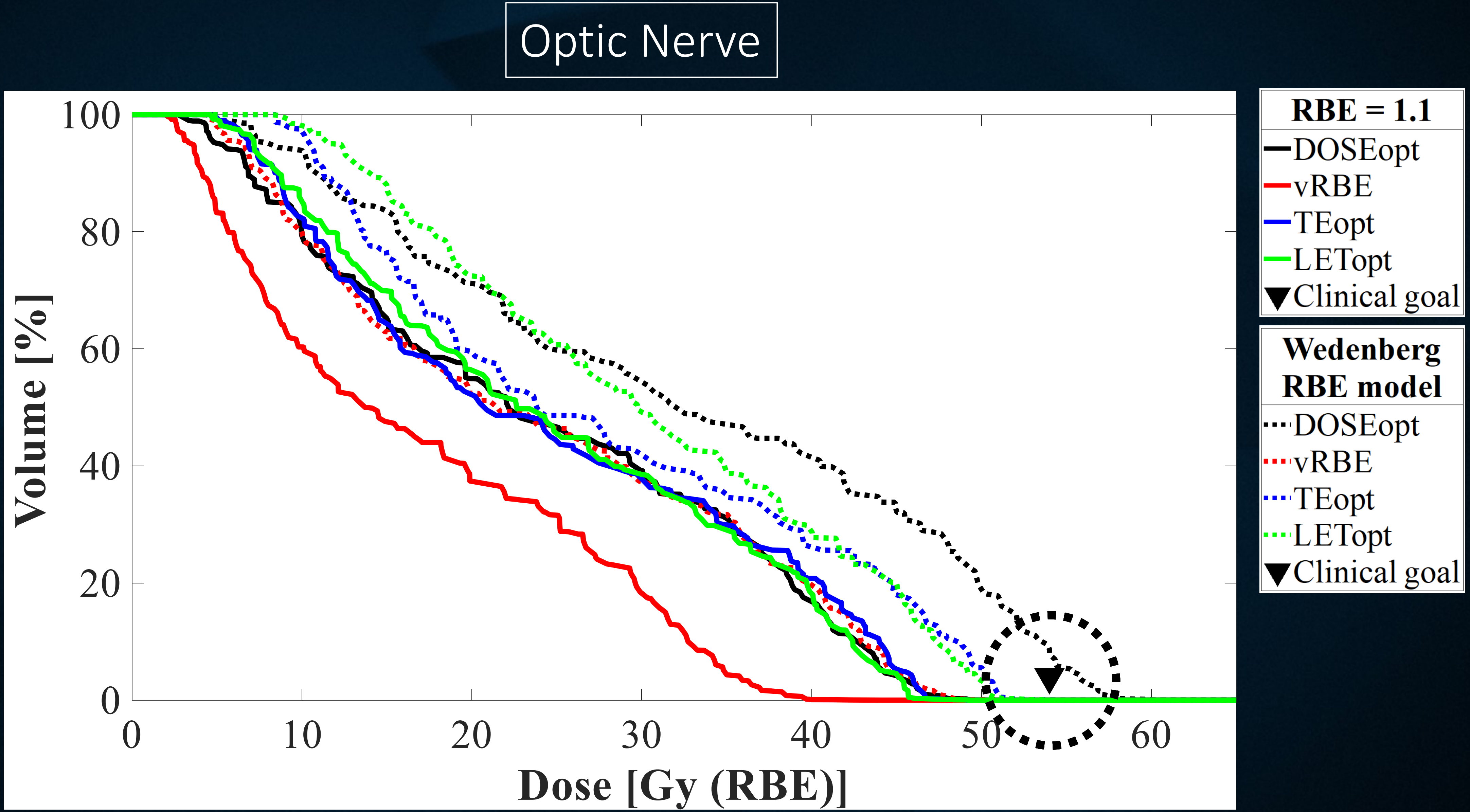


DVHs



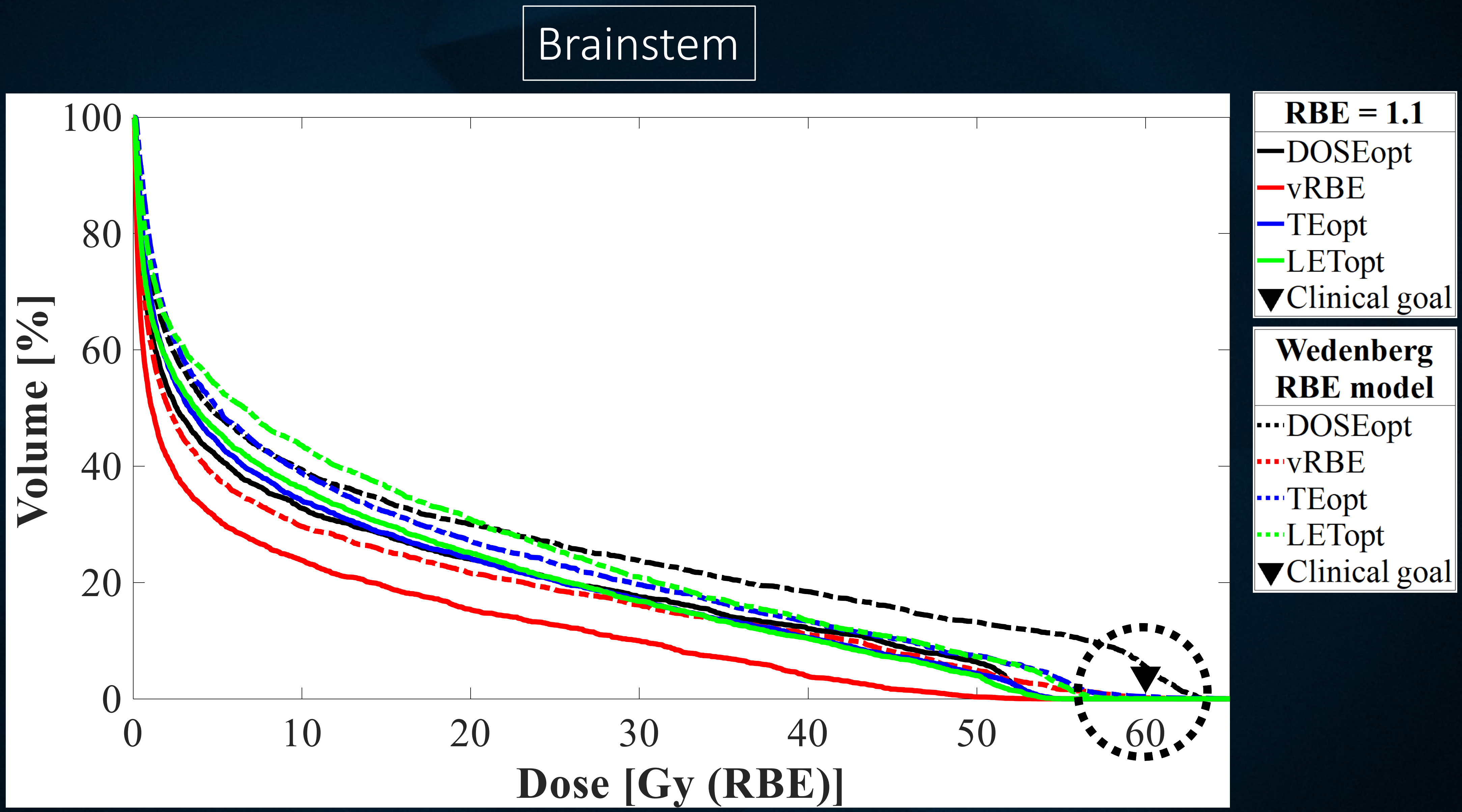
Target volume
100
80
60
40
20
0
Volume [%]
45
50
55
60
Dose [Gy (RBE)]
RBE = 1.1
DOSEopt
vRBE
TEopt
LETopt
Clinical goal
Wedenberg RBE model
DOSEopt
vRBE
TEopt
LETopt
Clinical goal

DVHs



Optic Nerve
100
80
60
40
20
0
Volume [%]
0
10
20
30
40
50
60
Dose [Gy (RBE)]
RBE = 1.1
DOSEopt
vRBE
TEopt
LETopt
Clinical goal
Wedenberg
RBE model
DOSEopt
vRBE
TEopt
LETopt
Clinical goal

DVHs


Brainstem
100
80
60
40
20
0
Volume [%]
0
10
20
30
40
50
60
Dose [Gy (RBE)]
RBE = 1.1
DOSEopt
vRBE
TEopt
LETopt
Clinical goal
Wedenberg RBE model
DOSEopt
vRBE
TEopt
LETopt
Clinical goal

Conclusions

- Proton optimization using LET, proton track-ends or variable RBE objectives is capable of…

  …*reducing* LET, RBE and potentially also NTCP in OARs…

  …*increasing* LET, RBE and potentially also TCP in tumor volumes…

  …while simultaneously fulfilling clinical goals based on RBE=1.1

- The resulting dose, LET and RBE distributions depend strongly on how…

  …the optimizer is implemented

  …the composite objective function

- Hence, results shown here might differ from other studies
  - One could argue that different optimization strategies at least have the potential of reaching similar solutions
  - Various opinions on this and how to move forward…

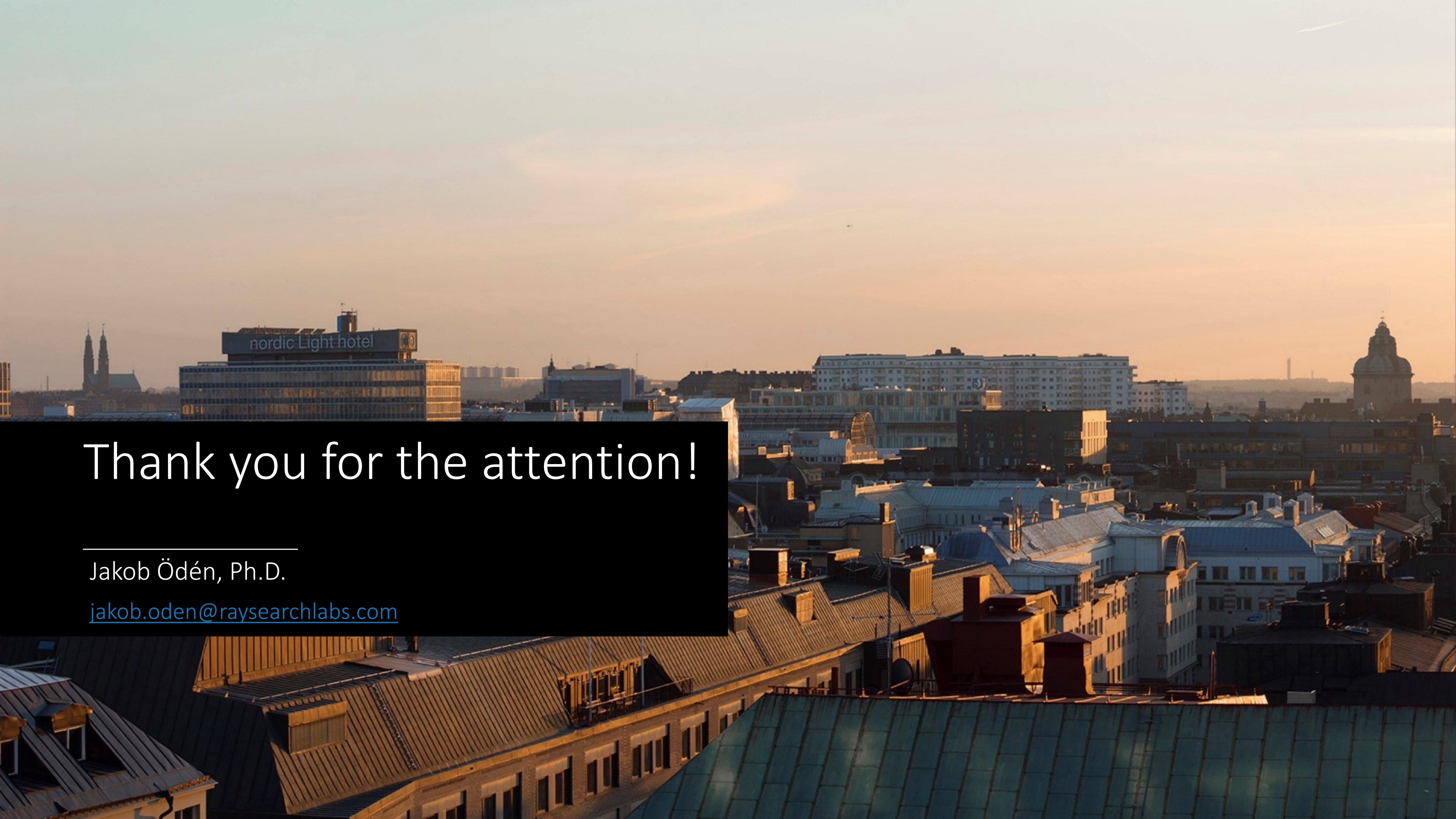
References & suggestions for further reading

- Proton RBE & RBE models
  - Carlson et al. *Radiat. Res.* 2008;169:447–59
  - Guan et al. *Sci. Rep.* 2015;5:9850
  - McNamara et al. *Phys. Med. Biol.* 2015;60:8399–8416
  - Ödén et al. *Med Phys* 2019;45:502–5
  - Paganetti et al. *Phys. Med. Biol.* 2014;59:R419–72
  - Paganetti et al. *Med. Phys. Phys. Med. Biol.* 2019;46:e53–78
  - Stewart et al. *Med. Phys.* 2018;45:925–52
  - Wedenberg et al. *Acta Oncol.* 2013; 52:580–588

- Variable proton RBE optimization
  - Frese et al. *Int. J. Radiat. Oncol. Biol. Phys.* 2011;79:80–88
  - Guan et al. *Int. J. Part. Ther.* 2018:5;160–71
  - Resch et al. *Phys. Medica* 2017:36 91–102
  - Sánchez-Parcerisa et al. *Med. Phys.* 2019;46:4276–4284
  - Unkelbach & Paganetti *Semin. Radiat. Oncol.* 2018;28:88–96

- LET optimization
  - An et al. *Med. Phys.* 2017;44:6138–6147
  - Bai et al. *Phys. Med. Biol.* 2019;64:025004
  - Bassler et al . *Acta Oncol.* 2014;53:25–32
  - Cao et al. *Phys. Med. Biol.* 2018;63:015013
  - Fager et al. *Int. J. Radiat. Oncol. Biol. Phys.* 2015;91:1057–1064
  - Giantsoudi et al *Int. J. Radiat. Oncol. Biol. Phys.* 2013;87:216–222
  - Tseung et al. *Int. J. Radiat. Oncol. Biol. Phys.* 2016;95:1535–1543
  - Unkelbach et al. *Int. J. Radiat. Oncol. Biol. Phys.* 2016;96:1097–106

- Proton track-end optimization
  - Ödén *Ph.D. thesis* 2019 (http://urn.kb.se/resolve?urn=urn:nbn:se:su:diva-174012)
  - Ödén et al. *Med Phys* 2020;47:342-351
  - Traneus & Ödén *Int. J. Radiat. Oncol. Biol. Phys.* 2019:103;747–757



Thank you for the attention!

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