Using comprehensive FLASH-RBE simulations to assess the potential clinical gain of FLASH proton therapy

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PURPOSE

The 'FLASH-RBE' concept (Mazal *et al.* 2020 [1]) allows ultra-high dose rates to be translated into a quantitative dose-effect, by ascribing an RBE<1 (i.e. tissue sparing) to dose delivered at FLASH conditions. The purpose of this study was to:

- **Implement and extend the FLASH-RBE concept** for spot-scanned proton therapy to take into account **delivery dynamics, threshold dose, threshold dose rate, and reoxygenation time**
- Use FLASH-RBE to quantify the FLASH-effect and assess the **potential clinical gain of FLASH proton therapy** for different **patient cases, treatment planning strategies and varying FLASH parameters.**

FLASH-RBE

FLASH-RBE activation in normal-tissues

- 'Moving window' analysis on voxel-dose time structure (Figure 1):
  1. For normal-tissue voxels, FLASH effect activated when:
     - Dose ≥ threshold dose <u>AND</u> dose rate ≥ threshold dose rate
  2. When activated, for all subsequent dose delivered to same voxel *within reoxygenation time,* regardless of dose/dose-rate:
     - **FLASH-RBE < 1**
  - For tumor voxels or non-FLASH dose:
     - **FLASH-RBE = 1**

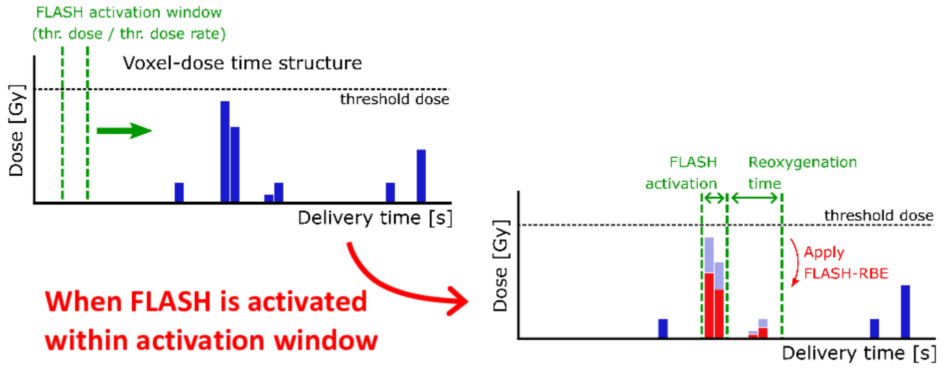

Figure 1. Moving window to identify 'FLASH activation' (i.e. threshold dose delivered at threshold dose rate). If activated, all dose delivered within FLASH activation window and reoxygenation time is ascribed a FLASH-RBE < 1.

METHODS

Patient cases

• Nasal cavity case	superficial tumor	PTV: 280 cc
• Pancreas case	deep-seated tumor	PTV: 104 cc

Spot-reduced treatment plans considered [2]

- **Bragg-peak-based IMPT:**
  - **Single-field or multi-field**
  - **Upstream energy modulation (degrader) or downstream energy modulation (range-shifter plates)**
  - Upstream multi-field IMPT plan = <u>reference plan</u>
- **Shoot-through (transmission) fields:**
  - **Single-field or multi-field**

Delivery settings

- Theoretical spot-wise beam intensities Varian ProBeam
- Spot switching 3 ms
- Energy switching:
  - Upstream 250 ms
  - Downstream 50 ms
- Time between fields (i.e. gantry rotation) > reoxygenation time

FLASH parameters investigated

• **FLASH activated RBE**	**0.67 (i.e. 33% sparing)**
• **Fraction doses**	**10 or 20 Gy**
• **FLASH dose thresholds**	**5 or 10 Gy**
• **FLASH dose rate thresholds**	**40 or 100 Gy/s**
• **Reoxygenation times**	**200 or 500 ms**

Evaluation

- Normal-tissue integral dose (ID; excluding PTV):
  - **FLASH-effect: ID reduction due to FLASH**
  - **Clinical gain: ID reduction compared with <u>reference plan</u>**

RESULTS

- FLASH effect was relatively low for conventional upstream energy-modulated Bragg-peak-based planning (see Figures 2 and 3):
  - **Advantageous planning strategies for FLASH:**
    - Shoot-through/transmission planning
    - Downstream energy modulation
    - Fewer fields
  - **Delivery/model parameters most affecting the FLASH effect:**
    - Higher fraction dose (strong effect)
    - Lower FLASH dose threshold (strong effect)
    - Lower FLASH dose rate thresholds (moderate effect)
    - Longer reoxygenation time (weak effect)
- **Clinical gain was typically limited**:
  - Shoot-through fields and downstream energy modulation (i.e. strong FLASH effect) result in considerably higher integral dose compared with the reference plan, for the deep-seated pancreas tumor in particular

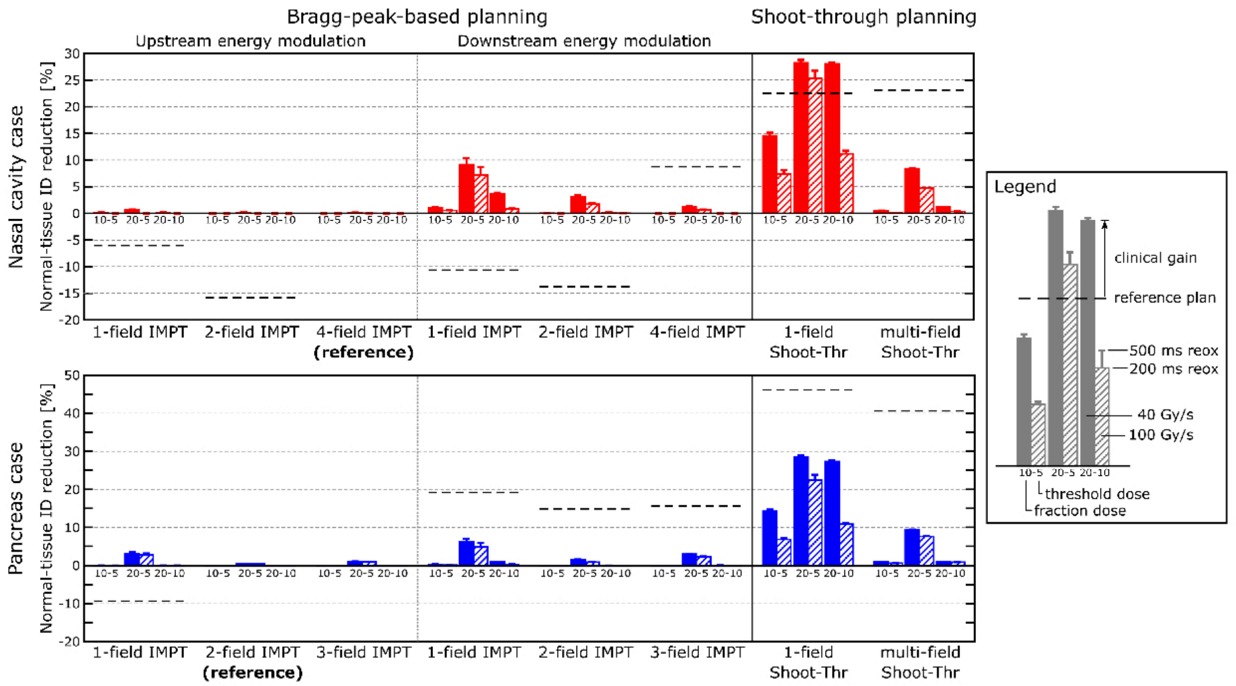

Figure 2. FLASH normal-tissue integral dose reductions for the nasal-cavity case (top) and pancreas case (bottom), for different planning strategies and FLASH parameters (fraction dose, threshold dose and dose rate, and reoxygenation time). Dashed black lines indicate the normal-tissue ID reduction if the reference IMPT plan would be used instead.

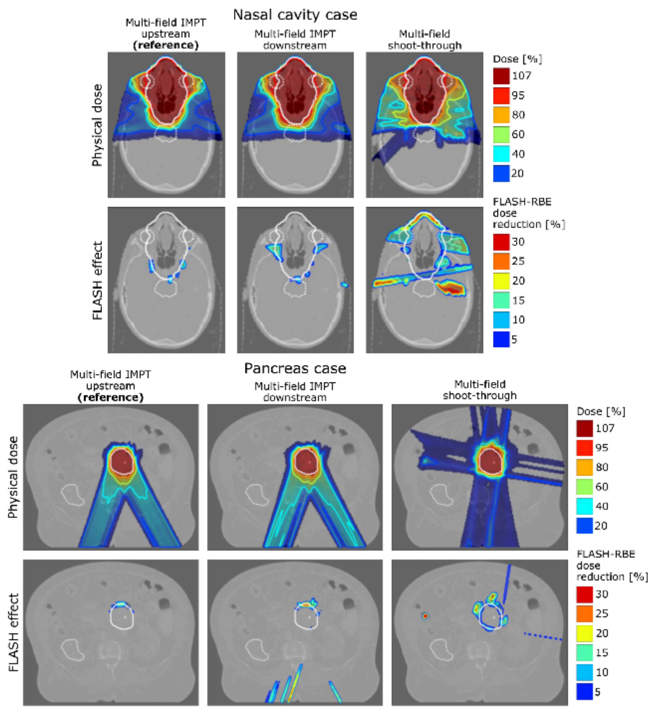

Figure 3. Physical dose distributions (top row) and FLASH-RBE dose reductions (bottom row) for 20 Gy fraction dose, 5 Gy threshold dose, 40 Gy/s dose rate threshold, and 200 ms reoxygenation time. White contours indicate PTV (solid) and organs-at-risk (dotted).

CONCLUSION

- **Substantial FLASH effects** could only be achieved when using **shoot-through fields or downstream energy modulation**, combined with **high fraction doses**
- **Planning/delivery strategies maximizing the FLASH effect** typically result in **increased normal-tissue dose compared with conventional IMPT planning**

For the FLASH parameters studied here, our results indicate that PBS proton based FLASH is unlikely to be more effective for general normal-tissue sparing (integral dose) than conventional IMPT. Further investigations are required to assess its effectiveness for more selective sparing.

REFERENCES AND ACKNOWLEDGMENTS

[1] A. Mazal *et al.*, FLASH and minibeams in radiation therapy: the effect of microstructures on time and space and their potential application to protontherapy, Br. J. Radiol. 2020.
[2] S. van de Water *et al.*, Towards FLASH proton therapy: the impact of treatment planning and machine characteristics on achievable dose rates, Acta Oncol. 2019.

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