

ABSTRACT

- IMRT has optimized of 3D spatial dose distributions allowing target coverage while reducing toxicity.
- We aim to optimize the fourth dimension of time through which RT is delivered to further reduce toxicity by increased sublethal damage through *temporally feathered radiation therapy (TFRT)*.
- Prior *in silico* modeling using a dynamic NTCP model of tissue response, accounting for recovery, has demonstrated NTCP reduction with TFRT plans .
- We demonstrate the ability of generating TFRT plans using current treatment planning systems.

MATERIAL AND METHODS

- Patients with oropharynx cancer treated to 70 Gy/ 35 fx were planned using conventional IMRT techniques and compared to TFRT technique.
- TFRT plans were generated as a composite of 5 iso-curative plans each with altered constraints on particular OARs of interest.
- For each of these plans, a single OAR is deprioritized such that it receives a higher dose (dH) while the remaining 4 OARs receive a lower dose (dL) than the standard fractional dose (dS) delivered in a conventional IMRT plan. Each plan is delivered a specific day of the week, which in effect leads to a dH delivered to each OAR once weekly and dL that is delivered to that OAR on the other 4 days. The OARs chosen for feathering depends on its proximity to the PTV.
- The dose delivered to the PTV is not altered, receiving 2 Gy per day.

Quick Guide to TFRT Model and Assumptions:

The dynamic NTCP model is a logistic differential equation that describes the recovery of normal tissues (N) from sublethal radiation-induced damage and is given by

$$\frac{dN}{dt} = \mu N(t)(1 - N(t)) - \delta(t_i) RT(d) N(t)(1 - N(t)).$$

Loss Term: The effect of radiation is included by the loss term $\delta(t_i) RT(d) N(t)(1 - N(t))$. This term models the additive effect of radiation therapy with progression through the treatment course.

The function $RT(d) = (1 - e^{-\alpha d - \beta d^2})$ represents the “injured fraction”, and is based on the radiobiological linear quadratic model.

Normal Tissue Recovery: We assume normal tissues recover from sublethal radiation damage. The organ-specific parameter $\mu > 0$ represents the recovery rate of radiation-induced damage.

Comparison to TFRT to standard IMRT plans: We denote $\Delta NTCP$ as the difference between normal tissue toxicity (radiation damage) induced by a standard NS(t) and a temporally feathered NTF(t) plan at the end of treatment. Positive values $\Delta NTCP > 0$ favor temporally feathered over conventionally fractionated plans.

RESULTS

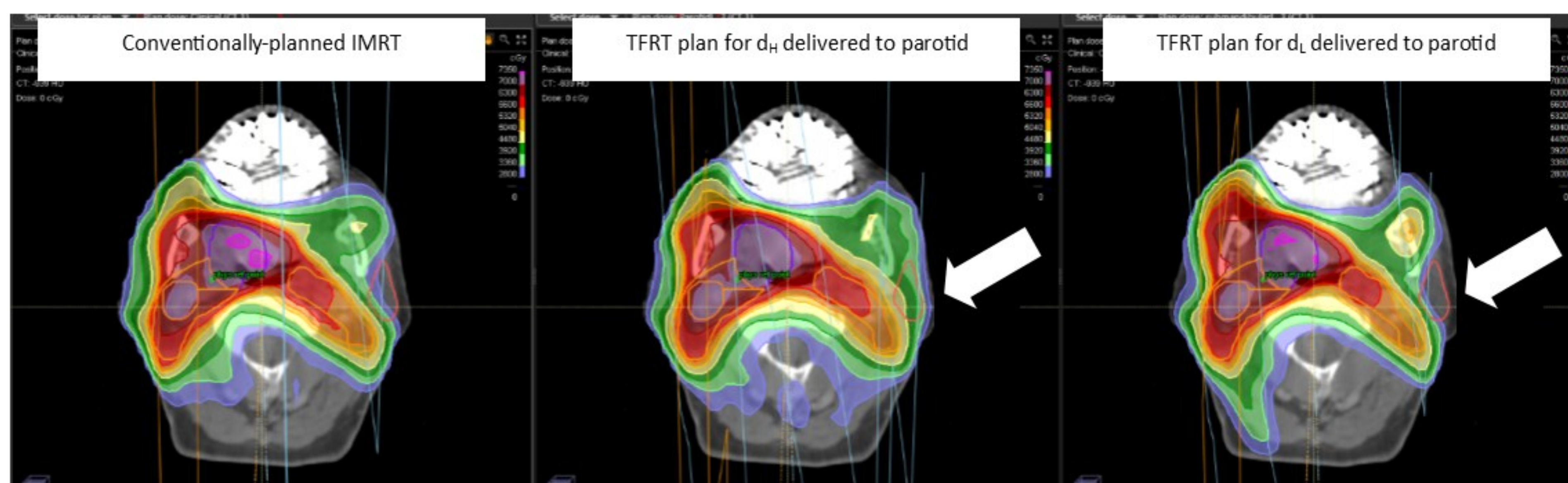
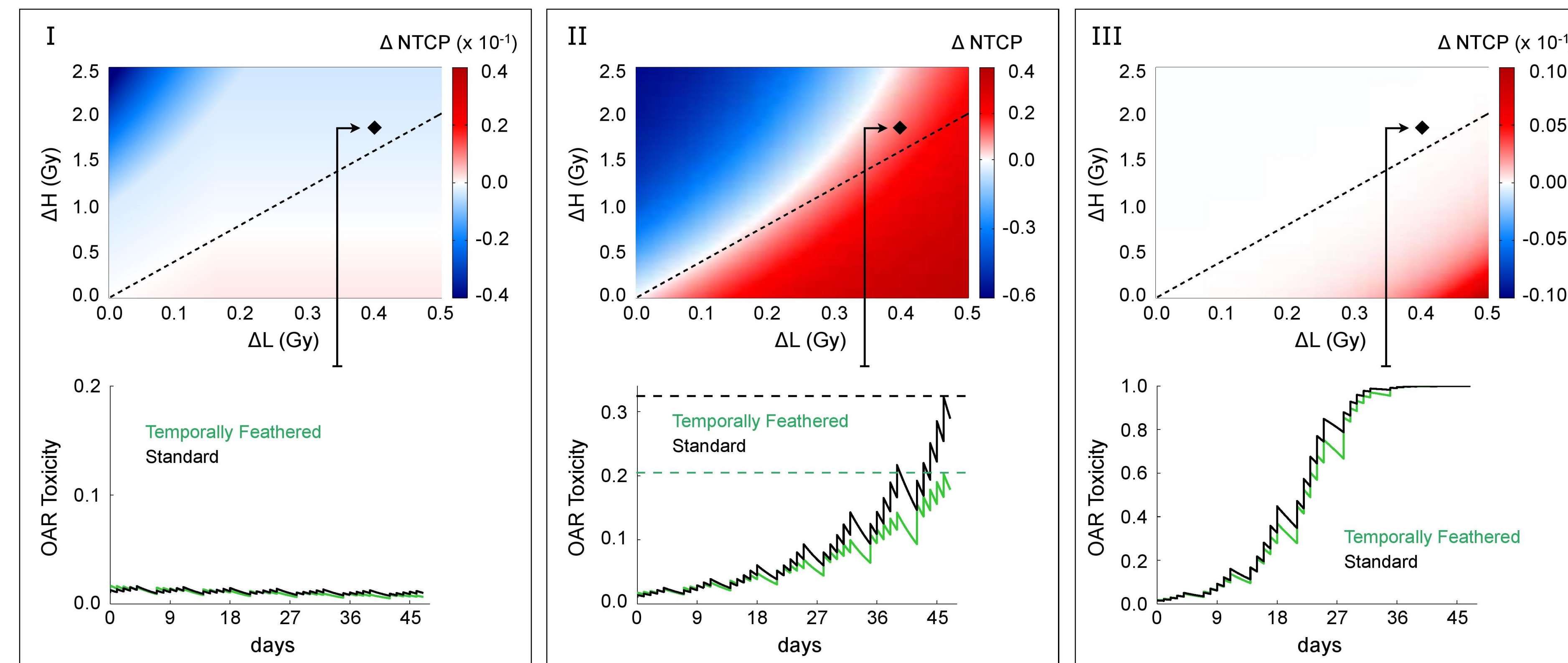
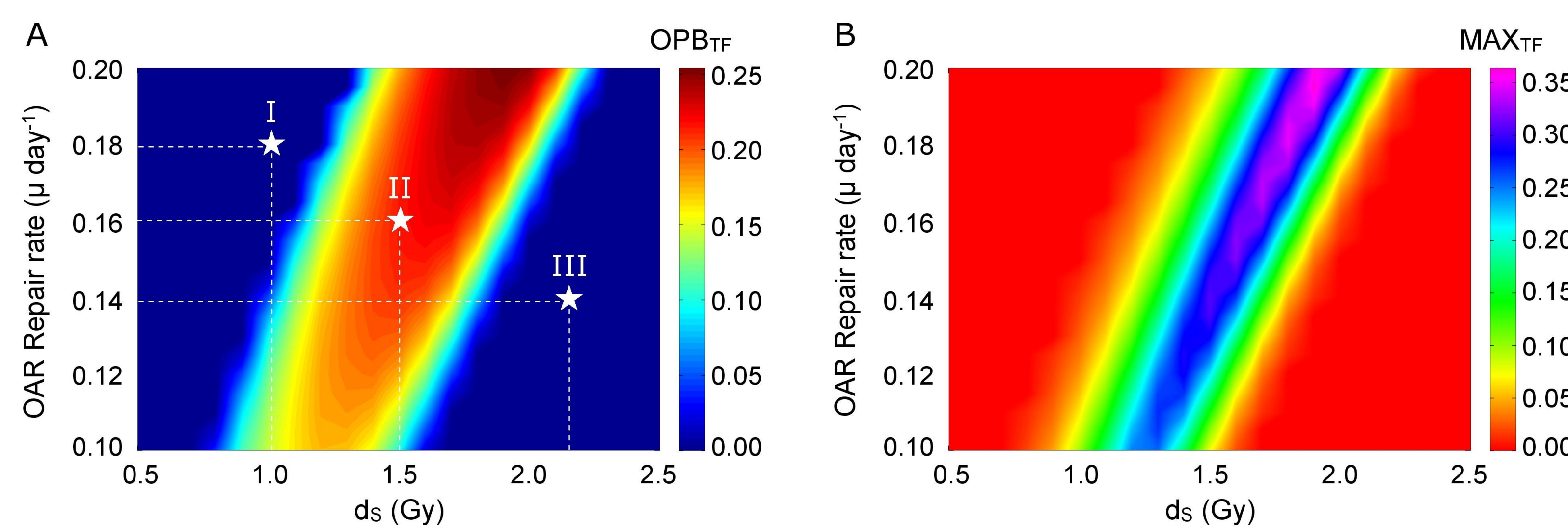
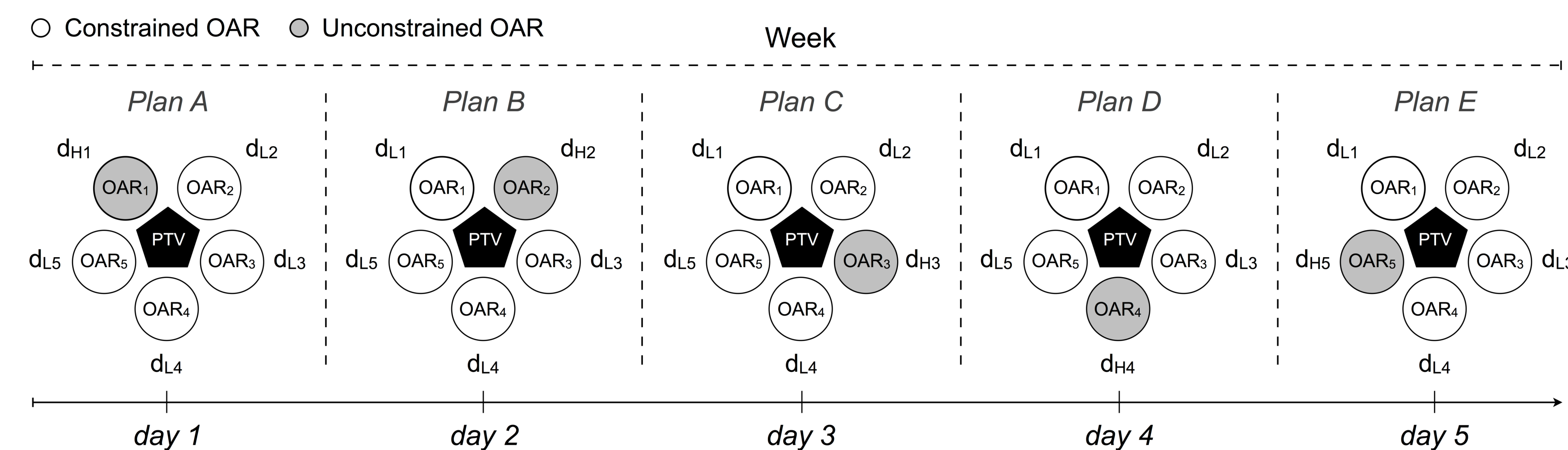
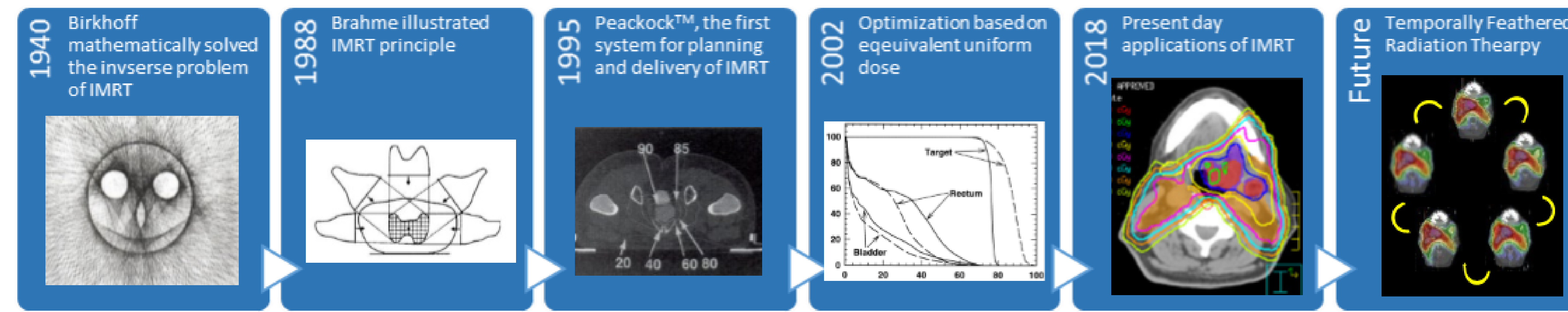


Figure 4. 3D dose distributions. Axial images of a head and neck plan with superimposed isodose lines for conventionally planned IMRT, a TFRT plan with dH delivered to the OAR, and a TFRT plan with dL delivered to the OAR (left to right).

Figure 1. Evolution of TFRT. Timeline reveals beginning IMRT was when Dr. Birkhoff solved the inverse problem of IMRT in the 1940s to concept of multiple conforming to a nonuniform target, then Peacock planning system for the first patient treated with IMRT, and the use of equivalent uniform dose to analyze dose distributions. In 2018, modern IMRT practices have optimized physical dose

Figure 2. Schematic representation of TFRT. The PTV is in close proximity to 5 OARs. Each OAR receives a higher fractional dose once weekly, dH, followed by lower fractional doses for the remaining four fractions, dL.

Figure 3. Overall potential benefit of TFRT with respect to the standard fractional dose (dS) and OAR damage repair rate (μ). For each combination of μ and dS, $\Delta NTCP$ values are obtained for an OAR with $\alpha/\beta = 3$ Gy as a result of comparing a standard plan delivering dS in 35 fractions and TFRT plans consisting in 28 fractions of $(d_S - 0.5) \leq d_L \leq d_S$ and 7 fractions of $d_S \leq d_H \leq (d_S + 2.5)$. Combinations of doses dL and dH remain unaltered during the course of treatments. **(A)** Overall potential benefit (OPBTF) is defined as the ratio of TFRT plans resulting in $\Delta NTCP > 0$ and delivering higher total doses than the corresponding standard plan to all simulated plans. **(B)** Maximum potential benefit (MAXTF) achieved with TFRT plans resulting in $\Delta NTCP > 0$ and delivering higher total doses than the corresponding standard plan. Top panels in I, II and III represent the single cases marked by stars in (A). The x- and y-axes represent $\Delta L = d_S - d_L$ and $\Delta H = d_H - d_S$ respectively. Bottom panels in I, II and III show time-evolution of OAR toxicity induced by the standard (black) and TFRT (green) plans corresponding to the location marked by diamonds in the top panels.

CONCLUSION

- OARs can be temporally feathered with small variations in the total dose delivered.
- The magnitude of NTCP reduction despite greater doses delivered to the OAR can be determined using a dynamic NTCP model which accounts for normal tissue recovery.
- This model requires parameters of alpha, beta, and recovery rates for OARs, which are currently unknown. This study warrants further evaluation in a prospective clinical trial.
- We prove the ability to conduct TFRT planning with current technology.