# High-Fidelity CT-on-Rails-Based Characterization of Delivered Dose Variation in Conformal Head and Neck Treatments

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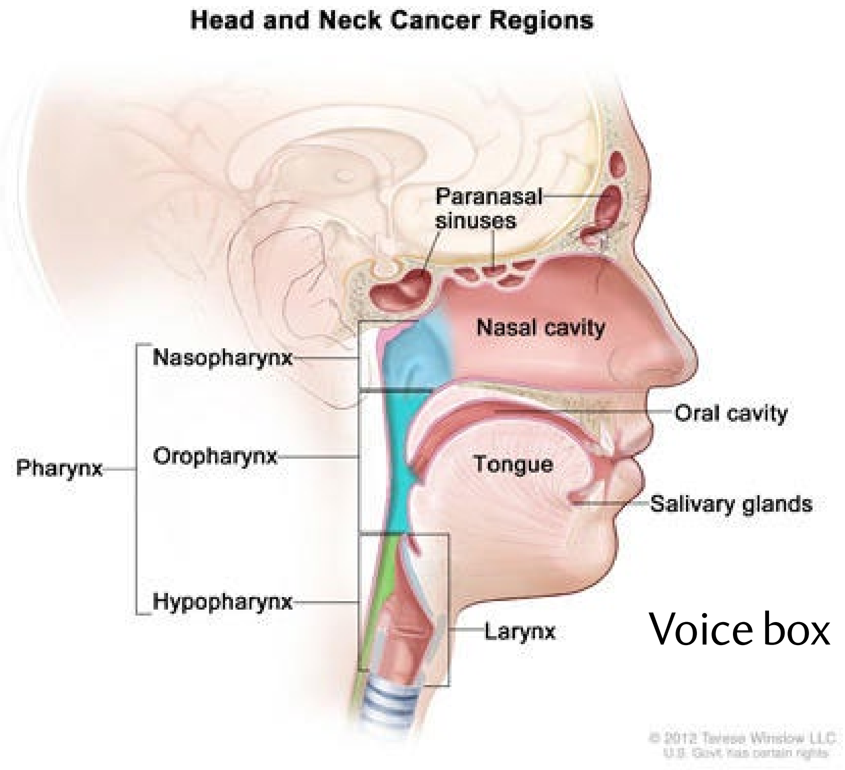
# What is Head-and-Neck Cancer?

From 2016-2020, in the United States, **232,535 new cases** of Oral Cavity and Pharynx cancer were reported, and **51,781 people died** of this cancer. For every 100,000 people, **12 new** Oral Cavity and Pharynx cancer cases were reported and **3 people died** of this cancer.




Throat

Voice box

Credit to Terese Winslow

## Surgery

## Radiation therapy

How to deliver the radiation therapy accurately to the tumor, but sparing the healthy tissues, with littlest cost?

Surgery:

- ✅ less pain, faster recovery
- ❌ can't completely remove the cancer for some patients

Radiation therapy:

- ✅ shrink a tumor to remove via surgery more easily
- ✅ kill missed cancer cells after surgery
- ❌ will receive radiation

Muratkoc, Getty Images

# Radiotherapy workflow (spatial)

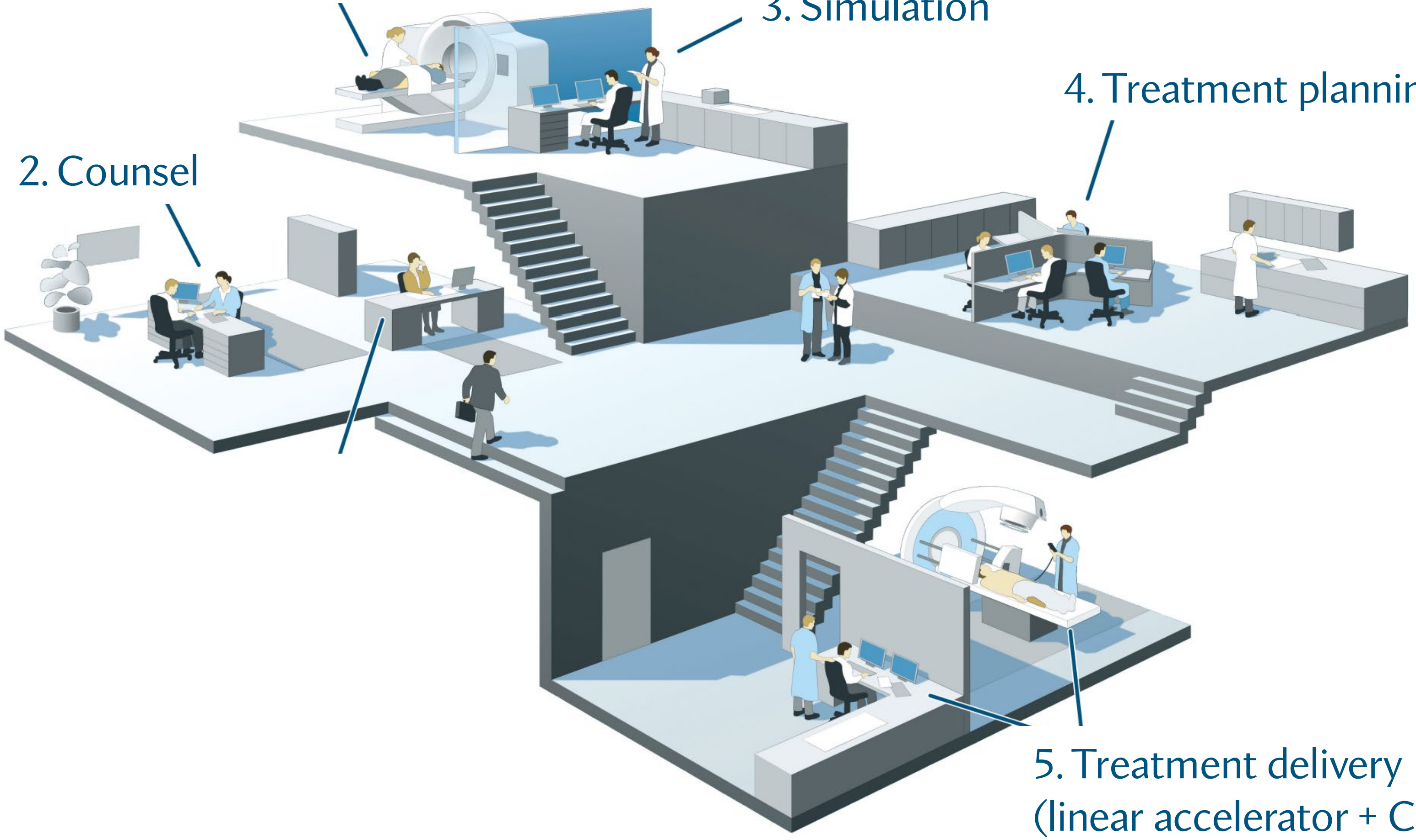
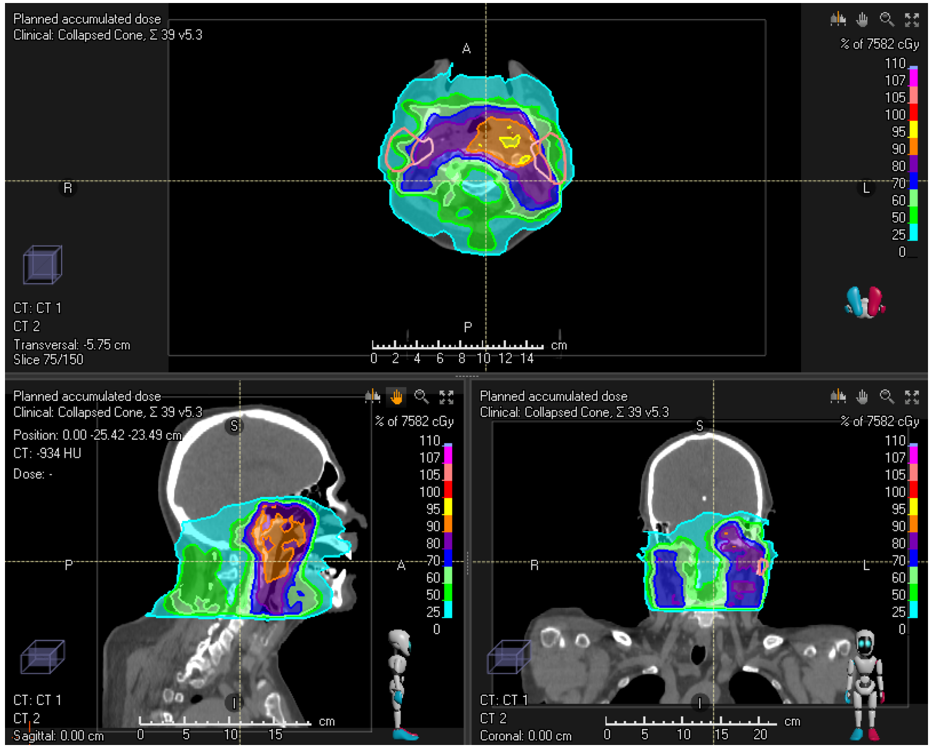
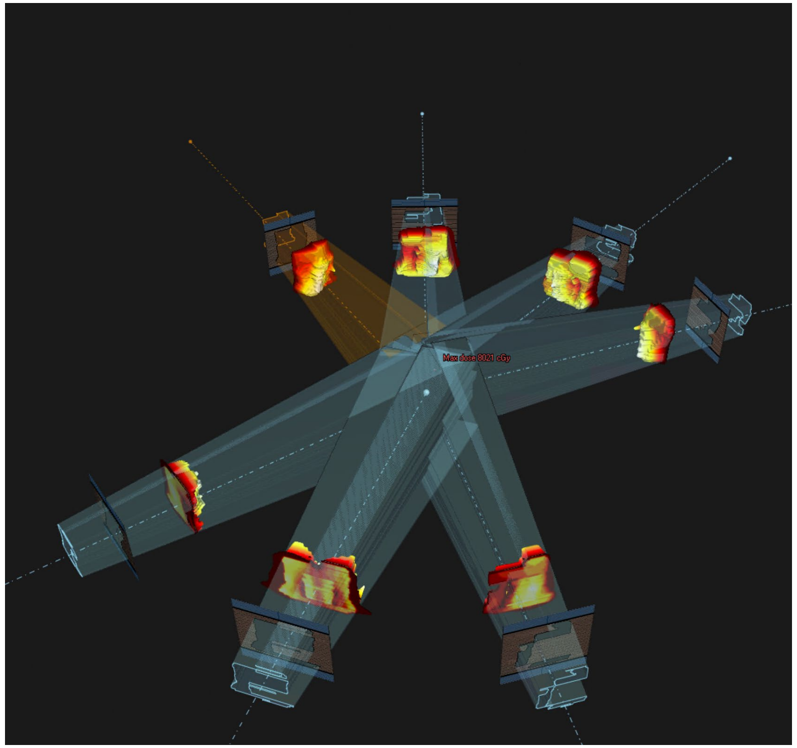



*figure credits to RayStation 9A user manual

# Treatment Planning

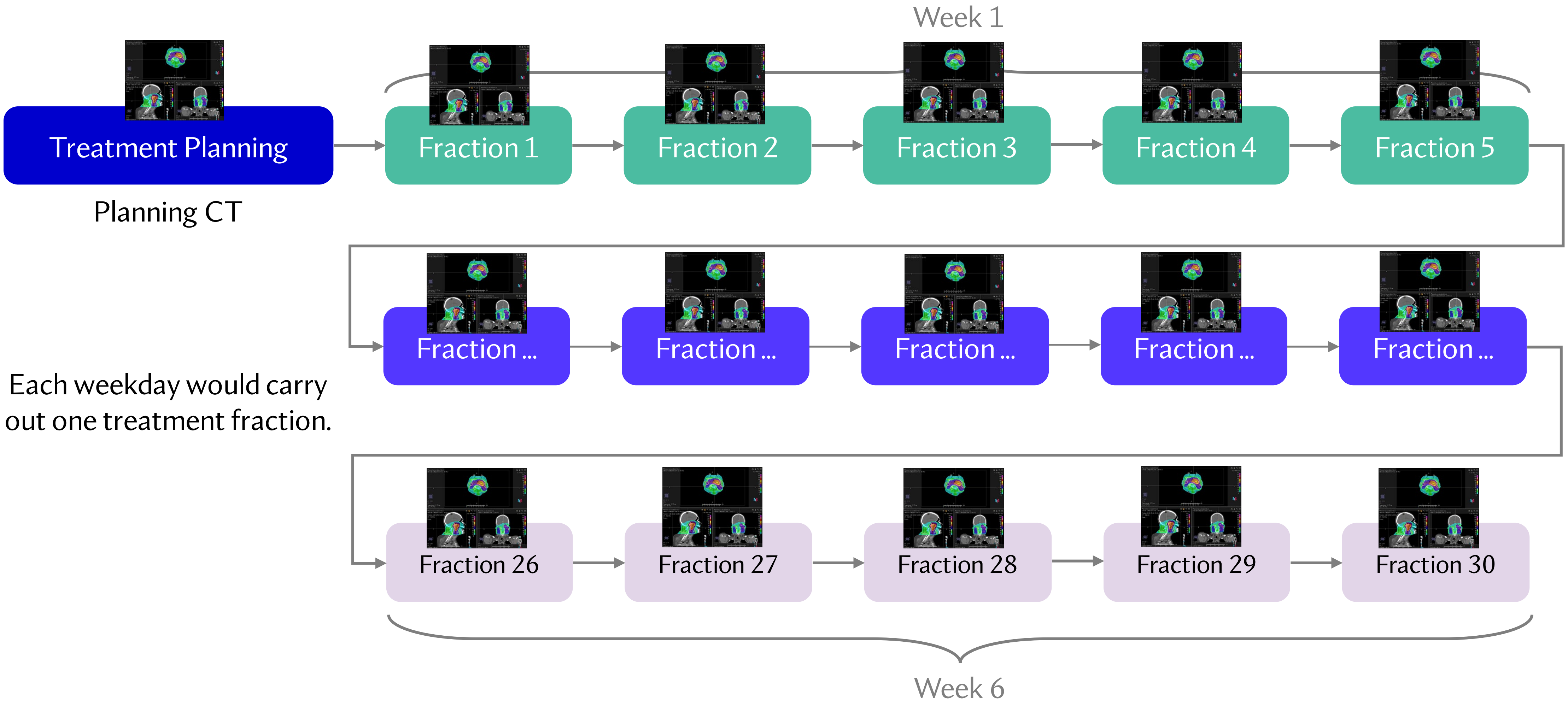



1. Take a planning CT



2. Design repeatable treatment plan

# After Treatment Planning

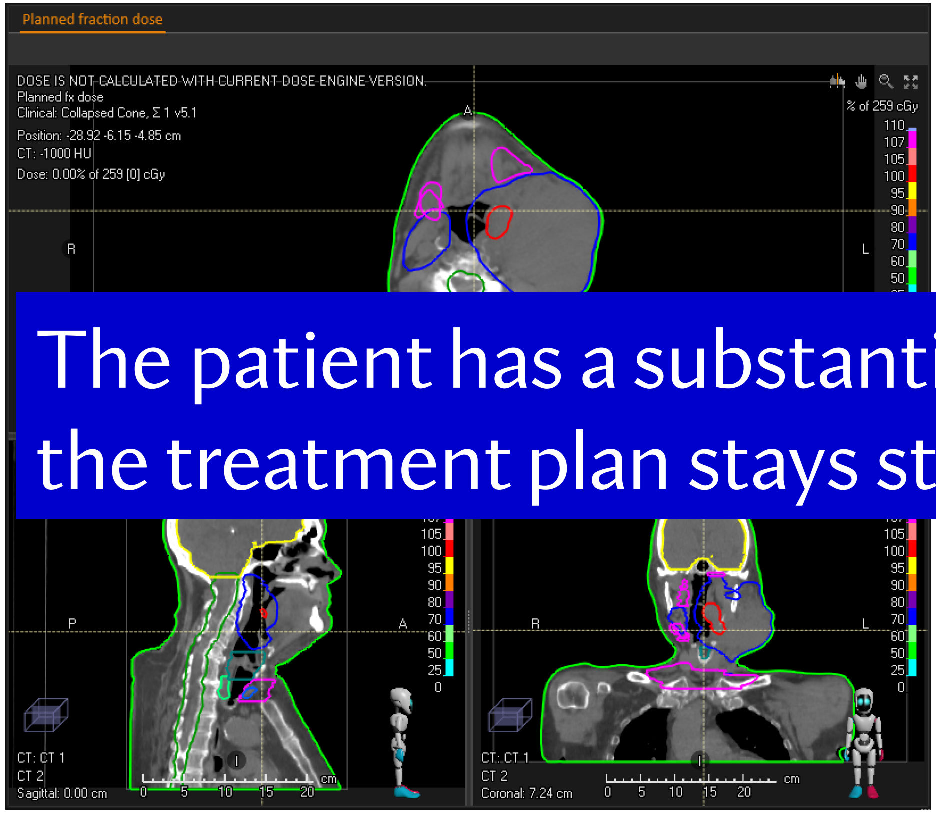


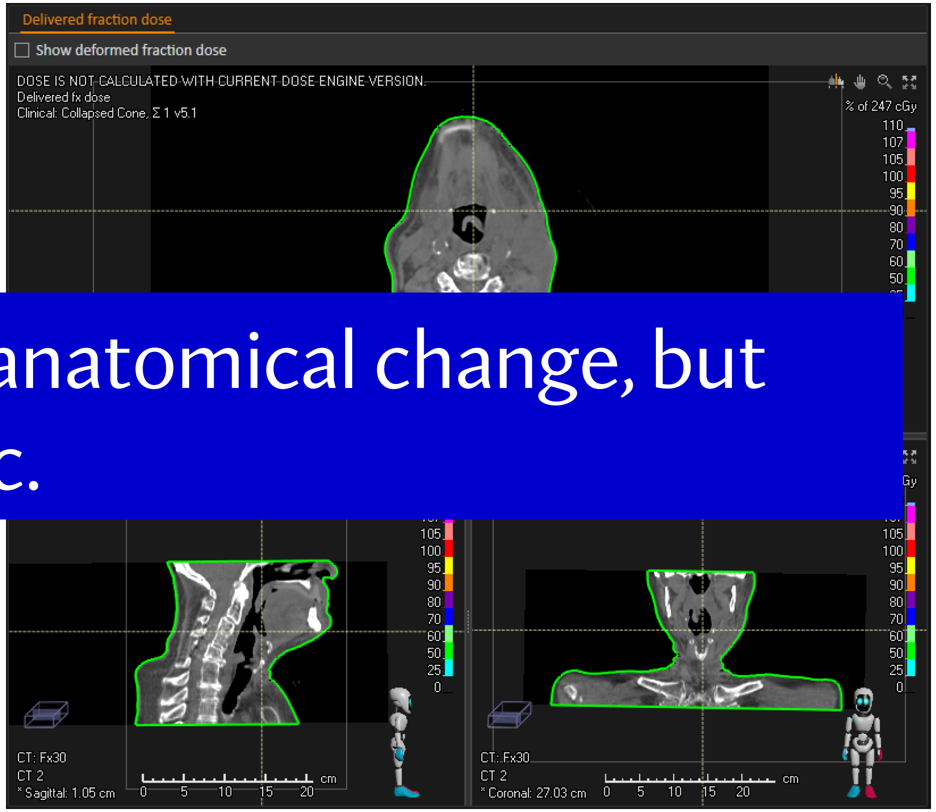

Each weekday would carry out one treatment fraction.

# However …

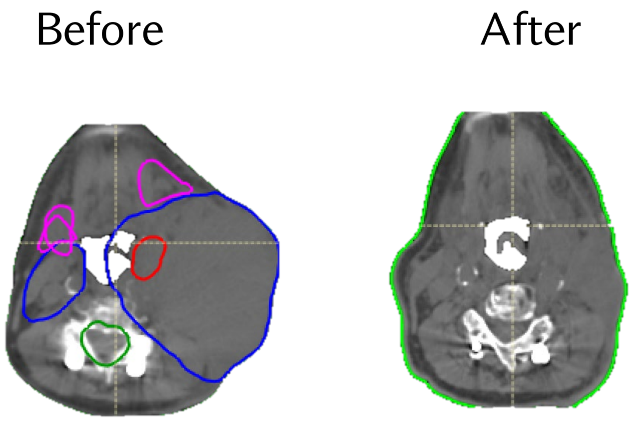
Planning CT
(at the beginning of the treatment)

Fraction 30 treatment CT
(at the end of the treatment)



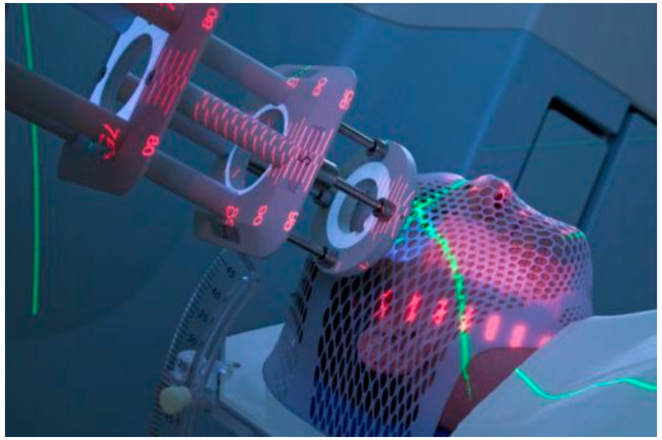




The patient has a substantial anatomical change, but the treatment plan stays static.




Head & Neck cancer
tumor response quick

Patients usually lose weight
substantially due to side effect

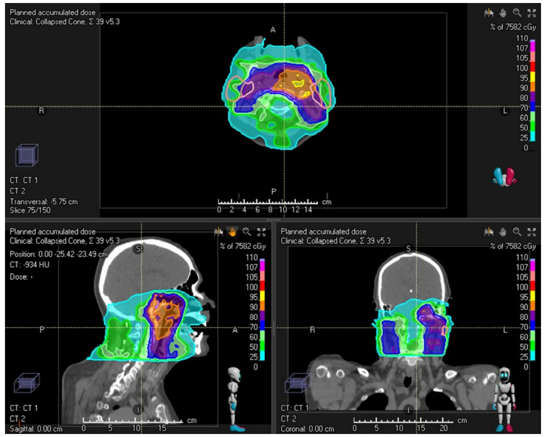


Position setup error
can accumulate

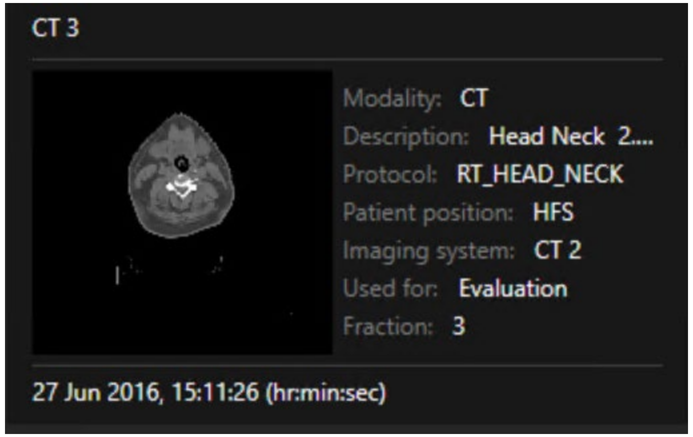
Can we identify the patients who may potentially be overdosed later using the early-stage data?

# Our dataset has 74 patients with HNC treated between 2012 and 2020. For each patient, there are:

1 treatment plan in planning CT space

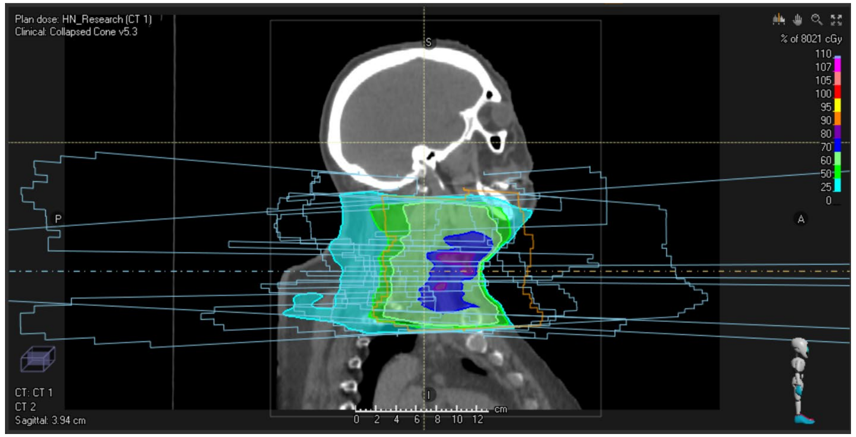


Set of daily FBCTs




Ranging from 10 to 39 daily FBCTs, with an average of 19.0 daily FBCTs per patient

Set of dose delivery distribution in daily FBCT space



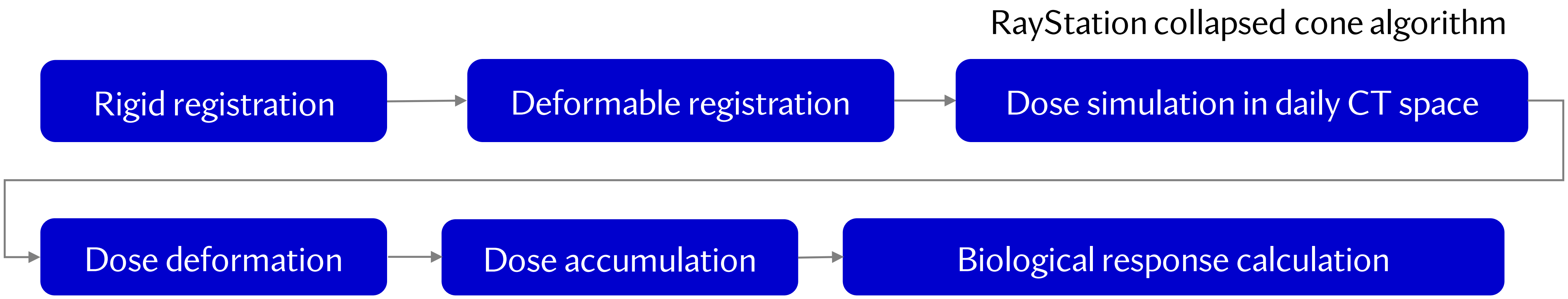
**More than half of the patients received a FBCT at least every second day during the treatment.**

# Patient cohort demographic

| PATIENT COHORT | |
|---|---|
| Patients, *n* | 74 |
| Sex, *n* | |
| Male | 63 (85.1%) |
| Female | 11 (14.9%) |
| Age, y | |
| Mean | 59.7 |
| Min | 23 |
| Max | 79 |
| Disease site, *n* | |
| Oropharynx | 49 |
| Thyroid | 5 |
| Nasopharynx | 4 |
| Sinuses | 4 |
| Neck Node (unknown primary) | 4 |
| Others | 8 |

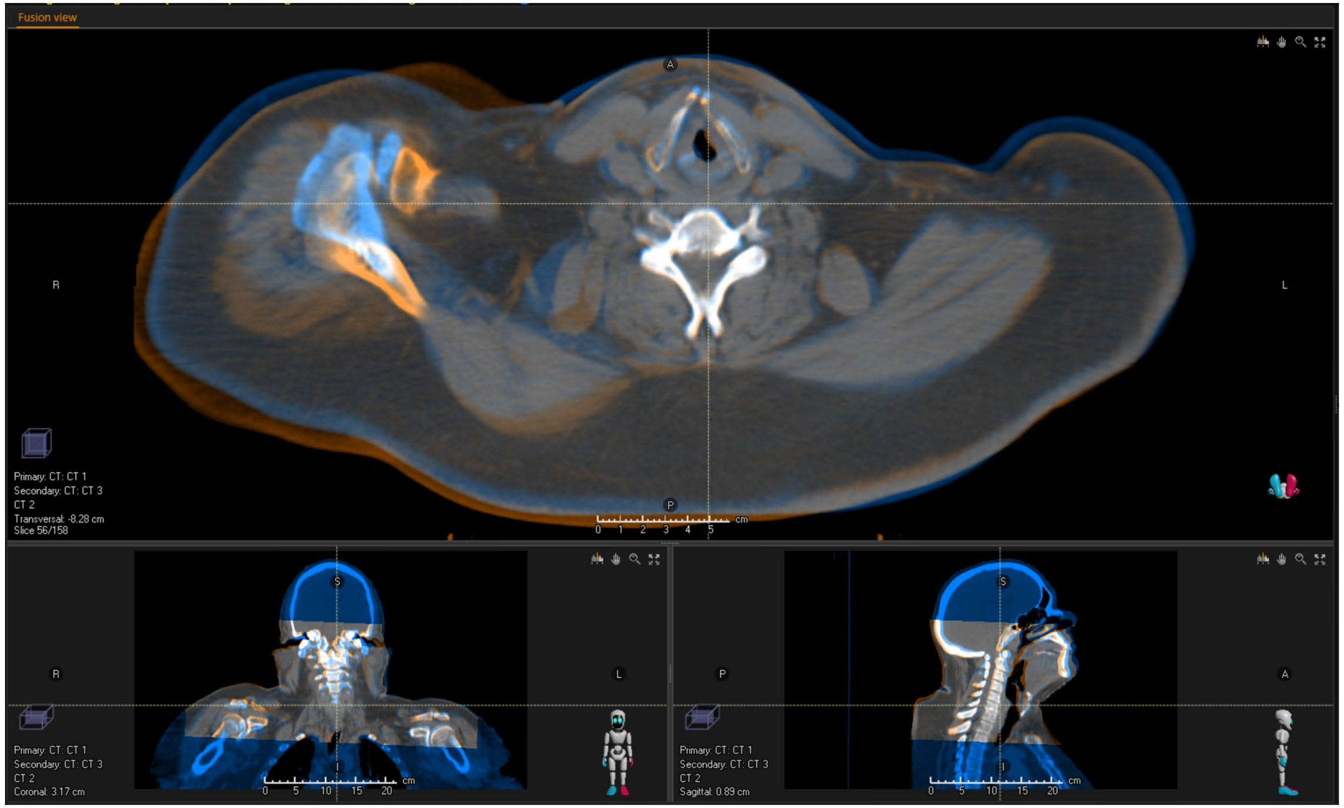
| | |
|---|---|
| Concurrent chemotherapy, *n* | 57 |
| Definitive radiation therapy, *n* | 64 |
| Fractions, *n* | |
| 30 | 49 (66.2%) |
| 33 | 9 (12.2%) |
| 35 | 9 (12.2%) |
| 39 | 4 (5.4%) |
| Others | 3 (4.0%) |
| Prescribed dose, cGy | |
| 6000 | 8 (10.8%) |
| 6600 | 23 (31.0%) |
| 6750 | 29 (39.2%) |
| 7000 | 9 (12.2%) |
| 7020 | 4 (5.4%) |
| Others | 1 (1.4%) |

# Dose tracking workflow on RayStation



# Rigid registration

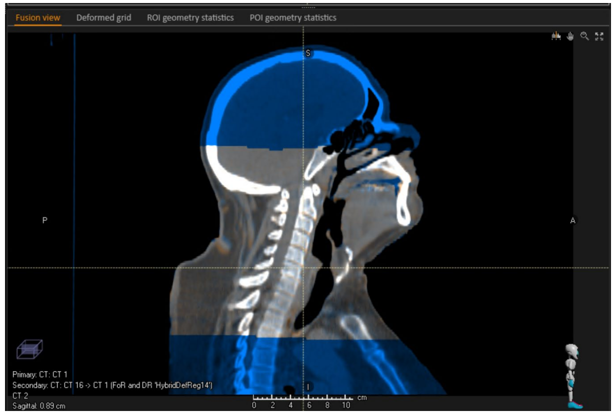
Rigid registration




rigid transformation = translation matrix + 3 rotation matrix (Pitch, Roll, Yaw)

# Deformable registration

Rigid registration → Deformable registration →




objective function = image similarity + grid regularization term

Image similarity

$$C(v) = \frac{\sum_i (R(x_i) - \bar{R})(T(M(x_i) + v_i) - \bar{T})}{\sqrt{\sum_i (R(x_i) - \bar{R})^2}\sqrt{\sum_i (T(M(x_i) + v_i) - \bar{T})^2}}.$$

Grid regularization term

$$H(v) = \sum_i \left\| v_i - \frac{1}{n_i} \sum_{j \in N_i} v_j \right\|^2,$$

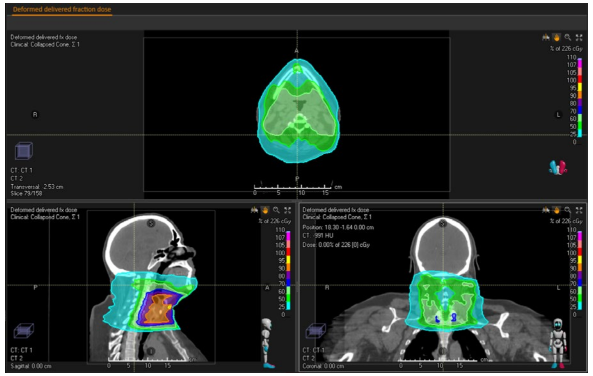
Weistrand, O. and Svensson, S., 2015. The ANACONDA algorithm for deformable image registration in radiotherapy. Medical physics, 42(1), pp.40-53.

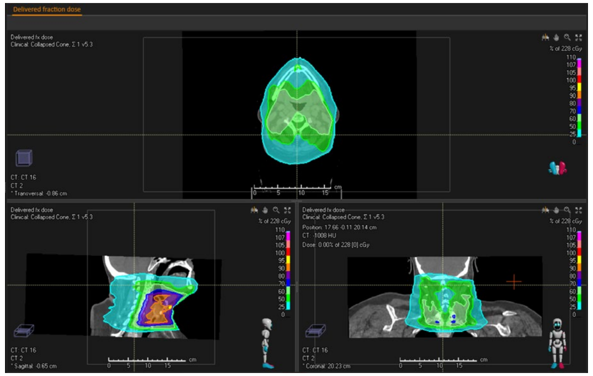
# Dose deformation

Goal: deform delivered fractional dose distribution ($S$) in daily FBCT space into planning CT space ($T$)

$T$: Deformed delivered fraction dose
$S$: Delivered fraction dose

Rigid registration → Deformable registration → Dose simulation in daily CT space → Dose deformation





$$T = S \circ \varphi \qquad \varphi: \mathbb{Z}^3 \to \mathbb{R}^3, S: \mathbb{R}^3 \to \mathbb{R}, T: \mathbb{Z}^3 \to \mathbb{R}$$

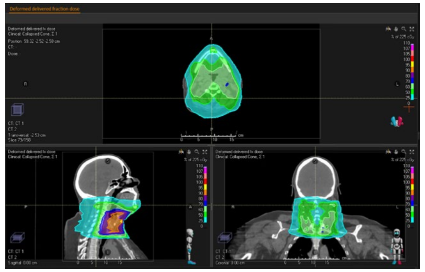
↑ Trilinear Interpolation

$$S: \mathbb{Z}^3 \to \mathbb{R}$$

# Dose accumulation

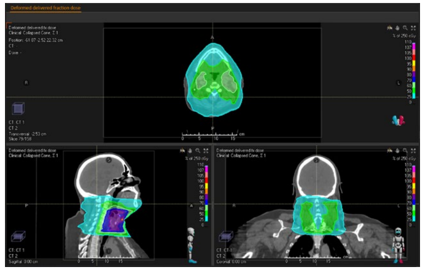
Rigid registration → Deformable registration → Dose simulation in daily CT space → Dose deformation → Dose accumulation →

Fraction 1



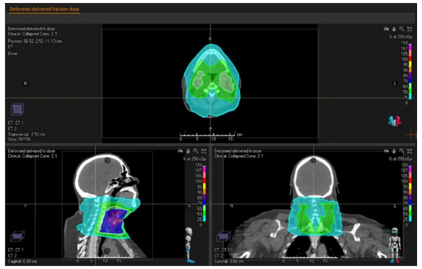
+...+

Fraction 10



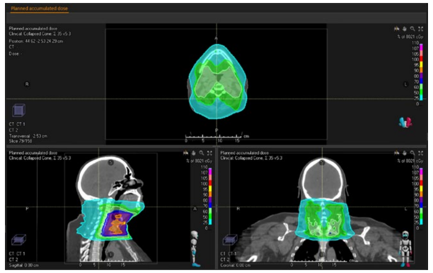
+...+

Fraction 20



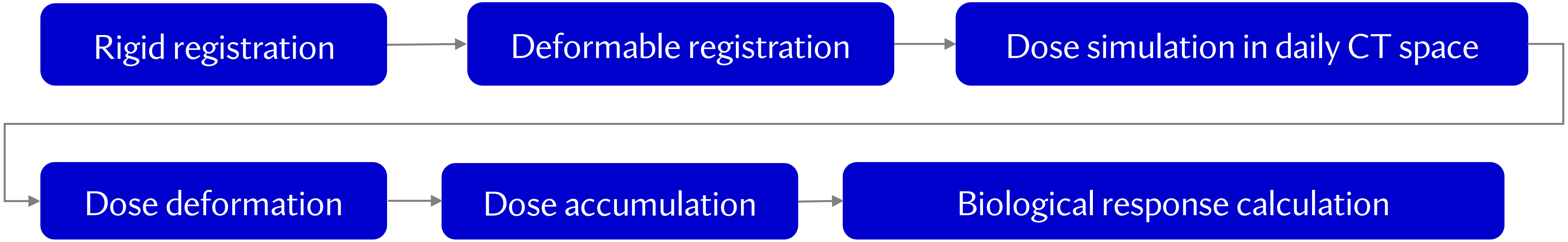
+ ... =

Total delivered dose



# Biological response calculation

We want to evaluate how sufficient high dose is delivered to the tumor, and how well the dose avoids the surrounding normal tissue.




Radiobiological models

- Tumor Control Probability (TCP): possibility of tumor would be under control
- Normal Tissue Complication Probability (NTCP): possibility of normal tissue develops complication

# Biological response calculation

**Definition 4.** **Normal tissue complications probability(NTCP-PoissonLQ)** model, based on the relative seriality model, is expressed as

$$\mathrm{NTCP}_{\text{P-LQ}}(D) = \left(1-\prod_{i=1}^{M}\left(1-\left[\exp\left(-N_0\exp\sum_{k=1}^{n}(-\alpha d_{k,i}-\beta d_{k,i}^2)\right)\right]^s\right)^{\frac{v_i}{V_{\mathrm{ref}}}}\right)^{\frac{1}{s}}$$
$$= \left(1-\prod_{i=1}^{M}\left(1-\left[\exp\left(-\exp\left(e\gamma-\frac{\mathrm{EQD}_{2,i}}{D_{50}}\cdot(e\gamma-\ln(\ln(2)))\right)\right)\right]^s\right)^{\frac{v_i}{V_{\mathrm{ref}}}}\right)^{\frac{1}{s}}$$

where

$$\mathrm{EQD}_{2,i,\mathrm{general}} = \frac{\sum_{k=1}^{n}\left(d_{k,i}\cdot\left(1+\frac{d_{k,i}}{\alpha/\beta}\right)\right)}{1+\frac{2}{\alpha/\beta}}.$$

| Symbol | Meaning |
|---|---|
| $M$ | total number of voxels |
| $D$ | total dose |
| $d_{k,i}$ | the dose of the $k^{th}$ fraction to voxel $i$ |
| $n$ | total number of fraction |
| $N_0$ | initial number of cells |
| $\alpha, \beta$ | parameters of the LQ model |
| $v_i/V_{\mathrm{ref}}$ | relative volume of voxel $i$ compared to the reference volume for which the parameter are obtained |
| $D_{50}$ | the dose giving a 50% response probability |
| $\gamma$ | the maximum normalized gradient of the dose response curve |
| $EQD_{2,i}$ | equivalent dose in voxel $i$ given in 2 Gy-fractions |

**Definition 2.** **Tumor control probability(TCP-PoissonLQ)** model is defined as

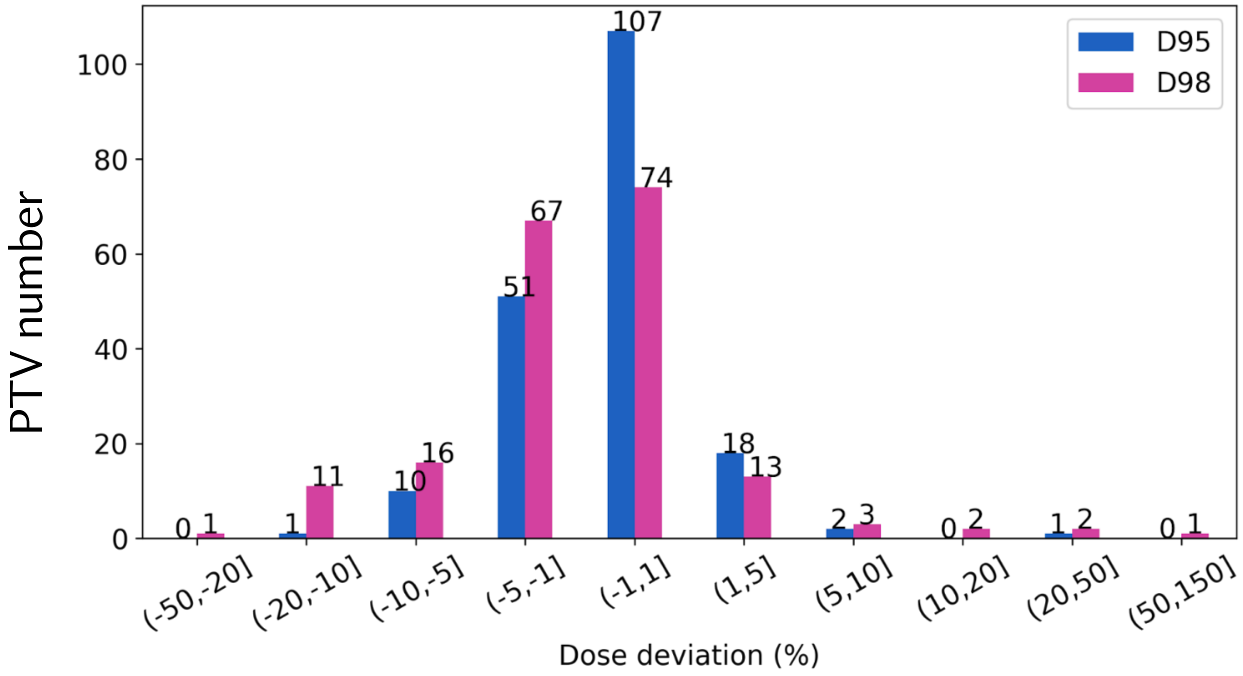
$$\mathrm{TCP}_{\text{P-LQ}}(D) = \prod_{i=1}^{M}\left(\exp\left(-N_0\exp\left(\sum_{k=1}^{n}(-\alpha d_{k,i}-\beta d_{k,i}^2)\right)\right)\right)^{\frac{v_i}{V_{\mathrm{ref}}}}$$
$$= \prod_{i=1}^{M}\left(\exp\left(-\exp\left(e\gamma-\frac{\mathrm{EQD}_{2,i}}{D_{50}}\cdot(e\gamma-\ln(\ln(2)))\right)\right)\right)^{\frac{v_i}{V_{\mathrm{ref}}}}$$

where

$$\mathrm{EQD}_{2,i,\mathrm{general}} = \frac{\sum_{k=1}^{n}\left(d_{k,i}\cdot\left(1+\frac{d_{k,i}}{\alpha/\beta}\right)\right)}{1+\frac{2}{\alpha/\beta}}.$$

The uncertainty of the biological response deviation stems only from the dose received by each voxel at each fraction.

# Deviation of D95/D98 of PTVs




$$dose\ deviation = \frac{delivered\ dose - planned\ dose}{planned\ dose}.$$

D95: the dose received by 95% of the volume;
D98: the dose received by 98 % of the volume.

A positive percentage indicates an increase ↑ from the plan and a negative percentage depicts a decrease↓ from the plan.

# Dose delivery in PTVs

**Table 2. Patients with PTVs Where D95 or D98 Decreased by >10% (Bold Font)**

| | D95 | | | | D98 | | | |
|---|---|---|---|---|---|---|---|---|
| PATIENT ID | PLANNED DOSE (CGY) | DELIVERED DOSE (CGY) | ABSOLUTE DIFFERENCE | RELATIVE DIFFERENCE (%) | PLANNED DOSE (CGY) | DELIVERED DOSE (CGY) | ABSOLUTE DIFFERENCE | RELATIVE DIFFERENCE (%) |
| HN089 | 5798.7 | 5813.0 | 14.3 | 0.3 | 5653.8 | 4055.8 | −1598.1 | **−28.3** |
| HN021 | 5880.5 | 5663.7 | −216.8 | −3.7 | 5826.6 | 4845.7 | −980.9 | **−16.8** |
| HN091 | 5220.2 | 4832.6 | −387.5 | −7.4 | 3883.1 | 3234.1 | −649 | **−16.7** |
| HN068 | 4929.6 | 4647.9 | −281.7 | −5.7 | 4174.3 | 3549.7 | −624.7 | **−15.0** |
| HN104 | 6732.2 | 6719.9 | −12.3 | −0.2 | 5039.1 | 4345.2 | −693.9 | **−13.8** |
| HN033 | 5202.5 | 5087.9 | −114.7 | −2.2 | 5067.2 | 4452.8 | −614.4 | **−12.1** |
| HN010 | 5800.2 | 5458.1 | −342.1 | −5.9 | 5660.5 | 4989.7 | −670.8 | **−11.9** |
| HN021 | 5307.7 | 4949.7 | −358 | −6.7 | 5105.9 | 4511.2 | −594.7 | **−11.7** |
| HN046 | 5310.5 | 4933.0 | −377.5 | −7.1 | 5166.5 | 4565.6 | −601 | **−11.6** |
| HN095 | 4958.0 | 4793.3 | −164.7 | −3.3 | 4665.7 | 4123.9 | −541.8 | **−11.6** |
| HN057 | 5184.3 | 4771.8 | −412.5 | −8.0 | 5060.8 | 4528.8 | −532 | **−10.5** |
| HN068 | 6170.8 | 5940.7 | −230.1 | −3.7 | 5736.3 | 5154.7 | −581.6 | **−10.1** |
| HN013 | 4502.5 | 3962.2 | −540.3 | **−12.0** | 2405.7 | 2734.4 | 328.7 | 13.7 |

*A positive percentage indicates an increase from the plan and a negative percentage depicts a decrease from the plan,*

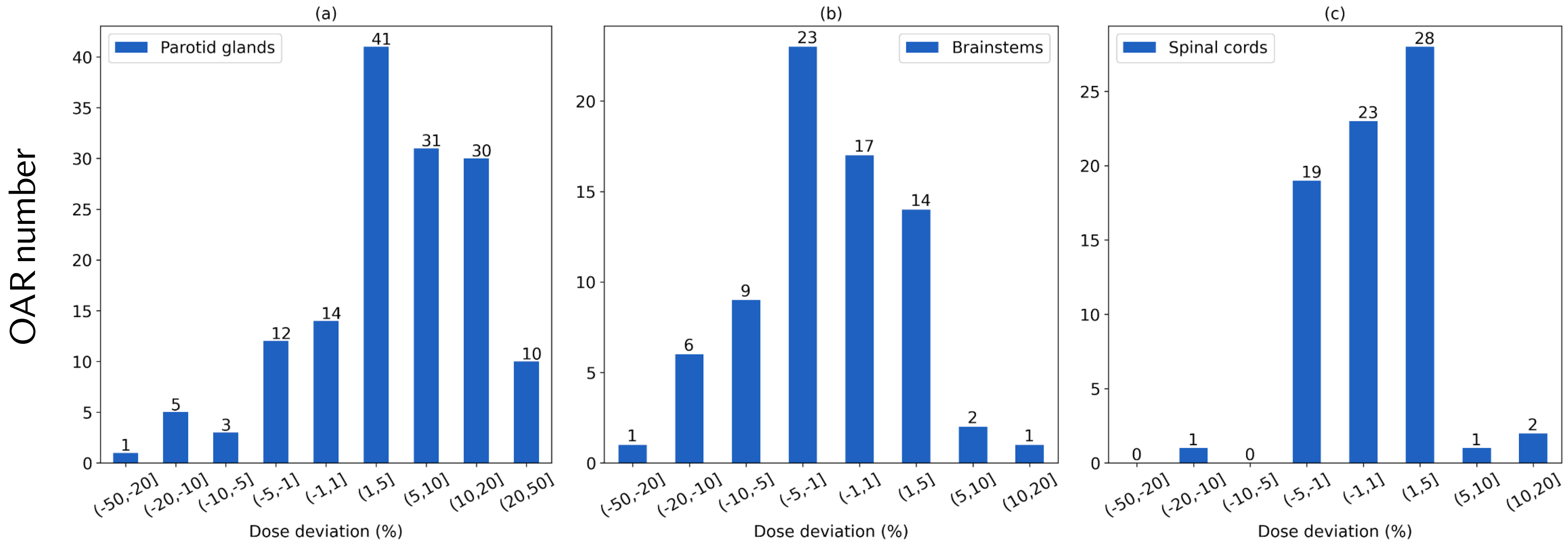
*Abbreviations: PTV, planning target volume; D95, dose received by 95%; D98, dose received by 95%.*

# Dose Deviation on OARs

mean dose deviation in parotid glands

maximum dose deviation in brainstems

maximum dose deviation in spinal cords




A positive percentage indicates an increase ↑ from the plan and a negative percentage depicts a decrease↓ from the plan.

# Dose delivery in Parotid Glands

We curated a set of patients of interest who had at least 1 parotid gland that was prescribed a greater than 26 Gy mean, initial planning dose.

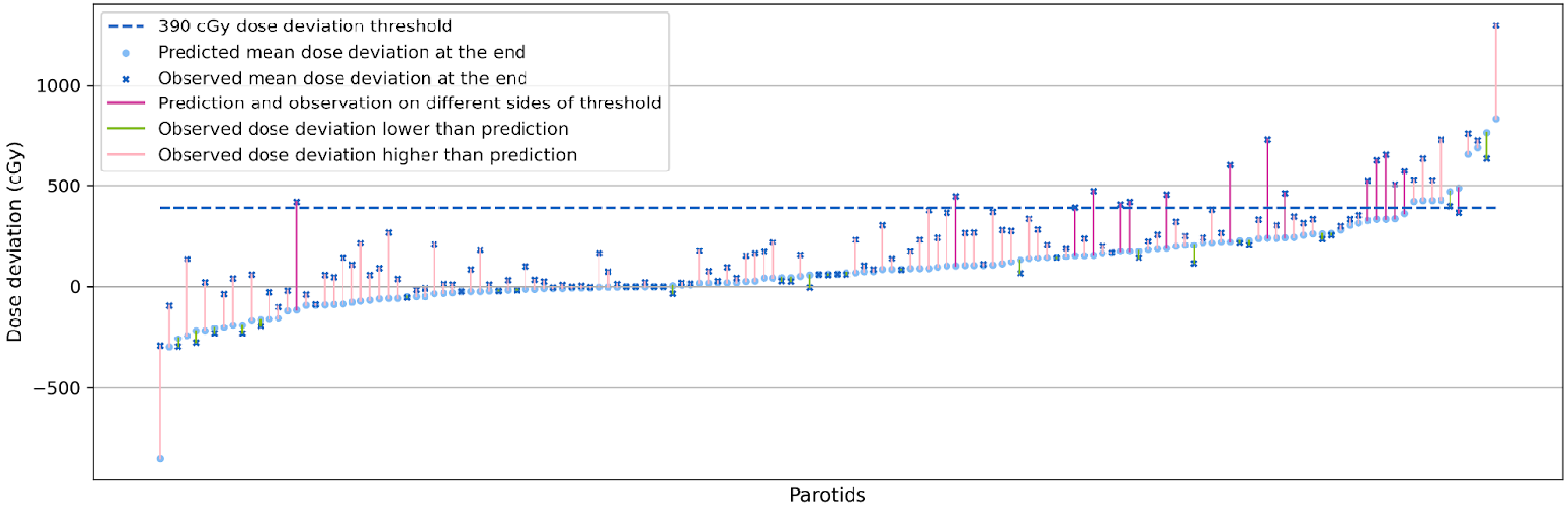
**Table 3. Comparison of Mean Dose (cGy) and NTCP of Parotid Glands in Planned and Delivered Doses**

| | LEFT PAROTID | | | | | | RIGHT PAROTID | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | PLANNED | | DELIVERED | | DIFFERENCE | | PLANNED | | DELIVERED | | DIFFERENCE | |
| PATIENT ID | DOSE | NTCP (%) | DOSE | NTCP (%) | DOSE | NTCP (%) | DOSE | NTCP (%) | DOSE | NTCP (%) | DOSE | NTCP (%) |
| HN010 | 2955.9 | 8 | 3616.3 | 31 | 657.4 | **23** | 2899.6 | 13 | 4197.8 | 57 | 1298.2 | **44** |
| HN011 | 3177.0 | 28 | 3638.6 | 41 | 461.6 | **13** | 2094.1 | 7 | 2514.7 | 14 | 370.7 | 7 |
| HN022 | 1956.1 | 15 | 2236.0 | 18 | 279.9 | 3 | 3007.0 | 36 | 3514.3 | 50 | 507.3 | **14** |
| HN023 | 2771.6 | 24 | 3410.6 | 38 | 639.0 | **14** | 2734.9 | 16 | 3261.0 | 26 | 526.1 | **10** |
| HN030 | 2185.1 | 5 | 2916.6 | 16 | 731.5 | **11** | 3582.9 | 25 | 4213.4 | 52 | 630.5 | **27** |
| HN046 | 5184.3 | 65 | 5709.3 | 82 | 525.0 | **17** | 2613.6 | 13 | 2823.6 | 32 | 210.0 | 9 |
| HN052 | 1944.2 | 2 | 2116.7 | 3 | 172.5 | **1** | 3544.0 | 18 | 4120.9 | 32 | 576.9 | **14** |
| HN060 | 4652.3 | 62 | 5378.2 | 79 | 725.9 | **17** | 826.8 | 0 | 867.5 | 0 | 40.8 | 0 |
| HN090 | 3211.7 | 21 | 3267.7 | 24 | 55.9 | 3 | 3678.0 | 31 | 4096.8 | 47 | 418.9 | **16** |
| HN129 | 4735.3 | 64 | 5207.6 | 75 | 472.3 | **11** | 4004.7 | 32 | 4612.6 | 39 | 607.9 | 7 |

*Bold font suggests a more than 10% NTCP increase. A positive percentage indicates an increase from the plan and a negative percentage depicts a decrease from the plan.*

*Abbreviation: NTCP, normal tissue complication probability.*

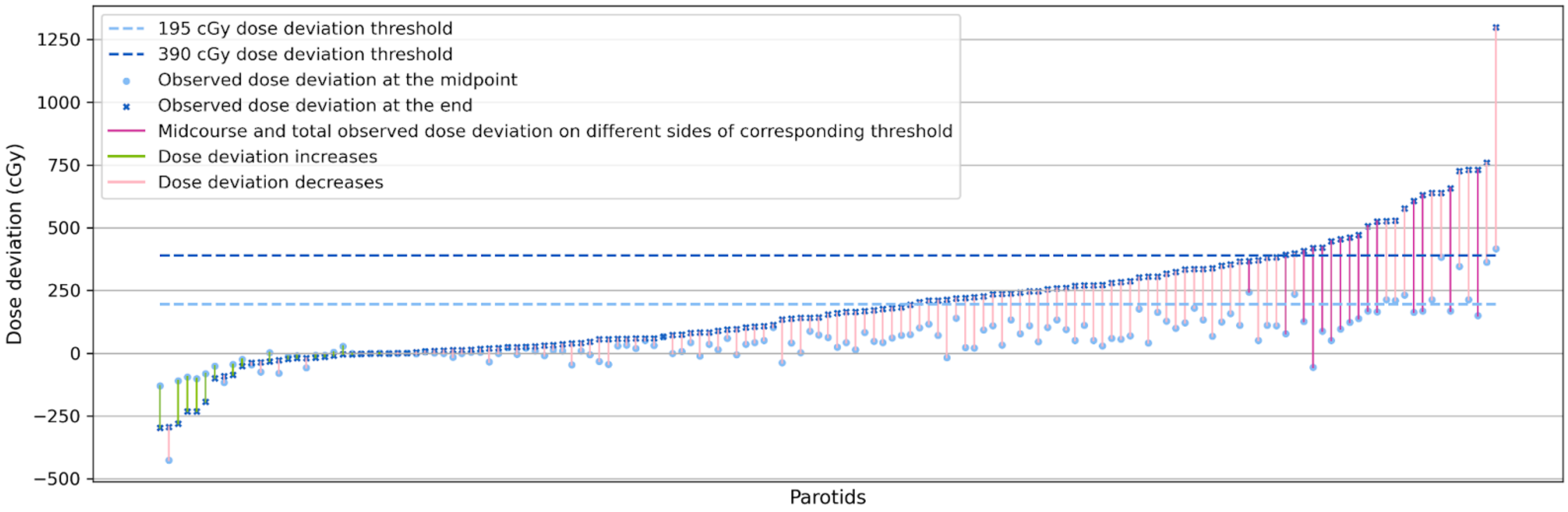
# Correlation between predicted mean dose deviation and observed total mean dose deviation




For the parotid glands where the predicted dose deviation did not surpass the 3.9Gy threshold, 14 of these saw the observed final dose deviation reach above the threshold, indicating an 89.8% negative predictive value (NPV).

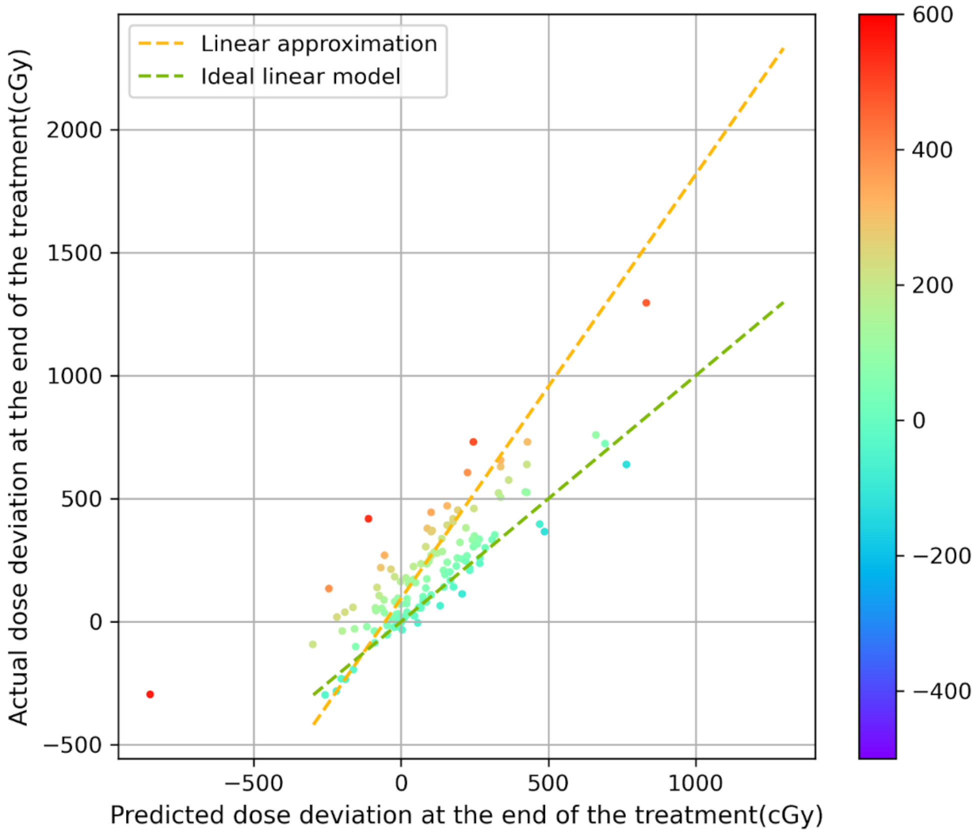
Thus, the sensitivity of this model is only 43.5% despite a 99.2% specificity.

# Correlation between observed mean dose deviation at midpoint/end of the treatment




In spite of the upward trend of the dark blue crossmarks representing different parotid glands' observed total mean dose deviation, we could not observe an upward trend in midcourse dose deviation (light blue points),regardless of the variance of the midcourse deviation increases with the trend of total dose deviation.

# 2D distribution of parotid glands in the space of final actual dose deviation—final predicted dose deviation at the end



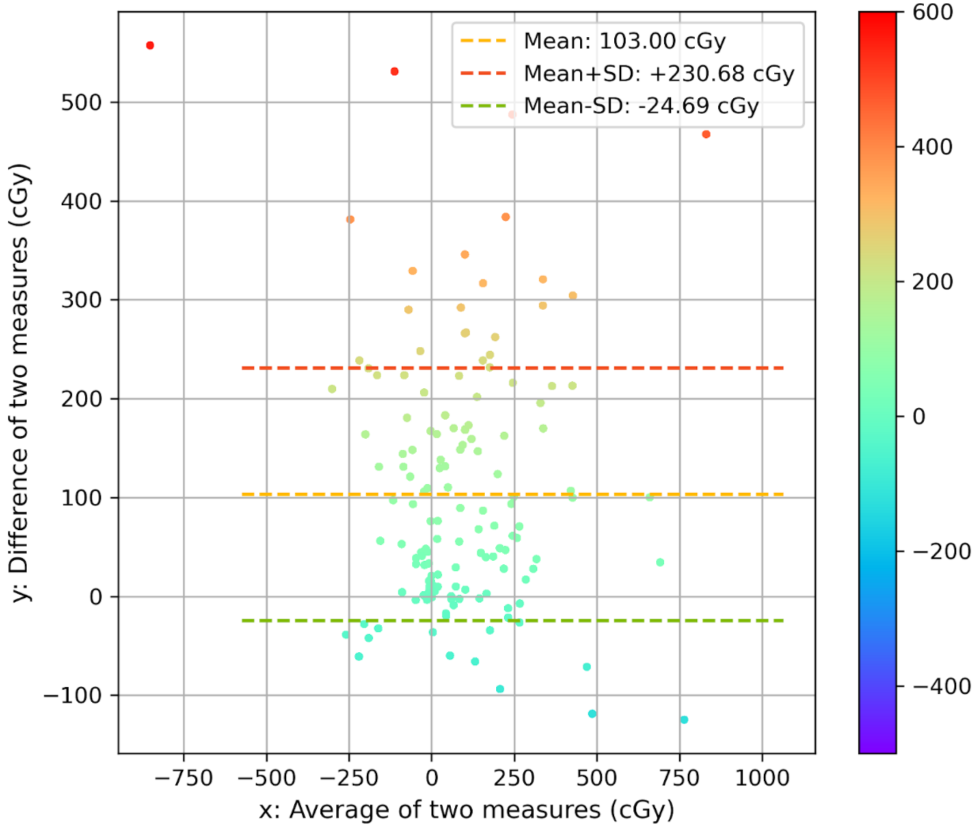

In this Figure, we plot 147 parotid glands in the 2D space with predicted total dose deviation on the x-axis and actual total dose deviation on the y-axis.

116 parotid glands saw an increase from predicted total dose deviation to observed total dose deviation (points located above the green dashed line), and 72 out of 147 parotid glands had a positive predicted dose deviation and an even larger actual dose deviation.

We observed that the majority of parotid glands (78.9%) received more dose in the latter half of the treatment than in the first half of the treatment.

The color of the sample points is proportional to the difference between the observed and predicted dose deviations. Redder → larger positive dose difference ; bluer → larger negative dose difference

# Bland-Altman plot of actual dose deviation and predicted dose deviation in parotid glands




Ideally, a reference measure should have all the sample points located on the y = 0 line (difference of 2 measures equals to 0). However, as shown in Figure, most of the sample points are located above the y = 0 line.

Difference between the predicted and observed total dose deviation is not strongly correlated with the predicted total dose deviation

Therefore, a midcourse evaluation of the need for replanning is unable to predict overdosing of critical OARs at the end of the treatment.