Relativistic optimization force concept for gEUD biological optimization and novel a-value selection viewpoint

Yusuke Anetai*,1,2, Hideki Takegawa1,2, Yuhei Koike1,2, Satoaki Nakamura1,2, and Noboru Tanigawa1,2

1)Department of Radiology, Kansai Medical University, Shin-machi 2-5-1, Hirakata-shi, Osaka 573-0101, Japan
2)Department of Radiation Oncology, Osaka University Graduate School of Medicine, Yamadaoka 2-2, Suita-shi, Osaka 565-0871, Japan

E-mail: *anetaiys@hirakata.kmu.ac.jp
Phone number: +81-6-6879-3482
Fax number: +81-6-6879-3482

Keywords: a-value, generalized equivalent uniform dose, optimization, intensity-modulated radiation therapy
Abstract

Generalized equivalent uniform dose (gEUD) optimization is a biological optimization method used for intensity modulated radiation therapy (IMRT). Although parametric analyses have been widely reported, the use of parameter \( a \)-value in the optimization method remains elusive. This study aims to clarify the mathematical characteristics of the gEUD and to provide effective a-value selection. The gEUD is typically obtained using a differential dose volume histogram (DVH). This can be rewritten using a cumulative DVH (cDVH) and applied to variational analysis. The equivalence between the gEUD and the dose is then obtained; a low or high a-value corresponds to a wide or narrow dose range of optimization, respectively. Next, we focused on the gEUD curve behavior against a-value shifts and it retained its curve characteristics despite optimization. Using differential geometry, this curve shift can be considered as a geodesic deviation between pre- and post-optimization by a relativistic optimization force. The total action enacted by the force includes the curvature of the gEUD curve. This idea provides a novel viewpoint that the curvature of the gEUD curve is influenced by the optimization effect. The curvature stationary point of the gEUD curve (the vertex point, \( a = a_k \)) is expected to be a special point that leads to effective a-value selection. Eleven head and neck patient cases were used to verify the curvature effect. We used the Photon Optimizer (PO) of Eclipse for optimization and focused the upper gEUD to simplify the dose constraint for the organ at risk (OAR) that requires balancing of the overlapped planning target volume (PTV). Static seven-field IMRT was used for optimization, changing the a-value of the affected side of the parotid and retaining PTV D95% = 70Gy at the different a-value optimization. Finally, cDVH shift (\( \Delta \text{DVH} \)), gEUD shift (\( \Delta \text{gEUD} \)), their average values, and \( a_k \) were evaluated. The \( a = a_k \) optimization showed an intermediate effect of lower and higher a-values on \( \Delta \text{DVH} \), \( \Delta \text{gEUD} \), and their averages. “Lower” (\( a = 0.5/1.0/2.0/3.0 \)), “middle” (\( a = 4.0/5.0/6.0/8.0/10/12/15/20/40 \)), and “higher” (\( a = 12/15/20/40 \)) were defined using \( a = a_k \) as a base point. Lower a-value optimization was effective for the low-dose region and weakly affected the whole range of cDVH weight. In contrast, higher a-value optimization addressed the high-dose region and strongly affected the high-dose range of the cDVH weight as theoretically predicted. In addition, the middle range of the a-value optimization induced a decrease in the clinically important middle-to-high dose range, which retained the high dose of the PTV. Interestingly, the average \( \Delta \text{DVH} \) and \( \Delta \text{gEUD} \) corresponded exponentially to the curvature and the gradient of the gEUD curve. Using our relativistic optimization force concept, gEUD optimization is represented as a gEUD curve shift, highlighting that the curvature of the gEUD curve is the essence of gEUD optimization. The curvature stationary point (\( a = a_k \)), namely the vertex point of the gEUD curve, played an intermediate role in the low-to-high a-value condition. We can effectively select a lower/middle/higher a-value from a base point of \( a = a_k \) under clinically complex optimization situation.
Introduction

In radiotherapy, intensity modulation radiotherapy (IMRT) planning, which includes the static-field technique and volumetric modulated arc therapy (VMAT), is calculated using the inverse optimization process.\textsuperscript{1} Dose-volume histogram (DVH)-based optimization is widely used for the optimization process.\textsuperscript{2-6} DVH-based optimization systematically addresses the three-dimensional (3D) dose distribution using the parameters of dose and volume with a priority weight ratio for optimization (hereinafter called the optimization weight), whereas treatment regions in the planning target volume (PTV) often occur near organs at risk (OARs), and this complicated balance often causes difficulties for the treatment plan.\textsuperscript{3} Therefore, the optimization process is usually dependent on the experience of the planner and treatment clinical goals that reflect the facility characteristics of radiotherapy.\textsuperscript{9}

Maximal and minimal dose-volume (DV) constraints are typically used to perform clinical inverse treatment planning,\textsuperscript{4,5} which is a standard criterion to evaluate whether the treatment plans are clinically acceptable.\textsuperscript{6,8} Moreover, DV optimization efficiently and effectively addresses the complicated relationship of between the tumor target and OARs. Although the organ evaluation criteria Pareto surface is naturally included by the DVH Pareto surface in the optimization,\textsuperscript{9,10} the volume control method is not always directly linked with the details of the dose distribution of interest. This is because it lacks the spatial information between the dose-volume and dose distribution. Biological optimization is an alternative solution to control the optimization;\textsuperscript{11} this is originally derived from the idea of introducing the radiation response in the tissue into the optimization process\textsuperscript{12}. The generalized equivalent uniform dose (gEUD) is one of the criteria for a biological dose, assuming a uniform dose proposed by Niemierko,\textsuperscript{13,14} which provides the same biological effect to the tissue as an inhomogeneous dose distribution; the tissue-specific difference is represented by the $\alpha$-value. However, this biological optimization allows a wide range of DV domain control; therefore, dose constraints for optimization become easier to implement. Multiple DV constraints can be replaced with a single EUD-based cost function\textsuperscript{15}. Meanwhile, biological optimization provides a wide range of dose-volume constraints, and it allows the voxels to deliver an inhomogeneous dose distribution to the same organ.\textsuperscript{16,17} For the proper use of biological optimization, it is essential to evaluate whether the optimized result and final dose distribution are clinically appropriate\textsuperscript{15}.

The Photon Optimizer (PO) In the Eclipse planning system (Varian Medical Systems, Palo Alto, CA, USA) is the optimization engine for IMRT and VMAT. This system provides gEUD optimization, which is primarily controlled by the $\alpha$-value and its optimization weight. The role of the gEUD during the optimization process has been reported by Fogliata et., al.\textsuperscript{18} They reported different $\alpha$-value effects for the OAR in the optimization process for a virtual phantom to investigate the $\alpha$-value and the distance between the OAR and target. The results indicate that the PO showed a trade-off between the tumor target and OAR dose, resulting in a decrease in the target high dose with an increase in the $\alpha$-value; however, the effectiveness of the variable $\alpha$-value and optimization weight of the OAR against the target have not been clarified under clinically complex optimization conditions. Originally, the $\alpha$-value represented a tissue-specific parameter, whereas the $\alpha$-value behaves as the DV cost function for
particular domains of the DVH in the optimization process. An appropriate use of the gEUD enables simple and effective optimization, whereas elusive characteristics that depend on an arbitrary DVH shape remain in the empirical usage. The aim of this study is to clarify the effect of different $a$-values in the optimization process among existing multiple-body optimization objectives by using the originally formularized concept of relativistic force in optimization. This provides a novel and effective use of the $a$-value in the optimization process under clinically complex situations such as when OARs are adjacent to the tumor target requiring harmful high doses for the normal tissue because of PTV marginal regions.

### Methods

**Mathematical characteristics of gEUD**

The DVH curve can be represented by the following two types: the cumulative DVH (cDVH) and the differential DVH (dDVH). The latter is used for gEUD calculations as follows:

$$gEUD = \left( \sum \left( \frac{v_i}{V_0} d_i^a \right)^{1/a} \right),$$  

(1)

where $v_i$ is the domain volume that received a dose of $d_i$, and $V_0$ is the total volume domain of the organ. The gEUD is a typical representation of the weighted Minkowski distance. In the integral expression for the derivative analysis form with the cDVH $V(D)$, Eq. (1) is naturally expanded as

$$gEUD = \left[ \int_0^{D_{\text{max}}} \frac{1}{V_0} \left( - \frac{dV(D)}{dD} \right) D^a dD \right]^{1/a}, V_0 = \int_0^{D_{\text{max}}} \left( - \frac{dV(D)}{dD} \right) dD,$$

(2)

where $D$ is the dose and $D_{\text{max}}$ is the maximum dose for the organ. This is a convex function for any $a \geq 1$. In contrast, the gEUD is concave when $a \leq 1$. As $a \rightarrow 0$, the gEUD approaches the geometric mean of $D$. In addition, as $a \rightarrow +\infty$, the gEUD approaches the maximum of $D$, and $a \rightarrow -\infty$, the gEUD approaches the minimum of $D^{20}$. This integral form of gEUD is now deemed as a functional. In addition, the gEUD is function of $a$, $\Omega(a)$, and allows a variety of function shapes owing to its dependence on an arbitrary function $V(D)$, which is monotonically decreasing and satisfies the condition $0 \leq V(D) \leq 1$. To be in accordance with the known characteristics of the gEUD (concave for $a < 1$ and convex for $a \geq 1$), as reported by Choi, the constraint condition represented below, using the minimum OAR dose $D_{\text{min}}$ and the maximum OAR dose $D_{\text{max}}$, requires sigmoid-like curves such as the logistic or Gompertz functions (Fig. 1a).

$$D_{\text{min}} \leq \Omega(a) \leq D_{\text{max}}, \quad \frac{d\Omega}{da} > 0.$$  

(3)

This constraint condition also denotes one-to-one correspondence between $D$ and $\Omega$ as well as $a$ and $D$. More basic mathematical characteristics of the gEUD are provided in Supplementary Information (Appendix A).

**Relativity model of gEUD optimization**
The dose distribution derived from modulating the intensity of radiation is optimized according to multiple dose constraints for the target and OARs, resulting in an optimized cDVH. Now, we consider the change in the cDVH during the optimization process, which results from the pre-optimized cDVH curve receiving an external force and changing its form into an appropriate optimized cDVH curve. During the cDVH curve change with proper time $\tau$ in the optimization, the corresponding gEUD curve $\Omega(a)$ changes its form as well retaining the relation of cDVH and gEUD which is provided by Eq. (2). Let the external force that addresses the gEUD curve change be the optimization force. Selecting an appropriate coordinate system, this gEUD curve deviation caused by the optimization force is represented by the following geodesic deviation system with an external force\textsuperscript{21}:

$$\frac{D^2 \xi^A}{D\tau^2} + R_{\mu\nu\sigma}^A \frac{dx^\mu}{d\tau} \frac{dx^\nu}{d\tau} = A^A,$$

(4)

where $x^\mu$ is a selected coordinate, $\xi^A$ is a displacement vector $\xi^A \equiv x^A - \chi^A$ between the pre-optimization and ongoing optimization gEUD curve, $R_{\mu\nu\sigma}^A$ is a Riemannian curvature tensor satisfying

$$R_{\mu\nu\sigma}^A = \partial_\nu \Gamma_{\mu\sigma}^A - \partial_\mu \Gamma_{\nu\sigma}^A + \Gamma_{\mu\alpha}^A \Gamma_{\nu\sigma}^\alpha - \Gamma_{\nu\alpha}^A \Gamma_{\mu\sigma}^\alpha$$

using Christoffel symbols of affine connection coefficients, and $A^A$ denotes an optimization force that represents an input factor as a priority weight of optimization, which is an arbitrary defined balancing factor between the targets and OARs. During the optimization, the optimization priority weight value is a variable parameter; however, this parameter is typically fixed. The absolute derivative operator $D/D\tau$ has the following expression:

$$\frac{D\xi^\mu}{D\tau} \equiv X^\mu \frac{\partial \xi^\beta}{\partial \tau} = \frac{dX^\mu}{d\tau} + \Gamma_{\nu\lambda}^\mu \frac{dx^\nu}{d\tau} \left(\frac{dx^\lambda}{d\tau}\right).$$

(5)

We define the orthogonal $p,q$ coordinate system to evaluate a non-linear $a, \Omega$ system as follows: the $p$-coordinate represents geodesic lines obtained from the gEUD curve $\Omega(a)$, and the orthogonal $q$-coordinate can be defined when $\Omega$ is selected during every change in the proper time. Therefore, we can obtain $p,q$ coordinates from the $a, \Omega$ coordinate transformation and its relation of inverse function is as follows:

$$p = p(a) = \int_0^a \sqrt{1 + (d\Omega/da)^2} \, da, \quad q = q(\Omega),$$

$$a = p^{-1}(p) = a(p), \quad \Omega = q^{-1}(q) = \Omega(q).$$

(6)

The metric tensor $g_{pq}$ from $g_{a\Omega}$ is:

$$g_{pq} = \begin{pmatrix} \frac{\partial a}{\partial p} & 0 \\ 0 & \frac{\partial a}{\partial \Omega} \end{pmatrix}^T \begin{pmatrix} 1 & 0 \\ 0 & 1 \end{pmatrix} \begin{pmatrix} \frac{\partial a}{\partial p} & 0 \\ 0 & \frac{\partial a}{\partial \Omega} \end{pmatrix} = \begin{pmatrix} \left(\frac{da}{dp}\right)^2 & 0 \\ 0 & \left(\frac{d\Omega}{dq}\right)^2 \end{pmatrix} \equiv \begin{pmatrix} \Phi^2(p) & 0 \\ 0 & \Psi^2(q) \end{pmatrix}$$

(7)

Therefore, the non-zero affine connection coefficients are:

$$\Gamma^p_{pp} = \frac{1}{\Phi} \frac{\partial \Phi}{\partial p}, \quad \Gamma^q_{qq} = \frac{1}{\Psi} \frac{\partial \Psi}{\partial q}.$$

(8)
We are now interested in the deviation between pre-optimization and post-optimization in the coordinates defined by Eq. (7). $\xi^\lambda$ represents the displacement vector by geodesic deviation against the optimization proper time $\tau$ and corresponds to $D^2 \xi^\lambda / D\tau^2$:

$$\frac{D^2 \xi^\lambda}{D\tau^2} = A^\lambda - R^\lambda_{\mu\nu} \frac{dx^\mu}{d\tau} \frac{dx^\nu}{d\tau} \xi^\lambda = A^\lambda - R^\lambda_{\mu\nu} \frac{dx^\mu}{d\tau} \frac{dx^\nu}{d\tau} \xi^\lambda,$$

(9)

where $R_{ik}$ is the Ricci curvature tensor and vanishes in the coordinates of $g_{pq}$, and the Gauss curvature $K = 0$ (Supplementary Information Appendix Eq. (B2)). Therefore, $p, q$ and $a, \Omega$ coordinate surfaces can transform each other without distortion by planar deployment. This characteristic of zero Gaussian curvature is called a developable surface in differential geometry. Here, we focus the total action $\int A^\lambda d\tau$, which is the term used for representing the effects of optimized conditions on the change in the gEUD.

Integrating both sides of Eq. (9) and arranging the terms, we obtain the following equation:

$$\int A^\lambda d\tau - \frac{D \xi^\lambda}{D\tau} = \int A^\lambda d\tau - \left[ \frac{d \xi^\lambda}{d\tau} + \left( R^\lambda_{\mu\nu} \frac{dx^\mu}{d\tau} \right) \xi^\nu \right] = F^\lambda,$$

(10)

where $F^\lambda$ is a constant vector against $\tau$. Eq. (10) indicates that the action of the optimization force is weakened by the reaction of the change in the gEUD. To maximize the action of the optimization force, i.e., to maximize $F^\lambda$, the following equations are required,

$$\frac{d \xi^p}{d\tau} + \frac{1}{\Phi} \frac{d\Phi}{d\tau} \frac{d c p}{d\tau} \xi^p = 0, \quad \frac{d \xi^q}{d\tau} + \frac{1}{\Psi} \frac{d\Psi}{d\tau} \frac{d c q}{d\tau} \xi^q = 0.$$

(11)

As for $\xi^p$, depicted in Fig. 1(b), by using the relations of Eq. (6), the former differential equation of Eq. (11) becomes

$$\frac{1}{\xi^p} \frac{d \xi^p}{d\tau} = \kappa(a, \tau) \left( \frac{\partial \Omega(a, \tau)}{\partial a} \right) \left( \frac{d \Omega(a, \tau)}{d\tau} \right),$$

(12)

where $\kappa$ represents the curvature of the gEUD curve in an $a, \Omega$ coordinate system (Supplementary Information Eqs. (B3) and (B4)),

$$\kappa(a, \tau) = \frac{(\partial^2 \Omega / \partial a^2)}{(1 + (\partial \Omega / \partial a)^2)^2}. \quad \kappa(a, \tau) = \frac{(\partial^2 \Omega / \partial a^2)}{(1 + (\partial \Omega / \partial a)^2)^2}.$$

(13)

Then, integrating both sides of Eq. (12) with $\tau$, the norm of $\xi^p$ becomes

$$|\xi^p| = \exp \left( \int \kappa \frac{\partial \Omega}{\partial a} d\tau \right).$$

(14)

Introducing time mean curvature $\kappa(a)$ against $\tau$ to Eq. (12), and considering that the magnitude of the velocity on the geodesic is constant (Supplementary Information Eq. (B6)), Eq. (14) can be rewritten with a constant value against $\tau$, $\Lambda(a)$, as follows:

$$|\xi^p| = \exp \left( \Lambda(a) \kappa(a) \int_0^{\tau_{opt}} \left( \frac{\partial \Omega}{\partial a} \right) d\tau \right).$$

(15)

The term of $(\partial \Omega / \partial a)$ converges to a specific value (a function of $a$) in a finite optimization time $\tau_{opt}$. Let the converged value of the integration term be $\beta(a)$ and its average $\bar{\beta}(a)$, then the final form is obtained
as a pure function of $a$:
\[
|\xi^p| = e^{\lambda \bar{\Omega}}.
\]

This relation exhibits the exponential curvature effect for the shifting gEUD. Let the newly defined $\Xi$ be the total optimization effect,
\[
\Xi(a) = \int |\xi^p| dp = \int e^{\lambda \bar{\Omega}} \left( \frac{dp}{da} \right) da = \int |\xi^a| da.
\]
where $\xi^a$ is displacement vector by focused on the $\Omega$-direction (Supplementary Information Eq. (B8)), and the surface area is constant because, $p, q$ and $a, \Omega$ coordinate surfaces are developable from each other.

**Figure 1.** Characteristics of the gEUD and optimization force concept. (a) The gEUD $\Omega(a)$ exhibits a sigmoid-like curve satisfying $D_{\text{min}} \leq \Omega(a) \leq D_{\text{max}}$, where $a = 1$ is a special point that indicates average dose, and $a = a_\kappa$ is a vertex point of the gEUD curve. (b) Optimization force deforms the gEUD curve in gEUD optimizations. $p$-coordinate is a gEUD curve represented as a geodesic line and is arranged orthogonal against $q$-coordinate. In particular, $p$-oriented displacement vectors $\xi^p$ are represented by the difference of between position vector $\bar{p}_1^p$ and $\bar{p}_2^p$ at the same $p$-coordinate during optimization time $\tau$.

**Evaluation of $a$-value changed effect for gEUD optimization**

Considering the relativistic optimization force, we focus on the gEUD curve shift and its curvature, expecting an effective $a$-value selection. Eq. (16) explicitly represents the curvature and gradient of the gEUD curve to essentially determine the optimization effect. The simplification of OAR dose constraints is one of our goals; therefore, we are limited in this study to the optimization cases where $a > 0$. A pre-optimized gEUD curve has the following characteristic points regarding the $a$-value. First, $a = 1$ represents the mean dose of cDVH $V(D)$. Second, $a = a_M$ indicates the maximization of the
optimization action. Finally, the vertex point of the gEUD curve \( a = a_k \) represents that the first derivative of curvature of the gEUD curve is 0, i.e., \( dk/da = 0 \). The vertex point is numerically obtained by the below Eq. (18) using the first, second, and third numerical derivative calculation of the gEUD curve with second-order accuracy, which is followed by solving the equation using the Newton method because the Eclipse PO is limited to receive only the first decimal place of the \( a \)-value; therefore, numerical accuracy is sufficient.

\[
\frac{dk}{da} = \frac{\left(\frac{d^3\Omega}{da^3}\right) \left(1 + \left(\frac{d\Omega}{da}\right)^2\right) - 3 \left(\frac{d\Omega}{da}\right)^2 \left(\frac{d^2\Omega}{da^2}\right)^2}{\sqrt{1 + \left(\frac{d\Omega}{da}\right)^2 \left(1 + \left(\frac{d\Omega}{da}\right)^2\right)^2}} = 0. \tag{18}
\]

Let \( \Delta DVH \) and \( \Delta gEUD \) be the cDVH and gEUD deviations from the control case, respectively. We used the following mean values for the evaluation of the optimized results:

\[
\bar{\xi}_p \propto \Delta DVH(a) = \left(\int_0^{D_{\text{max}}} \Delta DVH(a, D) dD\right)/\left(\int_0^{D_{\text{max}}} dD\right),
\]

\[
\bar{\xi}_a \propto \Delta gEUD(a) = \left(\int_0^{a_{\text{max}}} \Delta gEUD(a, a) da\right)/\left(\int_0^{a_{\text{max}}} da\right),
\]

(19) (20)

To numerically verify these evaluation from the theory, we used the following numerical summation for \( i = 1 \) to \( N \) corresponding to the optimization at \( a = 0.5, 1.0, 2.0, 3.0, 4.0, 5.0, 6.0, 8.0, 10, 12, 15, 20, 40, \) and \( a_k \):

\[
\bar{\kappa}(a) = \frac{1}{N} \sum_{i=1}^{N} \kappa_i(a),
\]

\[
\beta(a) = \int_0^{\tau_{\text{opt}}} \left(\frac{\partial \Omega}{\partial a}\right) d\tau = \frac{1}{N} \left(\sum_{i=1}^{N} \left(\frac{\partial \Omega}{\partial a}\right)\right) \int_0^{\tau_{\text{opt}}} d\tau.
\]

(21) (22)

Here the constant of the time integration (\( \tau_{\text{opt}} \)) and a scale factor \( \Lambda \) are fixed as 1 in this study. Then, the averaged magnitude of the displacement vector is numerically represented as

\[
\bar{\xi}_p \approx \exp(\bar{\kappa} \bar{\beta}), \quad \bar{\xi}_a \approx \sqrt{1 + \bar{\beta}^2 \exp(\bar{\kappa} \bar{\beta})}. \tag{23}
\]

Eleven head and neck cases (Case #00–#10) were selected to verify the application of the gEUD optimization in clinically complicated situations. Head and neck cases often require complex dose-volume parameters for optimization, depending on the empirical skill of the planner. In this study, we set the planning target volumes (PTVs) as 70, 60, and 50Gy (PTV70/PTV60/PTV50) and the more affected side of the parotid gland (H_Parotid) as the focused target and OAR; the H_Parotid includes PTV-overlapped regions. The PTV for the SIB-IMRT kernel is regionalized as shown in Fig. 2. Seven-field IMRT with gantry angles of 50°, 70°, 150°, 180°, 210°, 290°, and 310° were used, and the optimization weights for the regions are shown in Table 1. Case #00 was selected as a representative case to verify the optimization weight ratio between H_Parotid and the PTVs. The remaining ten cases were calculated with a fixed optimization weight ratio condition (PTVs vs OARs = 200:60). We changed the \( a \)-value of the
H\_Parotid and calculated 150 iterations for the optimization regarding input gEUD 5 Gy less than the control case (zero optimization weight for H\_Parotid). To normalize the optimization effect by optimization force, we obtained the cDVH and the shifted gEUD according to \( a \)-value changed optimization after the D95 normalization of PTV70opt defined in Fig. 2. Notably, these defined regions for OARs are the whole range of the organ itself, which might include margined tumor regions of PTV. Inversely, PTV simply represents the regions of 5 mm expanded of clinical tumor volume (CTV). MUs were also recorded as a simple criterion that represents the optimization stress against the control case, because an increase of MU shows the plan complexity especially in the fixed gantry angle IMRT.

**Figure 2.** Optimization target kernel model used for SIB-IMRT is depicted on the left side and the representative patient case (Case #00) is shown on the right side. PTV-opt is the PTV within 3.0 mm of the inner region of the body surface. Higher PTV regions are totally included by lower PTV regions, therefore, PTV50 \( \supseteq \) PTV60 \( \supseteq \) PTV70. Dose transitional regions are divided for each target dose level respectively. Dose transitional zone A is a region where natural dose attenuation is expected, and it has no dose constraint for optimization. PTV-opt1 is the moderate dose transitional region between the higher and lower doses and PTV-opt2 is the dominant regions of lower dose level. The transitional interval is an arbitrary length with 3D margins of higher PTV and is typically 2–4 mm. In this study, a value of 4 mm is applied to all transitional regions.
Table 1. Optimization objectives and conditions.

| Optimization objectives | Optimization conditions          |
|-------------------------|----------------------------------|
|                         | weight | Lower DVH (volume) | Upper DVH (volume) |
| [Targets]               |        |                   |                   |
| PTV70opt                | 200    | > 70.0 Gy (100%)  | < 71.5 Gy (0%)    |
| PTV60opt                | 100    | > 60.0 Gy (100%)  | < 67.0 Gy (0%)    |
| PTV60opt1               | 100    | > 60.0 Gy (100%)  | < 61.8 Gy (0%)    |
| PTV60opt2               | 100    | > 60.0 Gy (100%)  | < 61.8 Gy (0%)    |
| PTV50opt                | 100    | > 50.0 Gy (100%)  | < 57.0 Gy (0%)    |
| PTV50opt1               | 100    | > 50.0 Gy (100%)  | < 52.5 Gy (0%)    |
| PTV50opt2               | 100    | > 50.0 Gy (100%)  | < 52.5 Gy (0%)    |
| [OARs]                  |        |                   |                   |
| H_Parotid               | 0/40/60/80 | 0.5/1.0/2.0/3.0/4.0/5.0/    |
|                         |        | 6.0/8.0/10.0/12.0/15.0/     |
|                         |        | 20.0/40.0/ \(a_e\)       |
| L_Parotid               | 40     | 1                 | 15.0              |
| Oral_Cavity             | 30     | 1                 | 25.0              |
| Brainstem               | 30     | 10                | 23.0              |
| Brainstem PRV (+2mm)   | 30     | 15                | 25.0              |
| SpinalCord              | 30     | 10                | 25.0              |
| SpinalCord PRV (+5mm)   | 30     | 15                | 27.0              |

Results

First, we verified the optimization weight condition in the representative case with a detailed \(a\)-value (Fig. 3). The intended dose-volume naturally decreased with an increasing optimization weight of H_Parotid. The weak optimization weight ratio did not address the higher dose-volume and \(a\)-value but instead exacerbated it. In contrast, a strong optimization weight ratio can achieve preferable conditions for H_Parotid; however, this sacrificed the higher dose range of PTV and adversely influenced the D95 scaling. Therefore, in this study, we selected an optimization weight ratio between H_Parotid and PTVs as 60:200 for balancing.

Next, we verified the \(a\)-value changed effect for the optimization under clinically multi-body optimized objects. The average ± SD of the DV clinical criteria for the eleven head and neck cases are shown in Table 2. This table indicated that the gEUD optimization for the H_Parotid achieved the selective dose-range optimization with the change in \(a\)-value retaining the PTV condition of the high doses. The detailed analyses for the cDVH are as follows. The representative patient case (Case #00) is shown in Fig. 4, exhibiting dose distribution, the DVH, and the gEUD. In the extremely low \(a\)-value case \((a = 0.5)\), the optimization force weakly addressed the whole range of dose-volume and was not effective for the higher
The vertex point of \( a \) value optimization \((a = 1, 2, 3)\) was primarily effective for the lower-to-middle dose region (<30Gy) and achieved a mean dose decrease, whereas the gEUD shift was small. Higher \( a \) value optimization \((a = 12, 15, 20, 40)\) focused on the higher dose region (>60Gy) and the gEUD shift was large, whereas the eroded higher dose region of the PTV adversely influenced the D95 scaling and resulted in an increasing number of hot spots. Middle \( a \) values \((a = a_κ, 4, 5, 6, 8, 10)\) were effective for a wide range of clinically important dose region (20–70Gy). In particular, \( a = a_κ \) optimization played an intermediate role on lower and higher \( a \) values and achieved the dual purpose of retaining the PTV high dose and decreasing the middle-to-high dose of the OAR. These trends were the same for the other cases and were indicated by \( ΔDVH \) and \( ΔgEUD \), as shown in Figs. 5, 6(a), and 6(b). The rate of increase in the monitor unit (MU) against the control case was observed for almost all cases of \( a \) value changed gEUD optimization. However, the rate was not increased by more than 7.0%; that is, not more than approximately 80–100 MU (Fig. 6(c)). The vertex point of \( a = a_κ \) and the most shifted gEUD point \( a = a_M, ΔgEUD \) depended on the patient cases, whereas \( a = a_M \) was assembled at approximately \( a = 5 \) (Fig. 6(d)). Interestingly, the average \( ΔDVH \) corresponded to \( e^{\frac{a_κ}{b}} \) and \( e^R \), and the average \( ΔgEUD \) corresponded to \( \sqrt{1 + \beta^2e^{\frac{a_κ}{b}}} \), respectively (Figs. 7(a) and 7(b), respectively), and these results were in accordance with the theoretical expectation. The post-optimized gEUD curves for different \( a \) values were deformed compared with the control case, resulted in drifts of the curvature of the gEUD curve (Fig. 7(c)).

The length of the drifts did not exceed \( ±1~2 \) orders for each patient case excluding higher \( a \) value conditions, namely \( a = 20 \) and 40 (Fig. 8). Lower \( a \) value optimization intensified the low \( a \) value change in the gEUD curvature. In contrast, high \( a \) value optimization intensified the high \( a \) value change in the gEUD curvature, whereas it weakened the low \( a \) value change in the gEUD curvature. The middle \( a \) value optimization included \( a = a_κ \), which showed the intermediate effect of a low and high \( a \) value. The vertex point of the gEUD curve also exhibited a drift. This is equivalent to the curvature stationary point \( (dκ/da = 0) \), which was not scattered in the \( a \) range (Fig. 7(d)).
Figure 3. Optimization weight condition effect for gEUD optimization in Case #00, namely, the weight ratios of H_Parotid and PTV are 0:200, 40:200, 60:200, and 80:200, respectively. (a) Calculated optimized dose against the no-dose constraint condition. (b) Calculated optimized dose deviation between the input dose and output dose (output dose – input dose), where the optimization input is 5 Gy less than the no-dose constraint condition.

Table 2. Average and standard deviation for each clinical criterion obtained by the optimization for changes in the \(a\)-value for the eleven head and neck cases (Case #00–#10).
| Term | Clinical criteria | v = None | v = 0.5 | v = 1.0 | v = 1.5 | v = 2.0 | v = 2.5 | v = 3.0 | v = 3.5 | v = 4.0 | v = 4.5 | v = 5.0 | v = 5.5 |
|------|-------------------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|
| PTV50opt | 63.19 ± 2.89 | 63.54 ± 3.89 | 63.29 ± 3.84 | 63.14 ± 3.80 | 62.87 ± 3.83 | 62.38 ± 3.81 | 62.24 ± 3.71 | 61.82 ± 3.57 |
| D99% (Gy) | 69.56 ± 0.16 | 69.56 ± 0.15 | 69.56 ± 0.15 | 69.56 ± 0.17 | 69.56 ± 0.16 | 69.56 ± 0.20 | 69.49 ± 0.17 | 69.39 ± 0.19 |
| D95% (Gy) | 70.09 ± 0.03 | 70.09 ± 0.03 | 70.09 ± 0.03 | 70.09 ± 0.03 | 70.09 ± 0.03 | 70.09 ± 0.05 | 70.09 ± 0.03 | 70.09 ± 0.03 |
| D70% (Gy) | 70.34 ± 0.15 | 70.35 ± 0.13 | 70.34 ± 0.13 | 70.37 ± 0.13 | 70.54 ± 0.14 | 70.33 ± 0.15 | 70.32 ± 0.12 | 70.42 ± 0.10 |
| D60% (Gy) | 71.38 ± 0.65 | 71.31 ± 0.32 | 71.30 ± 0.32 | 71.36 ± 0.32 | 71.40 ± 0.34 | 71.42 ± 0.31 | 71.49 ± 0.28 | 71.51 ± 0.55 |
| D50% (Gy) | 72.74 ± 0.68 | 72.75 ± 0.66 | 72.75 ± 0.67 | 72.80 ± 0.67 | 72.80 ± 0.70 | 72.82 ± 0.62 | 72.90 ± 0.65 | 73.02 ± 0.65 |
| Max dose (Gy) | 74.24 ± 0.96 | 74.25 ± 1.08 | 74.55 ± 1.13 | 74.31 ± 1.18 | 74.56 ± 1.24 | 74.46 ± 1.16 | 74.40 ± 1.10 | 74.56 ± 1.10 |
**Figure 4.** (a) Examples of the dose distributions represented as colored isodose lines in Case #00 with different $a$-values. The optimization weight ratio between H_Parotid and PTV is 60:200. In this case, the no-dose constraint case ($a=$none) exhibits the vertex point of the gEUD curve at $a_{\chi} = 6.5$. The low $a$-value optimized a wide range of OAR doses. In contrast, the high $a$-value optimized only higher OAR doses. The vertex point showed an intermediate level of low and high $a$-values. (b)–(c) DVHs for the OAR (H_Parotid) and PTV with changes in $a$-value for Case #00. (d) gEUD curve shift for the OAR (H_Parotid) with changes in $a$-value for Case #00.
Figure 5. Deviations of dose-volume, $\Delta DVH$, and deviations of gEUD, $\Delta gEUD$, from the control case in the H_Parotid region. (a) Case #00 ($a_\kappa = 6.5$). (b) Case #05 ($a_\kappa = 4.0$). (c) Case #08 ($a_\kappa = 9.0$).
Figure 6. Trends of the gEUD optimization with changes in the \( a \)-value for eleven head and neck optimization cases of the H_Parotid gEUD 5.0 Gy less than the no-dose constraint condition demonstrated as (a) the average of \( \Delta DVH \) (\( \bar{\Delta DVH} \)), (b) the average of \( \Delta gEUD \) (\( \bar{\Delta gEUD} \)), (c) the rate of increase in the planned total MU against the control case, and (d) \( a \)-values at the vertex point of the gEUD curve of the control case \( (a = a_v) \), maximized \( \Delta DVH \) \( (a = a_{M,\Delta DVH}) \), and maximized \( \Delta gEUD \) \( (a = a_{M,\Delta gEUD}) \).
Figure 7. Comparisons between the curvature of gEUD and the average of ΔDVH (ADVH) or the average of ΔgEUD (AgEUD) in the representative case of Case #00 (a_k = 6.5). (a) ADVH corresponds to e^{p} and e^{r}, (b) AgEUD corresponds to \sqrt{1 + \beta^2 e^{p}}, and (c)-(e) the drift of \kappa, d\kappa/da, and d^2\kappa/da^2 according to the optimization for changes in the a-value, respectively.

Figure 8. Drifts of the vertex point (a = a_k) of the gEUD curve for optimization for changes in the a-value (excluding a = 40) among the eleven head and neck patient cases.

Discussion

Despite the fact that gEUD derives from a tissue-specific biological dose, gEUD optimization leads to an optimization object that has detailed dose range with natural optimization weights. To simplify the OAR dose constraints for the optimization, an effective gEUD use for the optimization is inevitable. Choi and O Deasy have reported the mathematical characteristics of the gEUD; however, they only focused on the convexity and concavity. The gEUD is a weighted Minkowski distance of dose-volume domains, and the gEUD is equivalent to the dose D = \Omega(a). The increase of the optimization target dose D and the gradual restriction of the range of optimization with an increasing a is known, as shown in Supplementary Information Figs. 1s and 2s. Higher a-value optimization attempts to achieve an input dose in the restricted D range, in contrast to the lower a-value, which uses a wide D range. These naturally yields an exponential optimization weight bias.

We applied the relativistic optimization force concept to the gEUD optimization and theoretically
elucidated the selection of effective $a$-values for the optimization regarding the case of an OAR adjacent to the tumor target under clinical multi-body optimization objects. The concept is focused on the fact that the gEUD of an optimization object retains its curve characteristics despite the optimization process. Such a group of curves can be treated as geodesics in differential geometry. The optimization effect is regarded as the deviation of the geodesics, deductively leading to the evaluation of the curvature of the gEUD curve as shown in Eqs. (4)–(17). The original optimization effect in this theory contains the proper time effect evaluated as the differential equation of Eq. (12). There is a possibility that the curvature of the gEUD provides a more effective method for optimization against local minima problems by applying dynamic $a$-value during optimization, which is beyond the scope of this study. The exponential relations of the curvature or the gradient of the gEUD curve to the average values $\overline{\Delta DVH}$ or $\overline{\Delta gEUD}$ were shown in this study, and these were in accordance with the theory, although there was a translation against the $a$-value (Figs. 7(a) and 7(b)). $\overline{\Delta DVH}$ grounds the $\Omega$ deviation at the same $D \simeq \Omega$, represented by $\xi^\Omega$, the dominant term is $|\xi| \ll 1$ for negative exponential due to $(\partial^2 \Omega/\partial a^2) < 0$. $\overline{\Delta gEUD}$ grounds the $\Omega$ deviation of the same $a$, the exponential effect is from the transformation of $\xi^\Omega \rightarrow \xi^a$ (Supplementary Information Eq. (B7)). The minus scale term $\Lambda$ is required for the exact match.

In this study, we used a moderate optimization weight ratio between the H_Parotid and PTVs to verify the relativistic optimization force. Parametric analysis for a change in the $a$-value has been widely evaluated$^{9,22-24}$ as a promising and effective tool to improve the OAR dose. The 0mm-cropped case, reported by Fogliata et. al.,$^{18}$ is in good agreement with the results of $\overline{\Delta DVH}$ and $\overline{\Delta gEUD}$ in this study. They concluded that the gEUD relationship to the $a$-value depends on the DVH shape, and there is no correlation between the gEUD and the mean dose. However, the gEUD optimization has been understood in an empirical manner, which is not essential comprehension. From our results, gEUD optimization was represented as the curvature of the gEUD curve and its change. The middle range of $a$-values was very effective, despite different level of PTV and other OAR optimization forces. In particular, $a = a_e$ indicated the intermediate optimization effect of lower and higher $a$-value effects (Figs. 5(a)–5(c), 6(a) and 6(b)). The representative dose distribution, with optimization for a changing $a$-value, explicitly depicted clinical applications (Fig. 4(a)). Focusing on the head and neck cases, a middle-to-high range of dose decrease was required to decrease the mean dose of the parotid gland. In other words, lower and middle $a$-value gEUD optimization was effective for this case. If a high dose region is a clinical matter such as the region adjacent to spinal cord, a higher $a$-value gEUD optimization is appropriate. Note that a higher $a$-value gEUD optimization required a trade-off of the erosion of the PTV dose coverage (Fig. 4(b) and 4(c)). In addition, gEUD optimization was only a range effect for the input dose; thus, it did not necessarily decrease the intended dose. However, this is useful and is permitted if the OAR is heavily prioritized over the PTV, such as aiming for a dose decrease of spinal cord to be hollowed out. Extremely low $a$-value gEUD optimization also encountered problems that required sequentially lower dose-range optimization, leading to the prevention of beam paths and increasing the tangential effect. However, this characteristic is very useful for limiting the lower dose of lung regions. The particular use of the $a$-value should depend on the clinical situation.
As mentioned above, “lower” or “higher” values are appropriate based on the vertex point of the gEUD curve \( a = a_\kappa \) (Fig. 9). We can determine the appropriate \( a \)-value using this, whereas the information for the gEUD curve of the control case is typically not visible. Additionally, gEUD curves deform; therefore, curvature drifts are observed during and post optimization, despite the fixed \( a \)-value condition, as shown in Fig. 8(c). However, the curvature stationary point is not scattered among optimizations that do not have extreme changes in the \( a \)-value as shown in Fig. 8(d) and Fig. 9. The outlier cases in Fig. 8 were mostly for \( a = 20 \) and excluded \( a = 40 \). The optimization for the extremely high \( a \)-values affected the lower dose to increase in addition to erosion of the higher dose regions, causing the vertex of the gEUD curve to shift to a lower \( a \)-value. Nevertheless, it is sufficient to grasp the current state of the gEUD curve and its vertex point to consider a strategy for better optimization. We propose the following process to maximize the gEUD optimization effect: (1) creating a temporal plan, which is a PTV-focused optimization with no dose constraint for the OARs; (2) obtaining \( a = a_\kappa \) for the gEUD curves of the OARs from the cDVH of the temporal plan; and (3) applying an appropriate \( a \)-value to the optimization, considering \( a = a_\kappa \) for lower than/ higher than/ both sides of the dose we intend to intensively decrease. This usage of \( a \)-value based optimization would help the planner to avoid the optimization labor without highly-diversified dose-volume setting and promotes an effective equalization of optimization cuisines without requiring the planner to have empirical knowledge.

**Figure 9.** Schematic concept of strategical optimization for a changing \( a \)-value. The vertex point of the gEUD curve becomes a base point against a “lower” dose and “higher” dose.
Conclusion

This study clarified further mathematical characteristics of the gEUD and the novelty that the gEUD optimization essentially corresponds to the curvature of the gEUD curve, which is derived from originally defined relativistic optimization force concept. We defined the vertex point of the gEUD curve as a base point and this leads to effective a-value selection against lower, higher, and both sides of the dose distribution. Thereby, the mathematical characteristics of the gEUD facilitate its effective use for optimization in a clinically complex situation without empirical manners.

Reference

1. Palma, D. et al. Volumetric modulated arc therapy for delivery of prostate radiotherapy: comparison with intensity-modulated radiotherapy and three-dimensional conformal radiotherapy. *International Journal of Radiation Oncology Biology Physics* **72**, 996-1001 (2008).

2. Babier, A., Boutilier, J. J., Sharpe, M. B., McNiven, A. L. & Chan, T. C. Inverse optimization of objective function weights for treatment planning using clinical dose-volume histograms. *Physics in Medicine & Biology* **63**, 105004 (2018).

3. Fu, A., Ungun, B., Xing, L. & Boyd, S. A convex optimization approach to radiation treatment planning with dose constraints. *Optimization and Engineering* **20**, 277-300 (2019).

4. Guo, C., Zhang, P., Gui, Z. & Shu, H. An efficient method for improving the dose-volume-based optimization plan quality. *IEEE Access* **5**, 7520-7531 (2017).

5. Hristov, D., Stavrev, P., Sham, E. & Fallone, B. On the implementation of dose-volume objectives in gradient algorithms for inverse treatment planning. *Medical physics* **29**, 848-856 (2002).

6. Kubo, K. et al. Dosimetric comparison of RapidPlan and manually optimized plans in volumetric modulated arc therapy for prostate cancer. *Physica Medica* **44**, 199-204 (2017).

7. Lyman, J. T. & Wolbarst, A. B. Optimization of radiation therapy, III: A method of assessing complication probabilities from dose-volume histograms. *International Journal of Radiation Oncology Biology Physics* **13**, 103-109 (1987).

8. Uehara, T. et al. Dose–volume histogram analysis and clinical evaluation of knowledge-based plans with manual objective constraints for pharyngeal cancer. *Journal of Radiation Research* **61**, 499-505 (2020).

9. Teichert, K. et al. Targeted multi-criteria optimisation in IMRT planning supplemented by knowledge based model creation. *Operations Research for Health Care* **23**, 100185 (2019).

10. Zarepisheh, M., Uribe-Sanchez, A. F., Li, N., Jia, X. & Jiang, S. B. A multicriteria framework with voxel-dependent parameters for radiotherapy treatment plan optimization. *Medical physics* **41**, 041705 (2014).

11. Feng, Z. et al. An integrated strategy of biological and physical constraints in biological
optimization for cervical carcinoma. *Radiation Oncology* **12**, 64 (2017).

Liang, X. *et al.* Radiobiological impact of dose calculation algorithms on biologically optimized IMRT lung stereotactic body radiation therapy plans. *Radiation Oncology* **11**, 10 (2016).

Niemierko, A. Reporting and analyzing dose distributions: a concept of equivalent uniform dose. *Medical physics* **24**, 103-110 (1997).

Niemierko, A. A generalized concept of equivalent uniform dose (EUD). *Med Phys* **26**, 1100 (1999).

Li, X. A. *et al.* The use and QA of biologically related models for treatment planning: Short report of the TG - 166 of the therapy physics committee of the AAPM. *Medical physics* **39**, 1386-1409 (2012).

Thieke, C., Bortfeld, T., Niemierko, A. & Nill, S. From physical dose constraints to equivalent uniform dose constraints in inverse radiotherapy planning. *Medical physics* **30**, 2332-2339 (2003).

Wu, Q., Mohan, R., Niemierko, A. & Schmidt-Ullrich, R. Optimization of intensity-modulated radiotherapy plans based on the equivalent uniform dose. *International Journal of Radiation Oncology*Biology*Physics* **52**, 224-235 (2002).

Fogliata, A. *et al.* On the gEUD biological optimization objective for organs at risk in photon optimizer of eclipse treatment planning system. *Journal of applied clinical medical physics* **19**, 106-114 (2018).

Jia, Q. *et al.* OAR Dose Distribution Prediction and gEUD Based Automatic Treatment Planning Optimization for Intensity Modulated Radiotherapy. *IEEE Access* **7**, 141426-141437 (2019).

Choi, B. & Deasy, J. O. The generalized equivalent uniform dose function as a basis for intensity-modulated treatment planning. *Physics in Medicine & Biology* **47**, 3579 (2002).

Hodgkinson, D. A modified equation of geodesic deviation. *General Relativity and Gravitation* **3**, 351-375 (1972).

Lee, T. *et al.* Dosimetric advantages of generalised equivalent uniform dose-based optimisation on dose–volume objectives in intensity-modulated radiotherapy planning for bilateral breast cancer. *The British Journal of Radiology* **85**, 1499-1506 (2012).

Mihailidis, D. N. *et al.* Superiority of equivalent uniform dose (EUD)-based optimization for breast and chest wall. *Medical Dosimetry* **35**, 67-76 (2010).

Widesott, L., Strigari, L., Pressello, M., Benassi, M. & Landoni, V. Role of the parameters involved in the plan optimization based on the generalized equivalent uniform dose and radiobiological implications. *Physics in Medicine & Biology* **53**, 1665 (2008).

**Acknowledgments**

This study was supported by a Grant-in-Aid for Young Scientists (No. 18K15650) from the Japan Society for the Promotion of Science.

**Ethics declarations**
Experimental protocols for this study are acknowledged by Institutional Review Boards and Independent Ethics Committees of Kansai Medical University (2019005). Informed consent forms were signed by all the patients. All methods were carried out in accordance with relevant guidelines and regulations.

Author contributions
Y. A. developed the original idea and wrote the main manuscript text, Y. A. prepared and drew all figures, and H. T. advised the study concept and the coding. Y. A. and Y. K. conducted the numerical calculation and listed the references. S. N. and N. T. supervised this study. All authors reviewed the manuscripts.

Competing interests
The authors declare no competing interests.