An Extended Generalized Equivalent Uniform Dose (eEUD) Accounting for Dose-Range Dependency of Radio-Biological Parameters

The Equivalent Uniform Dose (EUD) is an important means of ranking/evaluating treatment plans in radiotherapy regarding their probability of side-effects. Therefore, a better estimate of the EUD can help improve NTCP modeling and lead to a better prediction of clinical outcome. Here we propose an expansion of the phenomenological gEUD formula that takes a dose-range dependency of radio-biological parameters [1] into account. It is theoretically capable of representing more complex biological effects and may allow for improved clinical decisions in the future.

General concept of EUD:

The EUD is the uniform dose that has the same total effect $F_{\text{tot}}$ on tissue as a given heterogeneous dose distribution. For a differential DVH with dosebins $D_i$ the EUD is defined as

$$EUD = f^{-1}(F_{\text{tot}}) = f^{-1}\left(\sum_i v_i f(D_i)\right),$$  \hspace{1cm} (1)

where $f(D_i)$ is the effect of a dose $D_i$ with relative volume $v_i$ on the tissue. The biology underlying this effect might be quite complicated. Hence, mechanistic or phenomenological EUD models that approximate this effect are necessary.

Phenomenological estimates of EUD:

(1) The gEUD, introduced by Niemierko to describe normal tissues and tumors [2], is the most commonly used phenomenological EUD model. It estimates the effect of dose on tissue as $f(D_i) = D_i^a$ and can therefore be calculated as $\text{gEUD} = \left(\sum_i v_i D_i^a\right)^{\frac{1}{a}}$. It incorporates a single parameter $a$ that is positive for normal tissues and negative for tumors.

(2) For the eEUD, the effect of a dose $D_i$ on tissue is expressed as a piecewise polynomial function with an arbitrary number ($n$) of volume-effect parameters $a_0, a_1, \ldots, a_n$ each valid for a different dose region $(X_0, X_1], (X_1, X_2], \ldots$, as illustrated in Figure 1:

$$f(D_i) = \begin{cases} D_i^{a_0} & |0 = X_0 < D_i \leq X_1 \\ f(X_1) + D_i^{a_1} - X_1^{a_1} & |X_1 < D_i \leq X_2 \\ \cdots \\ f(X_n) + D_i^{a_n} - X_n^{a_n} & |X_n < D_i < \infty. \end{cases}$$

It can also be written explicitly as $f(D_i) = D_i^{a_N} + \sum_{j=1}^{N} \left(X_j^{a_{j-1}} - X_j^{a_j}\right)$, $|X_N < D_i \leq X_{N+1}$, for each piece, with $N = 0, \ldots, n$. The eEUD can be calculated numerically via equation (1). It can easily be proven that the effect $f$ is continuous in dose and one will obtain the same effect as used for the gEUD if $a_0 = a_1 = \cdots = a_n = a$. 

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Figure 1: In order to calculate the eEUD, the DVH is divided into dose regions \((X_0, X_1], (X_1, X_2], \ldots\), associated with parameters \(a_0, a_1, \ldots\), respectively.

**Practical implementation:**

The eEUD and its parameters need to be estimated using patient data in order to verify its practicality. This can be done for example by plugging the gEUD into EUD based NTCP models, such as the Lyman-EUD model, in the same way it is commonly done for the gEUD. Then the parameters can be obtained by using Maximum Likelihood estimation. It remains to be determined if the eEUD yields better fit to patient data than the gEUD, without over-fitting, and how many different volume-effect parameters are necessary/sufficient to adequately describe dose-response of certain tissues. Currently, studies are under way to apply the eEUD to patient DVHs of lung and rectal wall, in order to model the prediction of pneumonitis and rectal bleeding, respectively.

**References**
