

LETTERS TO THE EDITOR

Behind EUD

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To the Editor

In 1997, the concept of equivalent uniform dose (EUD) was first proposed by Niemierko [1]. Since then, this concept has been widely disseminated throughout the radiation oncology community. In 1999, Niemierko further extended the EUD concept to a more general form: the power-law based gEUD [2,3]. Many investigators have used the EUD concept to compare different radiotherapy (RT) modalities, including external-beam RT (EBRT), high-dose-rate (HDR) brachtherapy, low-dose-rate (LDR) brachtherapy, permanent implants etc., and to evaluate different RT regimens with respect to treatment efficacy and outcome, including tumor control probability (TCP) and normal tissue complication probability (NTCP). Furthermore, investigators began to use EUD or gEUD as an objective function to optimize treatment planning. In the past few years, we also have studied this concept and applied it to radiobiological-modeling studies [4–6]. In these studies, we have explored the nature of this concept, its value to clinical radiation oncology, and its relations with other long-established concepts in radiation oncology and radiobiology. In this letter, we share our understanding and comments on EUD with our colleagues of this community.

1. The SF₂-based EUD concept

Initially, EUD [1] was based on the classical radiobiological concept of the fraction of clonogens surviving a dose of 2 Gy (SF₂). It was defined as the equivalent dose, which if distributed uniformly across the target volume, would lead to the same level of cell killing as the actual dose distribution of interest. Based on the EUD concept, a complex dose

plan with 3D dose distribution can be reduced to a single EUD parameter, which relates to treatment outcome of a biologically equivalent dose delivered in 2-Gy fractions of EBRT. Therefore, it is useful to compare and evaluate various treatment plans. Essentially, for a given tumor, EUD is a segregator of mean SF or TCP, because EUD has a simple one-to-one relationship with either of them. However compared to SF or TCP, EUD is less sensitive to radiobiological parameters and is not dependent on the number of tumor clonogenic cells [4].

Furthermore, EUD can convert the RT regimens with different modalities and/or different fraction sizes into the standard EBRT regimens in 2-Gy fractions. In that sense, EUD is a concept similar to the well-known paradigm of biologically equivalent dose (BED). However, EUD is superior to BED in terms of clinical value. BED is a biological concept that represents a virtual dose, i.e., an equivalent dose delivered in infinitely low dose-rate or infinitely small fraction-size, which, of course, is not realistic. Therefore BED is not a practical concept. In contrast, EUD represents a dose delivered in the standard 2-Gy fractions, which closely matches conventionally fractionated dose schedules in the clinicians' experience. For example, in the hypofractionated EBRT of prostate cancer, a schedule of 60 Gy delivered in 20 fractions (3 Gy/fr) would give a BED of 120 Gy and an EUD of 72 Gy if an α/β ratio of 3 Gy were used and the repopulation effect in the short EBRT course were ignored [7,8]. Such an EUD value (72 Gy) provides clinicians a good estimate of therapy outcome based on the published clinical data [9]. In that sense, EUD is equivalent to the earlier concepts of equivalent dose in 2 Gy

fractions (EQD₂) established in clinical radiobiology text books [10], or to biologically equivalent dose (2 Gy/fr) as clarified in recent correspondence to *Acta Oncologica* [11].

2. The general EUD concept

In 1999, Niemierko proposed a more general EUD concept (gEUD) [2]. The gEUD is power-law based and has the following simple form,

$$gEUD = \left(\sum_i v_i D_i^a \right)^{1/a}, \quad (1)$$

where $\{D_i, v_i\}$ are bins of the dose-volume histogram and a is a tissue-specific parameter. The calculation of gEUD is simple and has only one to-be-determined parameter a . However, although this concept is simple, it lacks the capability to address the underlying biological mechanisms, such as the four “R”s: repair, repopulation, reoxygenation and re-sensitization. Therefore, the parameter a of gEUD depends not only on tissue type, but also on treatment modality (EBRT, HDR/LDR, permanent implant, and combinations etc.), dose rate, and fraction size. It means that the parameter a derived from EBRT data may not be applicable to brachytherapy, or from HDR to LDR or from standard fractionation to hyper/hypo-fractionation.

In some earlier studies, based on Lyman-NTCP model [12], we [6] and other investigators [13] derived an EUD formula for normal tissue, which has the following form,

$$EUD = \left(\sum_i v_i D_i^{1/n} \right)^n. \quad (2)$$

This formula has exactly the same appearance as Equation 1 with $n = 1/a$. The parameter n first appeared in Lyman’s article [12] as a volume parameter, which converts a non-uniformly irradiated volume to an effective volume V_{eff} corresponding to D_{max} [14]. Therefore, we can see that gEUD is nothing other than a well-established concept: volume effect, except for its extension from normal tissues to tumors. The parameter a , which corresponds to parameter n , can be interpreted as converting a non-uniformly distributed dose to an effective dose (EUD) to the entire volume of interest.

As shown in Equation 1, for $a = 1$, the gEUD becomes the arithmetic mean dose; when $a > 1$, it weighs more on the high-dose region; in contrast, when $a < 1$, it weighs more on low-dose region. For this reason parameter a is generally less than 1 for tumors, because only “cold” spots are related to failure of tumor control; and for normal tissues, a is generally greater than 1 because “hot” dose regions are associated with tissue complication. Many in-

vestigators have used the gEUD as an objective function in treatment planning, claiming that the gEUD optimization reduces “cold” spots in tumors. From the above discussion, we can clearly see that there is no magic in EUD; rather it is simply that, when $a < 1$, the low-dose regions are more severely “penalized”.

In summary, we found that EUD is a clinically useful concept. The original definition of EUD makes it similar to BED or EQD₂, and the general form (gEUD) describes the same dose-volume effect as the concept presented in References [12] and [14].

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