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Biological effects and equivalent doses in radiotherapy: A software solution

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ABSTRACT

Background: The limits of TDF (time, dose, and fractionation) and linear quadratic models have been known for a long time. Medical physicists and physicians are required to provide fast and reliable interpretations regarding delivered doses or any future prescriptions relating to treatment changes.

Aim: We, therefore, propose a calculation interface under the GNU license to be used for equivalent doses, biological doses, and normal tumor complication probability (Lyman model).

Materials and methods: The methodology used draws from several sources: the linear-quadratic-linear model of Astrahan, the repopulation effects of Dale, and the prediction of multi-fractionated treatments of Thames.

Results and conclusions: The results are obtained from an algorithm that minimizes an ad-hoc cost function, and then compared to an equivalent dose computed using standard calculators in seven French radiotherapy centers.

1. Background: problems of the biologically equivalent dose

It has long been known that radiation biology plays an important role and is necessary for radiotherapy treatments. The time of radiation effects on normal and malignant tissues after exposure range from a femtosecond to months and years thereafter.[1,2] Therefore, to optimize treatment, it is crucial to explain and understand these mechanisms.[3–5] Providing a conceptual basis for radiotherapy and identifying the mechanisms and processes that underlie the tumor and normal tissue responses to irradiation can help to explain the observed phenomena.[6] Examples include understanding hypoxia, reoxygenation, tumor cell repopulation, or the mechanisms of repair of DNA damage.[3,7,8] The different biological effects of radiation should be divided into several phases: the physical phase (interaction between charged particles and

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Nomenclature

α and β	fitting parameters of the linear quadratic model of cell survival (Gy^2 and Gy)
α_{UNSC}	adjustment parameter of the occurrence model of cancer radio-induced (Gy^{-1})
$\theta(x)$	Heaviside function
γ/a	parameter of the LQL model
μ	parameter adjustment necessary to take into account the poly-fractionation in the model LQ (h^{-1})
BED	biological equivalent dose (Gy)
D	physical dose (Gy)
d_t	dose per fraction from which the curve of cell survival becomes linear (Gy)
D_{prol}	proliferation dose (Gy/day)
D_1 et D_2	equivalent doses for the treatments 1 and 2 (Gy)
EQD_2	equivalent dose for a 2 Gy/fraction treatment (Gy)
EUD	equivalent uniform dose (Gy)
EUD^{2Gy}	EUD for an equivalent dose related to a reference of 2 Gy per fraction
f	cost function to minimize by the algorithm
ja	number of day-offs
H_m	LQ model correction taking account the poly-fractionation
$K_{incidence}$	occurrences probability of radio induced cancer (%)
m	fraction number and slope factor of the NTCP model
n	number of fraction
NTCP	complications rate of post radiation (%)
P_{UNSC}	parameter related to the occurrence of radiation-induced cancers (Gy^{-1})
ΔT	duration between two irradiations (heures)
T	overall time (day)
TD50	dose at which there is a 50% complication (Gy)
T_k	time at which repopulation begins after start of treatment (day)
T_{pot}	potential doubling time (day)
T_{stop}	days off during the treatment
u	boundary used in the NCTP calculus (Gy)

tissue atoms), chemical phase (the period during which the damaged atoms and molecules react with other cellular components in rapid chemical reactions), and biological phase (impact of the generated lesions on the biological tissue[4]). The following section describes the models most often used in radiotherapy. These are simplistic models that actual treatments are based on and that are validated and approved.[9–12]

1.1. *Reference models*

Numerous models exist to evaluate the biological equivalent dose, but the two most common ones are the nominal standard dose (NSD[13]) and linear quadratic (LQ[9]) models. The NSD uses the power law described in Eq. (1) (D_{tol} is the tolerance dose of the tissue, NSD is a constant, n and $t \in \mathbf{R}^+$, N the number of fractions, and T the overall treatment time). However, this model has been often criticized.[14] In short, some researchers consider and have even shown that the NSD formula is not a valid description for all tumors and normal tissues; instead, they maintain that the model incorrectly describes the effects of fraction number and treatment duration.

$$D_{tol} = NSD \cdot N^n \cdot T^t \quad (1)$$

The LQ model is most frequently used in radiotherapy units. It allows the equivalent dose to be easily evaluated for different fractionations. This concept involves theα/β ratio, as shown in Eq. (2) (D is the total dose for a fraction size of d gray).

$$EQD_2 = D\frac{d + (\alpha/\beta)}{2 + (\alpha/\beta)} \quad (2)$$

EQD_2 is the dose obtained using a 2 Gy fraction dose, which is biologically equivalent to the total dose D given with a fraction dose of d gray. The values of EQD_2 may be added in separate parts in the treatment plan. This formula may be adapted to fraction doses other than 2 Gy.

1.2. *Limitations of the LQ model*

The LQ model is frequently used for modeling the effects of radiotherapy at low and medium doses per fraction for which clinical data appear to fit reasonably well. The main disadvantage of the LQ approach is that the overall time factor is not taken into account, because in radiotherapy it is regarded to be more complex than previously supposed.[3] It is indeed very difficult to include this parameter in the LQ equation. However, a technique may be used to integrate a penalty term in Eq. (2). Thus, for T_{stop} days off treatment, the dose recovered would be $T_{stop} \cdot D_{prol}$, where D_{prol} is the proliferation factor (in Gy/day; for example, 0.22 for laryngeal edema or 0.15 for rectosigmoid complications). This methodology is essentially validated for discontinuation during treatment. As a general rule, the main limitations of using the LQ model are linked to repopulation (LQ does not take into account the dose protraction), bi-fractionated treatments and high-dose fractions (continuously bending survival curve versus linear behavior observed at least in some cell lines). Other more sophisticated models, however, do take into account these weaknesses. We will later see that the LQ model requires further theoretical investigation, especially in terms of a biologically effective dose (BED).

Given the difficulty of computing the BED, we conducted a study in seven radiotherapy centers in France: CHD Castelluccio (Ajaccio; two classical calculators used), Center de Cancérologie du Grand Montpellier (Montpellier), CRLCC Paul Lamarque (Montpellier), Clinique Saint-Pierre (Perpignan), Center de la République (Clermont Ferrand), CHU of Grenoble, and CHU of Nîmes. A questionnaire was sent to medical physicists working at these centers with the aim of comparing the results of equivalence (for standard radiotherapy planning). Table 1 presents the results of this survey which indicate that not all of the operators obtained the same results. The 95% confidence interval was often very large. Moreover, the relative