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A generalised method for calculating repopulation-corrected tumour EQD2 values in a wide range of clinical situations, including interrupted treatments.

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Abstract:	Any radiotherapy schedule can be characterised by its 2Gy per fraction equivalent dose (EQD2). EQD2s are easily calculated for late-responding normal tissues but for tumours significant errors may arise if no allowance is made for any repopulation which occurs in the reference and/or the derived EQD2 schedule. This article presents a systematic approach to calculating tumour EQD2 values utilising the concept of biologically effective dose (BED) with inclusion of repopulation effects. A factor (f) is introduced which allows the inter-dependence between EQD2 and its delivery time (and, hence, the amount of repopulation involved) to be embedded within the formulation without any additional assumptions. There exists a transitional BED below which simple methods of calculating tumour EQD2 remain valid. In cases where simpler approaches are inadequate, the correct EQD2 may be determined from the reference schedule BED (BEDref) by the relationship: EQD2 = A × BEDref – B, where A and B are constants which involve the same radiobiological parameters as are conventionally used in deriving tumour BED values. Some Worked Examples illustrate application of the method to fractionated radiotherapy and indicate that there can be substantial differences with results obtained from using over-simplified approaches. Since reference BEDs are calculable for other types of radiotherapy (brachytherapy, permanent implants, high-LET applications, etc) the methodology allows estimation of tumour EQD2 values in a wide range of clinical circumstances, including cases which involve interrupted treatments.

A generalised method for calculating repopulation-corrected tumour EQD2 values in a wide range of clinical situations, including interrupted treatments.

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Abstract

Any radiotherapy schedule can be characterised by its 2Gy per fraction equivalent dose (EQD2). EQD2s are easily calculated for late-responding normal tissues but for tumours significant errors may arise if no allowance is made for any repopulation which occurs in the reference and/or the derived EQD2 schedule. This article presents a systematic approach to calculating tumour EQD2 values utilising the concept of biologically effective dose (BED) with inclusion of repopulation effects. A factor (f) is introduced which allows the inter-dependence between EQD2 and its delivery time (and, hence, the amount of repopulation involved) to be embedded within the formulation without any additional assumptions. There exists a transitional BED below which simple

methods of calculating tumour EQD2 remain valid. In cases where simpler approaches are inadequate, the correct EQD2 may be determined from the reference schedule BED (BED_{ref}) by the relationship: $EQD2 = A \times BED_{ref} - B$, where A and B are constants which involve the same radiobiological parameters as are conventionally used in deriving tumour BED values. Some Worked Examples illustrate application of the method to fractionated radiotherapy and indicate that there can be substantial differences with results obtained from using over-simplified approaches. Since reference BEDs are calculable for other types of radiotherapy (brachytherapy, permanent implants, high-LET applications, etc) the methodology allows estimation of tumour EQD2 values in a wide range of clinical circumstances, including cases which involve interrupted treatments.

Introduction

The use of EQD2 (equivalent dose in 2Gy fractions) as an iso-effective descriptor of any radiotherapy treatment schedule is well-established [1]. The EQD2 metric allows, in principle at least, any schedule to be expressed in terms of the iso-effective total dose required if it were to be delivered using conventional 2Gy fractionation. Such an approach has been recommended as it is useful for clinicians seeking an appreciation of the likely effectiveness of relatively novel treatment patterns [2]. EQD2s are also of value for normalising a disparate group of fractionated treatment schedules in order to analyse or rank their outcomes [1-3]. More generally, EQD2 calculations may be used for other types of radiotherapy (e.g. brachytherapy) and to assess the impact of changes to treatment prescriptions, for example as may happen following unscheduled treatment interruptions, or for treatment inter-comparisons [4,5].

The alternative to using EQD2s is to use biologically effective doses (BEDs) as a measure of the effectiveness of treatment schedules. BEDs may be regarded as surrogate measures of cell survival and as such take numerical values which, seen in isolation, are difficult to relate to clinical experience. That is why the EQD2 metric is often suggested as being a better alternative, but even the simplest derivations of EQD2 employ the BED concept as a starting point.

Calculation of EQD2 values for late-responding normal tissues is straightforward and generally involves the following equation [6,7].

$$EQD2 = D_{ref}.\frac{d_{ref} + (\alpha/\beta)}{2 + (\alpha/\beta)} \quad (1)$$

where D_{ref} and d_{ref} are the total dose and fraction dose used in the reference schedule and α/β is that relevant to the end-effect in question.

Eq(1) is derived by equating the simplest form of the BEDs of the reference and EQD2 schedules and then solving for EQD2, i.e.:

$$D_{ref} \times \left[1 + \frac{d_{ref}}{(\alpha/\beta)}\right] = EQD2 \times \left[1 + \frac{2}{(\alpha/\beta)}\right] \quad (2)$$

Eq(2) leads directly to Eq(1) and the BED concept is thus inherent even within the most basic EQD2 formulation.

Eq(2) takes account only of the influences of total dose and fraction size, i.e. repopulation effects are not considered. The derived expression for determining EQD2 [Eq(1)] is therefore appropriate for late-responding tissues, for which any repopulation effect is usually zero or small enough to be ignored.

For tumours the situation is more complex since ongoing repopulation during the reference schedule may exert a significant negative influence on its overall effectiveness, meaning that the physical dose [D_{ref} in Eq(1)]

over-represents the efficacy of the schedule. The subsequently-derived EQD2 is thus also an over-estimate in such cases. Conversely, and even if there is no repopulation in the reference schedule, the associated EQD2 schedule itself might be long enough to allow repopulation to occur, in which case the EQD2 derived from Eq(1) would be an under-estimate. It thus follows that tumour EQD2s derived from Eq(1) alone will often be unrepresentative and that careful consideration of the possibly conflicting numerical influence of repopulation is required.

The issue may be addressed in part by using the fuller BED expression (which includes allowance for repopulation) as an alternative starting point. For fractionated radiotherapy the expression for the reference BED is then:

$$BED_{ref} = D_{ref} \times \left[1 + \frac{d_{ref}}{(\alpha/\beta)}\right] - K \times \left(T_{ref} - T_{delay}\right) \quad (3)$$

where T_{ref} is the overall treatment time, T_{delay} is the time elapsed from first treatment before repopulation begins and K is the daily BED-equivalent of tumour repopulation [8,9]. Eq(3) may then replace the term on the left hand side of Eq(2). If $T_{ref} < T_{delay}$ then the subtractive repopulation factor in Eq(3) is not required.

BEDs represent the total physical dose which would be required for a given observed endpoint if the treatment were to be delivered in an infinite number of vanishingly small fractions and it follows that K is a measure of the daily physical dose required to combat repopulation in that special case. This seemingly nebulous concept has the practical advantage that, when used in “real-life” situations (where fraction numbers and fraction sizes are both finite) K is the only repopulation parameter required. The relationship between K and the actual daily dose equivalent of repopulation for a given fraction size (sometimes referred to as D_{prolif} in the literature [7]) is:

$$K = D_{prolif} \times \left[1 + \frac{d_{ref}}{(\alpha/\beta)}\right] \quad (4)$$

and this inter-dependence is inherently accounted for within all BED formulations [8]. Since K is the associated BED-equivalent of repopulation for any given d_{ref} and tumour α/β it is always numerically greater than D_{prolif} in all practical circumstances.

Once a reference BED is calculated (including the repopulation correction where appropriate), any repopulation influence in the derived EQD2 might then be determined from the equality:

$$EQD2 \times \left[1 + \frac{2}{\alpha/\beta}\right] - K \times \left(t - T_{delay}\right) = BED_{ref} \quad (5)$$

where t is the overall time of the EQD2 schedule. The solution for EQD2 is thus:

$$EQD2 = \frac{BED_{ref} + K \times \left(t - T_{delay}\right)}{\left[1 + \frac{2}{\alpha/\beta}\right]} \quad (6)$$

However, even with this modification, there remains a problem since, prior to performing the calculation, t is unknown as it is itself dependent on the EQD2 value being sought.

As an example of the consequences of this inter-dependence between t and EQD2, suppose a tumour EQD2 is calculated to be 50Gy prior to any repopulation allowance being made. This EQD2 requires 25 treatment fractions which, if delivered conventionally (five fractions per week with weekends free) involves an overall time of 32 days. If this time exceeds the repopulation "kick-off" time (T_{delay}) then an appropriate compensatory dose needs to be added. If this is (say) 8Gy then the EQD2 has to be increased to 58Gy. But delivery of the additional 8Gy would involve four extra 2Gy fractions, i.e. the EQD2 treatment time is again

increased, allowing yet more repopulation, and the revised EQD2 is thus still an underestimate. An iterative approach could be adopted in order to settle on the correct EQD2 but such a step might be unnecessarily complicated.

Given the potential usefulness of EQD2s it is clearly desirable that any repopulation influences in the reference and derived EQD2 schedules be properly accounted for. Some suggestions for achieving this involve first calculating EQD2 by the simple method [Eq(1)] and then adding a compensatory factor involving an assumed dose-equivalent of daily repopulation (D_{prolif}) in conjunction with the differences in the overall times between the reference and EQD2 schedules [7]. This again may involve uncertainty over which t value to use, as described above. Overall, therefore, tumour EQD2 calculations using Eq(1) as a starting point may be misleading and further calculation steps might be required to make the necessary adjustments, resulting in a somewhat tedious and potentially error-prone procedure.

It should be noted that a number of freely-available web calculators make sole use of Eq(1) for calculating EQD2s, thereby inherently assuming that there are no repopulation influences to be considered when performing such evaluations for tumours.

Here we propose a more direct method for calculating tumour EQD2s for a wide variety of circumstances and which involves no new assumptions regarding the modelling methodology. The resultant approach may be easily incorporated into short computational algorithms.

Method

(In what follows all numerically-derived BEDs have a unit subscript which indicates the tumour-specific α/β used in the calculation process, e.g. Gy_{10}, $Gy_{3,}$ etc).

For any radiotherapy treatment schedule fraction number and overall treatment time are intrinsically linked in a way which depends on the pattern of fractionation employed. Allowance for the fractionation pattern can be incorporated in a factor (f), the mean inter-fraction interval, where f takes the approximated form f = 7/n and where n is the number of fractions delivered weekly [10]. For conventional scheduling (of the type usually assumed in EQD2 calculations) n = 5, in which case f = 7/5 = 1.4. For the purposes under discussion here close determination of overall time (t) from the total fraction number (N) may be accomplished via the relationship:

$$t = fN - 2 \qquad (7)$$

For all N >= 5 and for treatments beginning on a Monday Eq(7) generates t values which are always within +/1 one day of the true overall time.

The fraction number associated with any EQD2 value is EQD2/2 and therefore, since f = 1.4, Eq(7) may be re-written as:

$$t = 0.7 \times EQD2 - 2 \qquad (8)$$

thus allowing t to be expressible in terms of EQD2.

The EQD2 which properly corresponds to the derived BED of any reference schedule can then be obtained by modification of Eq(5), i.e.:

$$EQD2 \times \left[1 + \frac{2}{\alpha/\beta}\right] - K \times \left(0.7 \times EQD2 - 2 - T_{delay}\right) = BED_{ref} \quad (9)$$

Eq(9) now includes allowance for the overall time of the reference schedule (already incorporated within BED_{ref}), and for the overall time of the associated EQD2 schedule. No supplementary calculations are required to allow for any time differences between the two schedules.

As an example, application of Eq(9) to head and neck cancer with assumed parameter values of α/β = 10Gy; K = 0.9Gyday^{-1} and T_{delay} = 28 days [1,11] leads to the following equality:

$$EQD2 \times 1.2 - 0.9 \times (0.7 \times EQD2 - 2 - 28) = BED_{ref} \quad (10)$$

leading to:

i.e.: $$EQD2 = 1.754BED_{ref} - 47.37 \quad (11)$$

In cases where the reference schedule is completed before repopulation begins the subtractive factor in Eq(5) is not required and, provided the associated EQD2 treatment may also be completed in an overall time which is less than the repopulation "kick-off" time, both Eqs(5) and (10) simplify to:

$$EQD2 = \frac{BED_{ref}}{1.2} \quad (12)$$

However, if BED_{ref} is large enough to force the derived EQD2 schedule to require an overall time longer than the repopulation delay time (T_{delay}), then Eq(11) is required. For the specific parameters currently being considered the transition between Eqs(12) and (11) occurs at a BED_{ref} value which is determined by equating the two expressions:

$$\frac{BED_{ref}}{1.2} = 1.754BED_{ref} - 47.37$$

i.e. when BED_{ref} = 51.4Gy_{10}.

This parameter-dependent value is defined here as the transitional BED (BED_{tran}).

Using the above assumed parameters the required calculation steps for fractionated radiotherapy are as follows:

1) Calculate the BED_{ref} of the reference schedule using Eq(3).

2) If BED_{ref} <= 51.4Gy then Eq(12) may be used to determine EQD2.
3) If BED > 51.4Gy the EQD2 should be derived using Eq(11).

Eq(11) is of the general form:

$$EQD2 = A \times BED_{ref} - B$$

where A and B are constants derivable from the assumed radiobiological parameters. For use in software routines which can allow for a full range of user-specified parameters the steps involved in calculating A, B and BED_{trans} are set out in the Appendix.

Results

Some predictions of the method summarised in the Appendix are given in the following examples. For illustrative purposes the overall treatment times for the reference schedules are calculated as the time elapsed between first and last treatment by assuming treatment starts on a Monday. In individual cases involving other start days the patient-specific overall time should be used. As is common practice, the EQD2 schedules derived here are themselves assumed to involve five fractions per week [i.e. the f-factor in Eq(7) is fixed at 1.4] with treatment starting on a Monday. If required, EQD2s delivered in alternative fractionation patterns can be calculated after making the corresponding adjustment to Eq(7).

Since a number of web calculators utilise only Eq(1) for deriving tumour EQD2s the numerical predictions associated with that approach are also given for comparison purposes in each case.

Example 1.

A treatment schedule for some types of head and neck cancer involves 55Gy in 20 fractions delivered over four weeks [12]. For this we assume the same parameters as used above. Assuming a Monday start, the

reference schedule is completed in 25 days, i.e. within the T_{delay} time and therefore no repopulation correction is required when calculating the reference BED:

$$BED_{ref} = 20 \times 2.75 \times [1 + 2.75/10] = 70.1Gy_{10}.$$

Parameters RE, A, B and BED_{trans} are next calculated respectively using Eqs(A1), (A4), (A5) and (A6), yielding RE = 1 + 2/10 = 1.2, A = 1.754, B = 47.36 and $BED_{trans} = 51.4Gy_{10}$. Since $BED_{ref} > BED_{trans}$ Eq(A3) is required to find the relevant EQD2, i.e.: EQD2 = 1.754 × 70.1 – 47.36 = 75.7Gy, corresponding approximately to 38 × 2Gy fractions.

Using the simple method [Eq(1)] to calculate EQD2 yields a value of 58.4Gy, which is 23% lower.

Example 2.

A reported accelerated head and neck schedule involved 40 × 1.8Gy delivered 7 days per week (i.e. without weekend breaks) in an overall time of 39 days[11]. The radiobiological parameter values are taken to be the same as those assumed in Example 1 and the derived values for RE, A, B and BED_{trans}, are therefore unchanged. Because the treatment time exceeds T_{delay} the repopulation correction factor is required in this case and the reference BED for the schedule is:

$$BED_{ref} = 40 \times 1.8 \times [1 + 1.8/10] – 0.9 \times (39 – 28) = 75.1Gy_{10}$$

Since $BED_{ref} > BED_{trans}$ Eq(A3) is required to determine EQD2, i.e.:

$$EQD2 = 1.754 \times 75.1 – 47.36 = 84.3Gy.$$

Using the simple method [Eq(1)] to calculate EQD2 yields a value of 70.8Gy, i.e. 16% lower.

Example 3.

The Fast-Forward fractionation pattern for post-operative breast cancer is 5 × 5.2Gy delivered in one week [14]. In this case we assume radiobiological parameters of α/β = 3Gy, K = 0.6Gyday^{-1} and T_{delay} = 21 days [15,16]. As the reference schedule is completed well within the T_{delay} time no repopulation correction is required when calculating the reference BED, which is therefore:

$$BED_{ref} = 5 \times 5.2 \times [1 + 5.2/3] = 71.1Gy_3.$$

Parameters RE, A, B and BED_{trans} are next calculated as RE = 1 + 2/3 = 1.67, A = 0.802, B = 11.07 and BED_{trans} = 54.8Gy$_3$. Since $BED_{ref} > BED_{trans}$ then Eq(A3) is required to find the relevant EQD2, i.e.: EQD2 = 0.802 × 71.1 – 11.07 = 46.0Gy, corresponding approximately to 23 × 2Gy fractions.

Using the simple method [Eq(1)] to calculate EQD2 yields a value of 42.6Gy, i.e. 7% lower.

Example 4.

This is an example of the application of the method to an interrupted treatment. The schedule used in Example 1 is assumed to be interrupted for three weeks, i.e. the overall time is extended from 25 to 46 days. If the dose is not increased to compensate for the time extension then the reference BED becomes:

$$BED_{ref} = 20 \times 2.75 \times [1 + 2.75/10] - 0.9 \times (46 – 28) = 53.9Gy_{10}.$$

The parameters RE A, B and BED_{trans} remain as used in Example 1. Since $BED_{ref} > BED_{trans}$ Eq(A3) is required to determine EQD2, i.e.:

$$EQD2 = 1.754 \times 53.9 – 47.36 = 47.2Gy.$$

Using the simple approach [Eq(1)] to calculate EQD2 yields a value of 58.4Gy, as in Example 1, i.e. 24% higher.

Although this example represents an arguably extreme case, it demonstrates that, depending on the duration of the interruption, Eq(1) may also provide over-estimates of EQD2, in contrast to the under-estimates seen in the other examples.

Discussion

The EQD2 metric provides a useful way of expressing non-standard or novel fractionation treatments in terms of an equivalent schedule involving a pattern of fractionation which is likely to be familiar to most clinicians. For determining such equivalence in terms of late-reacting normal tissue response a simple calculation approach [involving Eq(1)] is entirely adequate in most cases. The derivation of a clinical EQD2 equivalence in terms of tumour response may also be calculated in a similar manner, but only if tumour cell repopulation effects are not present or are small enough to be ignored. Therefore, when repopulation is a significant issue, it should be allowed for within the EQD2 calculation process. The earlier examples demonstrate the potentially large numerical differences which can result if such allowance is omitted.

The methodology described here provides an algorithmic pathway for a more logically-based derivation of tumour EQD2s for all cases. i.e. when repopulation is present or absent in either the reference schedule or the equivalent EQD2 schedule. The point at which there needs to be a transition between the respective formulations required is incorporated directly within the methodology; no separate or supplementary calculations are required. The calculations involve familiar radiobiological parameters (α/β, K and T_{delay}); the only additional parameter is the f-factor which links overall time to fraction number for a specific pattern of fractionation.

No new mechanistic assumptions are involved here but the approach derives from the linear-quadratic (LQ) dose-effect formalism and thus inherits the same potential limitations. In particular caution is required when the reference schedules involve particularly large fraction sizes (typically > 10Gy) since in such cases Eq(3) will over-estimate the associated BED_{ref} on account of the increasing divergence away from LQ predictions at such doses [17]. Several authors have suggested modifications to the LQ formalism to correct for this phenomenon and these may be used as an alternative basis for calculating BED_{ref} [18-20]. No further alterations are then required when using the EQD2 methodology described here.

Regarding the parameter values of K, α/β and $T_{delay,}$ the same caveats apply as is the case with any other radiobiological assessment. The values used in the examples are those often chosen but should not be regarded as being definitive. Users of any radiobiological methodology are free to select their own choices of parameter values and these should be kept under review in light of evolving knowledge. Additionally, and following the usual convention, tumour repopulation is assumed here to follow a dichotomous form, being zero before the kick-off time and increasing mono-exponentially with treatment time thereafter. In practice it is more likely that the rate of repopulation builds up from an initially small value and that the T_{delay} parameter, rather than being the repopulation start time, more realistically represents the time at which the effect becomes significant enough not to be ignored. A continually changing rate could be consistent with a progressively decreasing cell loss factor [21,22], but allowance for such a phenomenon requires other parameter assumptions for which there is little experimental or clinical guidance. Also, and in line with the usual convention, repopulation rates are assumed to be unaffected by dose-rate or fraction size since currently

available clinical data provide insufficient information to reliably inform the use of more complex relationships.

Although this paper deals with the case of single-phase fractionated treatments, the same methodology will apply when determining tumour EQD2s for other types of radiotherapy, for example bi-phasic fractionation schemes, all forms of brachytherapy and high-LET therapy. It may also be used for fast-repopulating acute-responding normal tissues. In each case all that is necessary is to use the appropriate equations to determine the reference BED for the schedule in question and then use that as the starting-point to follow the same steps as set out in the Appendix. The necessary BED formulations for various types of brachytherapy and high-LET applications are described in detail elsewhere [23-27]. Reference BEDs may also be calculated for fractionation schemes which involve closely-spaced daily fractions [28].

The methodology may also be extended to allow the conversion of a reference schedule to any other iso-effective pattern of fractionation. For example, for fraction doses other than 2Gy only the fraction size in the RE factor [Eq(A1)] need be changed; the subsequent steps are unaltered. Similarly, when calculating equivalent dose schedules which are themselves assumed to be delivered using non-conventional fractionation patterns the value of f and the form of Eq(7) may be correspondingly adjusted.

Conclusion

This article demonstrates that incorporation of a systematic allowance for repopulation effects can significantly influence the subsequently-derived tumour EQD2 values. Non-allowance for repopulation can lead to erroneous tumour EQD2 predictions and the approach described here examines how calculation methodology might be improved whilst employing only commonly-accepted modelling assumptions. As is always

the case, radiobiological predictions exist to help inform clinical judgement, not replace it.

Several freely-accessible websites offer EQD2 calculation algorithms but most ignore the likelihood of repopulation and rarely, if ever, provide the necessary caveats which need to be observed when following the procedure for tumours. More refined calculations methods have been set out by others but, because they are not usually based around a matching of BEDs, may require a more tedious case-by-case approach. Although EQDs are more practical than BEDs as a "one-number" representation of a given treatment it is suggested here that all the calculations leading to EQD2 derivations are more logically performed by using the BED approach as a starting point. No new radiobiological assumptions are involved and the in-built factor for linking EQD2 doses with their associated overall treatment time introduces very little uncertainty.

The EQD2 metric finds use as a clinical reference in a variety of other clinical situations, e.g. in the radiobiological transformation of dose-volume histograms [6]. In some cases the effects of tumour repopulation are considered, but only in relation to the reference schedule, not in the derived EQD2 schedule [6,29]. The process described here would help in addressing such issues.

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Appendix.

[Here the factor f is shown as a floating parameter but would assume a fixed value of 1.4 for all conventional EQD2 calculations, (see main text)].

By definition, the Relative Effectiveness (RE) of an EQD2 schedule is:

$$RE = 1 + \frac{2}{\alpha/\beta} \quad \text{(A1)}$$

From Eq(9):

$$EQD2 \times RE - K \times \left(\frac{f}{2} \times EQD2 - 2 - T_{delay}\right) = BED_{ref}$$

which leads to:

$$EQD2 = \frac{BED_{ref} - K \times \left(2 + T_{delay}\right)}{RE - \frac{fK}{2}} \quad (A2)$$

and which may be written as:

$$EQD2 = A \times BED_{ref} - B \quad \text{(A3)}$$

where:

$$A = \frac{1}{RE - \frac{fK}{2}} \quad (A4)$$

$$B = K \times \left(2 + T_{delay}\right) \times A \quad (A5)$$

The transitional BED (BED_{trans}) is the solution for BED_{ref} of:

$$\frac{BED_{ref}}{RE} = A \times BED_{ref} - B$$

i.e.: $$BED_{trans} = \frac{B \times RE}{A \times RE - 1} \quad (A6)$$

To apply the methodology in its most generalised form software routines may be developed to step through the following:

1) Select appropriate values for f, α/β, T_{delay} and K.
2) Calculate RE for the EQD2 schedule [Eq(A1)].
3) If $T_{ref} < T_{delay}$ calculate BED_{ref} for the reference schedule as:

$$BED_{ref} = D_{ref} \times \left[1 + \frac{d_{ref}}{\alpha/\beta}\right] \quad (A7)$$

4) If $T_{ref} > T_{delay}$ calculate BED_{ref} as:

$$BED_{ref} = D_{ref} \times \left[1 + \frac{d_{ref}}{\alpha/\beta}\right] - K \times \left(T_{ref} - T_{delay}\right) \quad (A8)$$

5) Calculate parameters A and B using Eqs(A4) and (A5).
6) Calculate the transitional BED using Eq(A6).
7) If $BED_{ref} <= BED_{trans}$ then calculate EQD2 as:

$$EQD2 = \frac{BED_{ref}}{RE} \quad (A9)$$

8) If $BED_{ref} > BED_{trans}$ than calculate EQD2 using Eq(A3).

In cases where the reference schedule involves alternative delivery patterns (as in the case of brachytherapy or high-LET therapy) then steps 1 - 4 need to involve the appropriate calculation method to determine BED_{ref}. Steps 5 – 8 remain unchanged.