The clinical application of the "Timmerman tables" and the LQ approach to isoeffectiveness in the re-treatment setting

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ABSTRACT

Purpose: Organ at risk dose limits as a function of varying fractionation scheme are conveniently given in the well-known "Timmerman tables". Application of these limits in the re-treatment environment using the LQ approach (EQD2) can lead to overestimation of available dose for some OARs. In this work we describe a method to use the given limits and the EQD2 method in an isoeffective manner.

Methods: The physical dose limits for each OAR were converted to EQD2 and graphed as a function of fraction number. An LQ uncertainty boundary was delimited for physical dose above approximately 6Gy/fx. The average EQD2 for fractionation not exceeding the uncertainty boundary was delimited. If individual EQD2 values correspond to this average, the standard EQD2 method can be used directly to determine available dose. If individual EQD2 values appreciably exceed the average value, do not use directly. Convert previous OAR dose to EQD2 applying repair if applicable and then convert to physical dose for the current fractionation number. Subtract this physical dose from the current fractionation physical dose limit to determine available physical dose.

Results: The 5-fraction rectum physical max dose limit from Timmerman is 55Gy or 154Gy EQD2 assuming an α/β of 3Gy for late effects. The average EQD2 above the LQ uncertainty boundary is only 105Gy. Applying 0-50% repair to the average EQD2 (eg. previous dose) and the above method results in EQD2 values of 116-94Gy. An average EQD2 limit of 81Gy is found for HyTEC (4-5 fx).

Conclusions: When moving from high to low fractionation schemes, use the methods described to avoid overestimation of available dose. Moving from low to high fractionation schemes when the initial course is described by HyTEC limits, use EQD2 method. If the initial course is described by Timmerman limits, consider alternative re-treatment methods such as PLDR.

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INTRODUCTION

The dose limits given by Timmerman for some OARs and fractionations do not follow isoeffective behavior when converted to EQD2 and graphed as a function of fraction number. Using the standard EQD2 method may over-predict available dose during retreatment. This tends to occur for fractional doses above approximately 6Gy/fx where the LQ model is known to exhibit increased deviation of predicted vs. actual results. Using the physical dose approach described here allows for the use of the EQD2 method as well as the Timmerman limits, with or without repair, in a consistent manner that may result in OAR doses corresponding to known side effects.

METHODS AND MATERIALS

The dose limits as a function of fractionation in the Timmerman tables for all commonly used OARs were converted to EQD2 values. An α/β of 3Gy was utilized to reflect late effects. These EQD2 values were graphed as a function of fractionation to assess isoeffectiveness (ie. similar biological effect) and each value's utility for use in determining re-treatment dose limits. Each graph was segmented at an LQ uncertainty boundary of approximately 6Gy/fx (physical dose). The average EQD2 beyond this boundary was used to evaluate isoeffective behavior.

RESULTS

Figure 1. illustrates the isoeffective nature of the physical dose limits given for each fractionation scheme, converted to EQD2 for the spinal cord. The average EQD2 above the LQ uncertainty boundary is also displayed for comparison. It appears that all values, on either side of the boundary, result in values that may approximate isoeffective response. For comparison, physical doses provided in HyTEC, were also converted to EQD2 and graphed. Again, isoeffectiveness was similar to the values derived from the Timmerman tables.

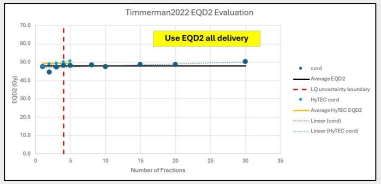

Figure 1. Spinal cord max dose limits converted to EQD2 as a function of fractionation. HyTEC values added for comparison. Values appear isoeffective (ie. parallel to the x-axis).

This process was repeated for the rectum and is illustrated in figure 2. It can be seen that the individual data points, converted to EQD2, do not appear to be isoeffective. This is clearly evident above the LQ uncertainty boundary located at approximately 10 fx delivery.

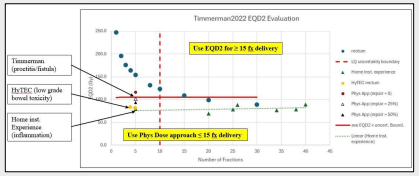

Figure 2. Rectum max dose limits converted to EQD2 as a function of fractionation. Timmerman values do not appear isoeffective below approximately 15 fractions. HyTEC and home institution values added for comparison. Timmerman values for 5 fx delivery (0-50% repair included) converted using physical dose method described. Resultant values lie near the isoeffective dose line (ie. 105.1 Gy ave EQD2 beyond uncertainty boundary).

The ramifications of direct usage in the re-treatment scenario are evident in the following example:

1) Assume prostate treatment in 2020; 80 Gy in 40 fxs. Rectum received 80 Gy max.
2) 80 Gy in 40 fxs → 80 Gy EQD2 → 40 Gy EQD2 **(50% repair)**
3) We intend to give 35 Gy in 5 fx to periprostatic node in 2026
4) 5 fx Timmerman2022 limit: 55 Gy (**154 Gy EQD2**) (**seems pretty high**)
6) 154 Gy EQD2 – 40 Gy EQD2 = 114 Gy EQD2 available
7) 114 Gy EQD2 in 5 fxs → **46.41 Gy physical** (note: this is **9.3 Gy/fx, physical**)
8) 40 Gy EQD2 in 5 fxs → 25 Gy physical
9) 25 + 46.41 = **71.41** Gy physical (>>55 Gy physical dose) **(30% higher than Timmerman)**

Same example but adopting a "**physical dose**" approach:

Convert previous treatment dose to OAR to EQD2 (apply repair if applicable)
80 Gy in 40 fxs → 80 Gy EQD2 → 40 Gy EQD2 (50% repair)

↓

Determine physical dose limit for "current" fractionation

We intend to give 35 Gy in 5 fx to periprostatic node in 2025

5 fx Timmerman2022 limit: 55 Gy

↓

Convert previous treatment OAR EQD2 to physical dose (ie. what physical dose would result in this EQD2 in the current number of fractions)

40 Gy EQD2 in 5 fxs → 25 Gy physical

↓

Subtract this physical dose from the physical dose limit for the current fractionation.

55 - 25 = **30 Gy physical dose available**

↓

30 Gy in 5 fxs → 54 Gy EQD2

40 Gy EQD2 + 54 Gy EQD2 = 94 Gy EQD2

DISCUSSION

The resulting values from applying this method and assuming the initial course received the isoeffective dose (105.1Gy EQD2) and 0-50% repair are shown to lie near the isoeffective line. For comparison, the 5fx HyTEC limit of 38 Gy (80.6Gy EQD2) and 5fx FCCC clinical experience values of 37.7Gy ave (79.5Gy EQD2) were added. Their proximity to the isoeffective line helps support the method described.

Deviation of the 3 data sets from the isoeffective line may be attributable to the variation in the grade 3 toxicities tracked. The increase in dose is reflected in the severity between FCCC (inflammation), HyTEC (low grade bowel toxicity) and Timmerman (proctitis/fistula) and is demonstrated in figure 2.

The example given assumes 5fx SBRT delivery for the re-treatment course of radiotherapy. While this fractionation schedule is commonly used, caution should be exercised when using fewer fractions as the resulting EQD2 values will increase and deviate from the isoeffective line.

Depending on fractionation, the physical dose approach may be prudent in 11 of the 16 structures evaluated. These include the bladder, colon, duodenum, esophagus, great vessels, heart, jejunum/ileum, optic pathway, rectum, stomach and trachial-brochial tree. It appears that for the remaining structures evaluated including the brachial plexus, brainstem, cauda equina, sacral plexus and spinal cord, direct application of the EQD2 method using the given limits may be appropriate.

CONCLUSIONS

For some structures, the physical doses given in the tables and converted to EQD2 exhibit an isoeffective behavior and can be safely used to determine physical dose limits in the re-treatment setting, regardless of fractionation.

For structures that result in inordinately high EQD2 values upon conversion at lower fractionation, the "physical dose" approach may allow for determination of physical dose limits in the retreatment setting that approximate isoeffectiveness for these fractionation schemes.

REFERENCES

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