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**PHYSICS CONTRIBUTION**

# A SIMPLE METHOD OF OBTAINING EQUIVALENT DOSES FOR USE IN HDR BRACHYTHERAPY

SUBIR NAG, M.D., AND NILENDU GUPTA, PH.D.

Division of Radiation Oncology, Arthur G. James Cancer Hospital and Research Institute, Ohio State University, Columbus, OH

**Purpose: To develop a simple program that can be easily used by clinicians to calculate the tumor and late tissue equivalent doses (as if given in 2 Gy/day fractions) for different high-dose-rate (HDR) brachytherapy regimens. The program should take into account the normal tissue sparing effect of brachytherapy.**

**Methods and Materials: Using Microsoft Excel, a program was developed incorporating the linear-quadratic (LQ) formula to calculate the biologically equivalent dose (BED). To express the BED in terms more familiar to all clinicians, it was reconverted to equivalent doses as if given as fractionated irradiation at 2 Gy/fraction. Since doses given to normal tissues in HDR brachytherapy treatments are different from those given to tumor, a normal tissue dose modifying factor (DMF) was applied in this spreadsheet (depending on the anticipated dose to normal tissue) to obtain more realistic equivalent normal tissue effects.**

**Results: The spreadsheet program created requires the clinician to enter only the external beam total dose and dose/fraction, HDR dose, and the number of HDR fractions. It automatically calculates the equivalent doses for tumor and normal tissue effects, respectively. Generally, the DMF applied is $< 1$ since the doses to normal tissues are less than the doses to the tumor. However, in certain circumstances, a DMF of $> 1$ may need to be applied if the dose to critical normal tissues is higher than the dose to tumor. Additionally, the $\alpha/\beta$ ratios for tumor and normal tissues can be changed from their default values of 10 Gy and 3 Gy, respectively. This program has been used to determine HDR doses needed for treatment of cancers of the cervix, prostate, and other organs. It can also been used to predict the late normal tissue effects, alerting the clinician to the possibility of undue morbidity of a new HDR regimen.**

**Conclusion: A simple Excel spreadsheet program has been developed to assist clinicians to easily calculate equivalent doses to be used in HDR brachytherapy regimens. The novelty of this program is that the equivalent doses are expressed as if given at 2 Gy per fraction rather than as BED values and a more realistic equivalent normal tissue effect is obtained by applying a DMF. Its ease of use should promote the use of LQ radiobiological modeling to determine doses to be used for HDR brachytherapy. The program is to be used judiciously as a guide only and should be correlated with clinical outcome. © 2000 Elsevier Science Inc.**

**HDR brachytherapy, Time–dose-effect, Linear-quadratic, Biologically equivalent dose.**

## INTRODUCTION

Most radiation oncologists are familiar with low-dose-rate (LDR) brachytherapy. Recently, there has been a trend towards increased use of high-dose-rate (HDR) brachytherapy due to its advantages, namely that it eliminates radiation exposure to caregivers, requires only short treatment times, and that its dose distribution can be optimized by varying the dwell times. HDR is generally given as fractionated treatments to decrease normal tissue toxicity. The dose effect relationship in radiation therapy is not linear, but may be assumed to follow a linear-quadratic (LQ) function (1). Hence, doses from different treatment modalities cannot be added linearly to determine the combined effect. Many radiation oncologists are not very familiar with the fractionation schemes to be used in HDR brachytherapy. Further, there is a marked difference between the biological effects in the tumor and those in late reacting normal tissue (1). Besides, patients are often treated with external beam radiotherapy combined with HDR brachytherapy, which poses the added challenge of determining the combined effect of the two treatments.

One way to calculate the biologically equivalent doses (BEDs) of different dose fractionation schemes is to use the LQ equation (eq. 1 in Appendix 1). In this equation, the $\alpha/\beta$ ratio is usually taken to be 10 Gy for tumor/early effects and 3 Gy for late effects (2). The concept of LQ modeling is familiar to most radiation oncologists. However, this calculation is cumbersome, and the resultant BED values are not familiar to the clinicians. Further, it does not take into

Reprint requests to: Subir Nag, M.D., Chief of Brachytherapy, The Arthur G. James Cancer Hospital, Ohio State University, 300 West Tenth Avenue, Columbus, OH 43210. E-mail: nag.1@osu.edu

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Table 1. The BED and equivalent doses (given as 2 Gy/fraction) for different HDR regimens using DMF for HDR of 0.7

| EBRT total dose (Gy) @ 1.8 Gy/fx | # of HDR fractions | HDR dose/fx (Gy) | Tumor BED ($Gy_{10}$) | BED ($Gy_3$) (late effects no DMF) | Equiv. dose for tumor effects (Gy) | Equiv. dose (Gy) (late effects no DMF) | Equiv. dose (Gy) (late effects with DMF) |
|---|---|---|---|---|---|---|---|
| 0 | 3 | 5.0 | 22.5 | 40.0 | 18.8 | 24.0 | 13.7 |
| 0 | 3 | 7.0 | 35.7 | 70.0 | 29.8 | 42.0 | 23.2 |
| 0 | 4 | 4.0 | 22.4 | 37.3 | 18.7 | 22.4 | 13.0 |
| 0 | 4 | 5.0 | 30.0 | 53.3 | 25.0 | 32.0 | 18.2 |
| 0 | 5 | 4.0 | 28.0 | 46.7 | 23.3 | 28.0 | 16.2 |
| 0 | 5 | 5.0 | 37.5 | 66.7 | 31.3 | 40.0 | 22.8 |
| 0 | 5 | 6.0 | 48.0 | 90.0 | 40.0 | 54.0 | 30.2 |
| 0 | 5 | 7.0 | 59.5 | 116.7 | 49.6 | 70.0 | 38.7 |

$\alpha/\beta$ for tumor effects = 10 Gy; $\alpha/\beta$ for late effects = 3 Gy.
DMF = dose modifying factor; BED = biologically equivalent dose; HDR = high dose rate; EBRT = external beam radiation therapy.

consideration that, in brachytherapy, doses to normal tissues are generally lower than doses to tumor tissues. For these reasons, radiobiological modeling is not widely used on a routine basis. However, simplifying the calculations for the LQ radiobiological model, applying a dose modifying factor (DMF) to take into consideration that the doses to normal tissues are different from the doses to the tumor, and expressing the results in terms of equivalent doses given at 2 Gy per day rather than as the BED would make it more likely that the LQ model would be used clinically.

With these considerations in mind, we developed a program that could be run on commonly available personal computers. This program quickly performs the calculations and express the results in clinically familiar equivalent doses given at 2 Gy per day, applying a DMF. The details of all calculations and formulations used in this article are explained in Appendix 1. The reader can program these calculations into an Excel spreadsheet; alternatively, a computer disk with this program can be made available to those requesting it.

## METHODS AND MATERIALS

Excel program was selected because it is a commonly available spreadsheet for personal computers and is accessible to most clinicians. Inputs to this spreadsheet fall into two categories:

a. Parameters affecting tissue characteristics and equivalence calculations: $\alpha/\beta$ ratio for early and late effects, dose per fraction for equivalence calculation, and normal tissue dose modifying factor for HDR brachytherapy (DMF). The default values of these parameters are set as follows: $\alpha/\beta$ ratio (late) = 3 Gy, $\alpha/\beta$ ratio (tumor or early reacting tissues) = 10 Gy, DMF = 0.7. The above parameters are usually kept constant for day-to-day use, but can be changed, if required, to suit special circumstances. Note that the dose per fraction for dose equivalency calculations ($D_{eq}$) is generally kept at 2 Gy, since most clinicians are familiar with the use of 2 Gy/fraction. However, even this parameter can be changed if preferred.
b. Treatment parameters: External beam radiation therapy (EBRT) total dose, EBRT dose per fraction, HDR dose per fraction, and number of HDR fractions. These variables are entered for the treatment regimen to be calculated.

Table 1 shows the setup of the spreadsheet and illustrates the equivalent doses for some common HDR fractionation schemes. Since there is no EBRT in these regimens, the EBRT dose is entered as 0. The spreadsheet has an input area on the top (not shown in the table for simplicity) where parameters to be used globally such as the EBRT dose/fraction, the $\alpha/\beta$ ratio for late and tumor/early reacting tissues, and the DMF are entered. The number of HDR fractions are entered in column 2, and the HDR dose per fraction in column 3. The BED for tumor effect is calculated in column 4 using the LQ formula shown in eq. 1 and the default $\alpha/\beta$ ratio of 10. The BED for late tissue effects is calculated in column 5 using the same formula with a default $\alpha/\beta$ ratio of 3 and no DMF. The BED was converted (see Appendix 1, Formula 2) to more familiar equivalent doses ($D_{Eq}$) as though given as conventionally fractionated irradiation (2 Gy/fraction) in columns 6 (Tumor) and 7 (Late Effects).

The late effects column (column 7) gives the equivalent dose if the doses delivered to the normal tissues were equal to doses delivered to the tumor. However, with HDR brachytherapy, this circumstance rarely occurs, because the dose given to normal tissues is generally lower due to the sharp fall-off in dose with distance. For example, if the dose to normal tissue is estimated to be 70% of the prescribed dose to the tumor, a DMF of 0.7 would need to be applied to calculate the modified, more realistic late normal tissue effects in column 8. The spreadsheet is designed to apply the DMF only to the HDR brachytherapy dose to calculate the equivalent dose for late effects for the chosen regimen. It is to be noted that the DMF (in this case 0.7) is applied to

Table 2. The equivalent doses for various combined external beam and HDR for prostate cancer using DMF of 0.7

| EBRT total dose (Gy) @ 1.8 Gy/fx | # of HDR fractions | HDR dose/fx (Gy) | Tumor BED ($Gy_{10}$) | BED ($Gy_3$) (late effects no DMF) | Equiv. dose for tumor effects (Gy) | Equiv. dose (Gy) (late effects no DMF) | Equiv. dose (Gy) (late effects with DMF) |
|---|---|---|---|---|---|---|---|
| 50.4 | 4 | 4 | 81.9 | 118.0 | 68.2 | 70.8 | 61.4 |
| 45 | 3 | 5.5 | 78.7 | 118.8 | 65.6 | 71.3 | 59.0 |
| 50.4 | 3 | 5.5 | 85.0 | 127.4 | 70.9 | 76.4 | 64.2 |
| 46 | 2 | 9.5 | 91.3 | 152.8 | 76.1 | 91.7 | 69.8 |
| 46 | 3 | 6.5 | 86.5 | 135.4 | 72.0 | 81.2 | 64.8 |
| 36 | 4 | 6.0 | 80.9 | 129.6 | 67.4 | 77.8 | 58.8 |
| 39.6 | 4 | 6.0 | 85.1 | 135.4 | 70.9 | 81.2 | 62.2 |
| 45 | 4 | 5.5 | 87.2 | 134.3 | 72.7 | 80.6 | 64.3 |

$\alpha/\beta$ for tumor effects = 10 Gy; $\alpha/\beta$ for late effects = 3 Gy.

the HDR dose (column 3) and not to the equivalent dose (column 5 or 7).

Tables 2 and 3 show examples of the use of HDR brachytherapy in conjunction with EBRT for treating different clinical sites using the two modalities. Although it is not meaningful to add the EBRT dose to the HDR dose, the BED of EBRT and HDR can be added to obtain the BED of a combined treatment regimen. Therefore, in Table 2 the EBRT dose and dose per fraction are entered in column 1. The HDR number of fractions and dose per fraction are entered in columns 2 and 3 respectively. Columns 4 and 5 show the sum of the BED of EBRT and the HDR treatments for tumor and late effects, respectively. The respective equivalent doses are given in columns 6 and 7. Note that, for simplicity, columns 4 and 5, which show the BED values, are generally hidden during regular use (e.g., in Tables 3 and 4), expressing only the equivalent doses as if given at 2 Gy per day. The columns showing the BED can be easily revealed by using the "unhide" function of Excel.

## RESULTS

Following are some examples of the use of this program.

*Example 1.* The Radiation Therapy Oncology Group (RTOG) wished to develop a protocol that would allow the use of HDR brachytherapy to treat cancer of the cervix. Various doses of pelvic EBRT were to be allowed. We needed to determine the HDR dose per fraction required to deliver an equivalent tumor dose of about 85 Gy while keeping the equivalent dose for late effects below 75 Gy. The clinicians entered the various allowable pelvic EBRT doses in column 1, Table 3. A practically manageable number of HDR fractions were entered in column 2. The values of HDR dose per fraction (column 3) were adjusted so that the equivalent tumor doses (column 4) were about 85 Gy, while ensuring that the equivalent late effects (column 6) were below 75 Gy. Note that the DMF of 0.7 used to obtain column 6 is probably reasonable since the dose to the critical normal structures, namely bladder and rectum, is about 70%, as shown in the recent survey by the American Brachytherapy Society (3). It is comforting to note that the HDR doses obtained from this program are within the range of clinically used HDR.

*Example 2.* A clinician wished to develop a protocol using HDR brachytherapy alone to treat prostate cancer, treating twice a day using either 5 or 6 fractions to complete the treatment over 3 days. Since EBRT was not to be used, a value of 0 was entered under EBRT, and the column was hidden for clarity (Table 4). The equivalent tumor effect is now shown in column 3 and equivalent late effect in column

Table 3. Equivalent tumor and late effect doses for various doses of EBRT and HDR brachytherapy (using DMF of 0.7) for cervical cancer

| EBRT total dose (Gy) @ 1.8 Gy/fx | # of HDR fractions | HDR dose/fx (Gy) | Equiv. dose for tumor effects (Gy) | Equiv. dose (Gy) (late effects no DMF) | Equiv. dose (Gy) (late effects with DMF) |
|---|---|---|---|---|---|
| 19.8 | 7 | 6.7 | 84.7 | 110.0 | 69.5 |
| 19.8 | 6 | 7.4 | 83.9 | 111.4 | 69.9 |
| 39.6 | 5 | 6.6 | 84.6 | 101.4 | 73.2 |
| 39.6 | 6 | 5.8 | 84.8 | 99.3 | 72.4 |
| 45 | 5 | 6.0 | 84.3 | 97.2 | 73.4 |
| 45 | 6 | 5.3 | 84.8 | 96.0 | 73.1 |
| 50.4 | 4 | 6.3 | 83.8 | 95.3 | 74.5 |
| 50.4 | 5 | 5.5 | 85.1 | 95.1 | 74.8 |

$\alpha/\beta$ for tumor effects = Gy; $\alpha/\beta$ for late effects = 3 Gy.

Table 4. The equivalent doses given as (2 Gy/fraction) for HDR alone for prostate cancer using DMF of 0.6, 0.7, 0.8

| # of HDR fractions | HDR dose/fx (Gy) | Equiv. dose for tumor effects (Gy) | Equiv. dose (Gy) (late effects no DMF) | Equiv. dose (Gy) (late effects with DMF for HDR = 0.6) | Equiv. dose (Gy) (late effects with DMF for HDR = 0.7) | Equiv. dose (Gy) (late effects with DMF for HDR = 0.8) |
|---|---|---|---|---|---|---|
| 6 | 7.0 | 59.5 | 84.0 | 36.3 | 46.5 | 57.8 |
| 6 | 8.0 | 72.0 | 105.6 | 44.9 | 57.8 | 72.2 |
| 6 | 9.0 | 85.5 | 129.6 | 54.4 | 70.3 | 88.1 |
| 5 | 8.0 | 60.0 | 88.0 | 37.4 | 48.2 | 60.2 |
| 5 | 9.0 | 71.3 | 108.0 | 45.4 | 58.6 | 73.4 |
| 5 | 10.0 | 83.3 | 130.0 | 54.0 | 70.0 | 88.0 |

$\alpha/\beta$ for tumor effects = 10 Gy; $\alpha/\beta$ for late effects = 3 Gy.

5. Since there is sparse clinical experience with the use of HDR alone in treating prostate cancer, it seems prudent to perform a dose escalation trial starting with 6 fractions of 7 Gy (row 1, Table 4) or 5 fractions of 8 Gy (row 4) to give an equivalent tumor effect of about 60 Gy while keeping the equivalent late effect to the rectum low. The DMF used in column 5 of Table 4 is 0.6, since some authors have reported that the rectal dose in prostate HDR was 60% of the prescribed dose. However, the percentage of rectal dose varies with the technique employed. Hence columns 6 and 7 of the table were created using DMF of 0.7 and 0.8 respectively to show the equivalent late effects if the rectal doses were different. Note that if the rectum were to receive the prescribed dose (i.e., no DMF is applied, as in column 4), all the above regimens could be expected to produce unacceptably high late rectal toxicities.

*Example 3.* The recently completed RTOG phase I/II study of EBRT, brachytherapy, and chemotherapy for localized cancer of the esophagus (RTOG 92-07) revealed a high incidence of esophageal fistulae (4). The EBRT dose was 50 Gy in 25 fractions, and the HDR dose was initially 15 Gy given at 5 Gy per fraction. Table 5a shows that the equivalent dose for late effects (using a DMF of 0.7) was 63.7 Gy, which should not have caused undue toxicity. However, although a value of 0.7 for DMF is reasonable to determine cardiotoxicity (since the dose given to the heart can be about 70% of the prescribed dose), the incidence of esophageal fistula depends on the dose to the esophageal mucosa (not the dose to the heart). The dose to the normal esophageal mucosa is much higher (at least twice) than the prescribed dose. Therefore, in this case, a DMF of about 2 should be applied, as shown in Table 5b. Now the explanation for the esophageal fistula becomes clear, since the equivalent dose for late effects is 128 Gy if a DMF of 2 is applied. Subsequently, because of undue toxicity, the HDR dose was reduced to 10 Gy in 2 fractions (5 Gy per fraction). This reduced the equivalent dose for late effects to 102 Gy (row 2 in Table 5b), which is still high. Our model shows that keeping the number of HDR fractions at 3, but reducing the dose per fraction to 3.3 Gy (instead of keeping the dose per fraction at 5 Gy and reducing the number of fractions to 2) would have produced an equivalent late effects dose of

Table 5a. Dose modifying factor for HDR = 0.7

| EBRT total dose (Gy) @ 1.8 Gy/fx | # of HDR fractions | HDR dose/fx (Gy) | Equiv. dose for tumor effects (Gy) | Equiv. dose (Gy) (late effects no DMF) | Equiv. dose (Gy) (late effects with DMF) |
|---|---|---|---|---|---|
| 50 | 3 | 5.0 | 68.8 | 74.0 | 63.7 |

Table 5b. Dose modifying factor for HDR = 2.0

| EBRT total dose (Gy) @ 1.8 Gy/fx | # of HDR fractions | HDR dose/fx (Gy) | Equiv. dose for tumor effects (Gy) | Equiv. dose (Gy) (late effects no DMF) | Equiv. dose (Gy) (late effects with DMF) |
|---|---|---|---|---|---|
| 50 | 3 | 5.0 | 68.8 | 74.0 | 128.0 |
| 50 | 2 | 5.0 | 62.5 | 66.0 | 102.0 |
| 50 | 3 | 3.3 | 61.1 | 62.6 | 88.6 |

Tables 5a and 5b give the equivalent doses for EBRT and HDR for esophageal cancer using a) DMF of 0.7, b) DMF of 2.0. For both tables the following parameters were used: $\alpha/\beta$ late effect = 3 Gy, $\alpha/\beta$ early effect = 10 Gy, dose per fraction for equivalence calculations = 2 Gy, dose per fraction for EBRT = 2 Gy.

88.6 Gy and therefore a greater reduction of late tissue effects (Table 5b).

## DISCUSSION

Various empirical formulas, such as the nominal standard dose (NSD), cumulative radiation effect (CRE), and time-dose-fractionation (TDF), have been used to determine the equivalent doses of various dose fractionation schemes in the past (5). The LQ formula currently used is considered a better model because it is based on the radiation effect in deoxyribonucleic acid (DNA) and can account for differences between tumor and normal tissue response (1, 2, 6–11). The LQ equation can be used to calculate the BED for HDR. While this is very useful, most radiation oncologists find these calculations difficult. Orton (12) simplified the procedure by creating a table of BED values for HDR brachytherapy. However, the resultant BED values are difficult for clinicians to interpret and correlate with their daily treatment schemes. It is easier for the practicing physicians to think of equivalent doses as if they were given in a standard fraction size of 2 Gy. In this regard, Barton has produced tables to convert common fractionation schemes to an equivalent in 2 Gy/fraction, using the LQ formula (13). While this helps the clinicians, it has limited applicability since the tables were constructed only for $\alpha/\beta$ values of 1, 3, and 10 Gy and for limited doses per fraction. It has to be noted that the $\alpha/\beta$ values for tumor tissues vary from 6 to 13 Gy (average = 10 Gy) and the $\alpha/\beta$ values for late reacting normal tissues vary from 1 to 7 Gy (average = 3 Gy) (1). Therefore, although the default value for $\alpha/\beta$ values for tumor and late reacting tissues in our program are set at 10 Gy and 3 Gy respectively, they can be changed according to the individual circumstance to automatically update all calculations.

Another limitation of the Barton tables was that since they were designed primarily for fractionated EBRT, in which EBRT doses to tumor and normal tissues are essentially the same, there was no need to apply a DMF. However, because normal tissues generally receive a lower dose in HDR brachytherapy, DMF is an important consideration for HDR brachytherapy treatments. Although it is common knowledge that the normal tissues receive a lower dose than tumor tissues in HDR brachytherapy, it is not common clinical practice to apply a normal tissue DMF while calculating the late normal tissue effects. When equivalent dose for late tissue effects is calculated without applying a DMF, an extremely large equivalent dose can be obtained (e.g., 88 Gy for 5 fractions of 8 Gy HDR brachytherapy dose, Table 4, row 4). This may dissuade some clinicians from using HDR brachytherapy, unless they are aware that a DMF should be applied to account for the reduced dose given to normal tissue.

In the preceding example, if the normal tissues were to receive 60%, 70%, or 80% of the dose given to tumor, the equivalent late effects would be 37.4, 48.2, or 60.2 Gy respectively (row 4 in Table 4). This would be within normal tissue tolerance. On the other hand, if there were no dose reduction to normal tissues, the equivalent late effect (88 Gy) would be too toxic to allow this regimen to be used clinically. Clinical judgment must be exercised to decide if the treatment can be safely given, depending on the expected DMF to normal tissues. It should be realized that this DMF is usually only an estimate, unless actually measured.

In some circumstances (like intraluminal brachytherapy), the dose to normal tissues may even be higher than the prescribed dose, such as in Table 5b. In these circumstances, a DMF with a value of $> 1.0$ should be applied. The equivalent doses for late effects to the normal tissues will now be larger. The HDR dose per fraction should therefore be adjusted in these circumstances to keep the equivalent dose to the normal tissues within tolerance limits. This also stresses that one must carefully consider where the critical normal tissues are and what the expected doses to these tissues will be before deciding on the value of DMF to be applied.

Another consideration, especially in intraoperative HDR brachytherapy, is that, in the operating room, doses to be used must be determined quickly, since the patient is under anesthesia. Often the physicist cannot return to the computer room in the radiation oncology department to perform bioequivalence calculations; therefore, such calculations are rarely performed. This spreadsheet program can be used in the operating room (using a portable laptop/notebook personal computer) to perform bioequivalence calculations quickly and therefore it serves as an invaluable aid.

Although the above examples show the value of this bioequivalence program, its limitations must be kept in mind. Like any mathematical model, this program should be judiciously used only as a guide and should always be correlated with clinical judgment and outcome results. Specifically, it should be used with caution if large fraction sizes and/or small numbers of fractions are used, since their clinical results are not well known. It should be noted that tumor cells proliferate between treatment fractions. This factor is small if the treatments are performed over a relatively short duration. Therefore, to keep the calculations simple, we have opted not to account for tumor proliferation. However, if the treatments are rather protracted (e.g., if there is a long time interval between EBRT and HDR), the tumor proliferation can be considerable, and the equivalent tumor doses given in this program would overestimate the actual effect. It should also be recognized that the $\alpha/\beta$ value of a particular patient's tumor or normal tissue is never known accurately. The default values of 10 Gy and 3 Gy are estimates only. For example, some prostate tumors that may proliferate very slowly may have an $\alpha/\beta$ value of 1.5 Gy rather than the default value of 10 Gy (14). The equivalent doses obtained will depend on the $\alpha/\beta$ value used for that particular calculation.

## SUMMARY

A simple Excel spreadsheet program has been developed to assist clinicians to easily calculate equivalent doses to be used in HDR brachytherapy regimens. The novelty of this program is that the equivalent doses are expressed as if given at 2 Gy per fraction rather than as BED values, and a more realistic equivalent normal tissue effect is obtained by applying a DMF. Its ease of use should promote the use of LQ radiobiological modeling to determine HDR brachytherapy doses. The program is to be used judiciously as a guide only and should be correlated with clinical outcome.

## REFERENCES

1. Hall EJ. Time, dose, and fractionation in radiotherapy. In: Hall EJ, editor. Radiobiology for the radiobiologist. 4th ed. Philadelphia: J.B. Lippincott; 1994. 211–229.
2. Dale RG. The application of the linear quadratic dose-effect equation to fractionated and protracted radiotherapy. *Br J Radiol* 1985;58:515–528.
3. Nag S, Young D, Orton C, Erickson B. Survey of the Brachytherapy Practice for Carcinoma of the Cervix: A Report of the Clinical Research Committee of the American Brachytherapy Society. *Gynecol Oncol* 1999;73:111–118.
4. Gaspar LE, Qian C, Kocha WI, Coia LR, Herskovic A, Graham M. A phase I/II study of external beam radiation, brachytherapy and concurrent chemotherapy in localized cancer of the esophagus (RTOG 92-07): Preliminary toxicity report. *Int J Radiat Oncol Biol Phys* 1997;37:593–599.
5. Ellis F. Is NSD-TDF useful to radiotherapy? *Int J Radiat Oncol Biol Phys* 1985;11:1685–1697.
6. Barendsen GW. Dose fractionation, dose-rate and iso-effect relationships for normal tissue responses. *Int J Radiat Oncol Biol Phys* 1982;8:1981–1997.
7. Fowler JF. The linear-quadratic formula and progress in fractionation. *Br J Radiol* 1985;58:515–528.
8. Thames HD. An "incomplete-repair" model for survival after fractionated and continuous irradiation. *Int J Radiat Biol* 1985;47:319–339.
9. Brenner DJ, Hall EJ. The origins and basis of the linear-quadratic model. *Int J Radiat Oncol Biol Phys* 1992;23:252.
10. Brenner DJ, Hlatky LR, Hahnfedlt PJ, Huang Y, Sachs RK. The linear-quadratic model and most other common radiobiological models result in similar predictions of time–dose relationships. *Radiat Res* 1998;150:83–91.
11. Dale RJ, Jones B. The clinical radiobiology of brachytherapy. *Br J Radiol* 1998;71:465–483.
12. Orton C. Radiobiology. In: Nag S, editor. Principles and practice of brachytherapy. Armonk, NY: Futura; 1997. 27–45.
13. Barton M. Tables of equivalent dose in 2 Gy fractions: A simple application of the linear quadratic formula. *Int J Radiat Oncol Biol Phys* 1995;31:371–78.
14. Brenner DJ, Hall EJ. Fractionation and protraction for radiotherapy of prostate carcinoma. *Int J Radiat Oncol Biol Phys* 1999;43:1095–1101.

## APPENDIX 1: BIO-EQUIVALENCE CALCULATIONS FOR MULTIPLE MODALITY RADIATION TREATMENTS

The dose effect relationship in radiation therapy is not a linear relationship, but follows a LQ function. Hence, doses delivered by different modalities cannot be added to each other to predict the effect of the combined modality treatment. One way to calculate the BEDs of different dose fractionation schemes is to use the LQ equation, using the formula

$$\mathrm{BED} = nd\left[1+\frac{\mathrm{d}}{(\alpha/\beta)}\right] \tag{1}$$

where $n$ = the number of fractions and $d$ = the dose per fraction. To express the results in terms more familiar to clinicians, the BED was converted back to equivalent doses ($D_{\mathrm{Eq}}$) as though given as conventionally fractionated irradiation given at 2 Gy/day for tumor and late effects respectively using the formula

$$\mathrm{D_{Eq}} = \frac{\mathrm{BED}}{\left(1+\frac{\mathrm{d_{REF}}}{(\alpha/\beta)}\right)} \tag{2}$$

where $d_{\mathrm{REF}}$ = the reference dose per fraction for a conventionally fractionated external beam treatment to be used for calculating the equivalent dose (which for the purposes of this paper has been assumed to be 2 Gy/fraction).

If the equivalent dose for late effects is calculated using eq. 2 above, the implicit assumption in this calculation is that doses delivered to the normal tissues were equal to doses delivered to the tumor (which is true for external beam radiotherapy). However, under certain circumstances (e.g., with HDR brachytherapy), this assumption may not be true, because the dose given to normal tissues is reduced due to the fall-off in dose with distance. For example, if the dose to normal tissue is estimated to be 70% of the prescribed dose to the tumor in HDR brachytherapy, a dose reduction factor (DMF) of 0.7 would need to be applied to obtain the modified, more realistic late normal tissue effects using the formulas

$$\mathrm{BED_{HDR}} = n{*}d{*}\mathrm{DMF}{*}\left(1+\left(\frac{d{*}\mathrm{DMF}}{\alpha/\beta}\right)\right) \tag{3}$$

$$\mathrm{D_{Eq}} = \frac{\mathrm{BED_{HDR}}}{\left(1+\frac{d_{REF}}{\alpha/\beta}\right)} = \frac{n{*}d{*}\mathrm{DMF}{*}\left(+1\left(\frac{d{*}\mathrm{DMF}}{\alpha/\beta}\right)\right)}{\left(1+\frac{d_{\mathrm{REF}}}{\alpha/\beta}\right)} \tag{4}$$

The numerator in eq. 3 is the BED for the HDR treatment incorporating the DMF for HDR.

For multiple treatment modalities with different fractionation schemes the total BED can be calculated by extending eqs. 1 and 3 in the following manner:

$$\mathrm{BED}_{\mathrm{combined}}=\mathrm{BED}_{\mathrm{modality1}}+\mathrm{BED}_{\mathrm{modality2}}+\mathrm{BED}_{\mathrm{modality3}}+\ldots \quad (5)$$

For the specific example of a combined EBRT and HDR brachytherapy treatment, the BED will be given by:

$$\mathrm{BED}_{\mathrm{Ext+HDR}}=\left(n_{\mathrm{Ext}}{*}d_{\mathrm{Ext}}{*}\left[1+\left(\frac{d_{\mathrm{Ext}}}{(\alpha/\beta)}\right)\right]\right)+\left(n_{\mathrm{HDR}}{*}d_{\mathrm{HDR}}{*}\mathrm{DMF}_{\mathrm{HDR}}{*}\left[1+\left(\frac{d_{\mathrm{HDR}}{*}\mathrm{DMF}_{\mathrm{HDR}}}{(\alpha/\beta)}\right)\right]\right) \quad (6)$$

For the combined multimodality treatments, eq. 4 can be expanded to the generic form shown below to recalculate the equivalent dose for the combined treatment for the $d_{\mathrm{REF}}$ (2 Gy/fraction for our examples):

$$\mathrm{D}_{\mathrm{Eq}}=\frac{\mathrm{BED}_{\mathrm{Combined}}}{\left(1+\frac{d_{\mathrm{REF}}}{\alpha/\beta}\right)}=\frac{\mathrm{BED}_{\mathrm{modality1}}+\mathrm{BED}_{\mathrm{modality2}}+\mathrm{BED}_{\mathrm{modality3}}}{\left(1+\frac{d_{\mathrm{REF}}}{\alpha/\beta}\right)} \quad (7)$$

For the specific example of a combined EBRT and HDR brachytherapy treatment, the equivalent dose for the combined treatment is given by:

$$D_{\mathrm{Eq}}=\frac{\left(n_{\mathrm{Ext}}{*}d_{\mathrm{Ext}}{*}\left[1+\left(\frac{d_{\mathrm{Ext}}}{(\alpha/\beta)}\right)\right]\right)+\left(n_{\mathrm{HDR}}{*}d_{\mathrm{HDR}}{*}\mathrm{DMF}_{\mathrm{HDR}}{*}\left[1+\left(\frac{d_{\mathrm{HDR}}{*}\mathrm{DMF}_{\mathrm{HDR}}}{(\alpha/\beta)}\right)\right]\right)}{\left(1+\frac{\mathrm{d}_{\mathrm{REF}}}{\alpha/\beta}\right)} \quad (8)$$

For the external beam treatment the DMF does not show up since DMF = 1 for EBRT, as explained above.