www.prostate-cancer-radiotherapy.org.uk

NOTES AND INSTRUCTIONS FOR USING THE DISEASE FREE SURVIVAL PROBABILITY CALCULATOR FOR EBRT, BRACHYTHERAPY AND THE TWO COMBINED.

The derivation of the expression for the probability of disease free survival is contained in the paper on LQ modelling as REVIEW 2 (web page 14). It is a semi-empirical expression but it has some advantages over the type of nomogram developed by the Memorial Sloan-Kettering Cancer Center in that it has a physical model at its foundation in terms of the LQ model for survival fraction and the Munro and Gilbert expression relating survival fraction to disease free survival probability.

The formula derived in review 2 for the calculation of disease free survival probability *P(t)* is

$$P(t) = e^{-\lambda P_{SA}\left(1-e^{-\frac{t}{T_c}}\right)S_f} \qquad (1)$$

where P_{SA} is the PSA in ng/ml., T_c is the time constant for the approach to the long-term disease free probability (taken to be 3 years in everything that follows), S_f is the fraction of cells surviving after the radiation treatment and λ is a constant determined from reference conditions.
For external beam radiotherapy,

$$S_f = e^{-(\alpha+\beta d)D} \qquad (2)$$

where D is the total radiation dose (Gy) and d is the acute dose fraction (Gy).
For brachytherapy

$$S_f = e^{-\alpha D_\infty - \beta\frac{\tau}{T_d}D_\infty^2} \qquad (3)$$

where D_∞ is the total radiation dose delivered by the seeds (Gy), T_d is the time constant for the decay of the seed radiation and is 1.4427 times the seed half-life.
α and β are two constants associated with the cell response to radiation and τ is a cell repair time constant.
For brachytherapy combined with external beam radiotherapy, the cell survival fraction is the product of the two survival fractions expressions equations (2) and (3).

USE OF THE CALCULATOR.

There are two versions of the Excel calculator that can be used. One uses macros, which will need to be enabled to use the spreadsheet. If you don't want to enable macros, you can download a straightforward spreadsheet version but it is easier to make mistakes with this version. Both versions are not completely crash proof in the sense that if extreme values for any of the parameters are entered, it can 'crash' the calculations or, at least, give absurd results. This will be changed in later versions.

There are two tables on the spreadsheet. Table 1 is used to evaluate the constant, λ, by ensuring that equation (1) fits a reference external beam radiotherapy clinical datum for the disease free survival. This spreadsheet is set up by default with the Brenner and Hall constants and a disease free survival probability of 63% at five years for a PSA of 15 ng/ml and 70Gy of external beam radiotherapy given in 2Gy fractions without hormones. However, if more convincing data becomes available for the cell constants or the survival probability, the data values can be changed to accommodate these new values. With these default values, the value of λ is calculated to be 22. The default values can be reset at any time by clicking on the green *Default data* button.

Table 2 is the main table and calculates the long-term disease free survival probability (DFSP) for a particular PSA and for specific radiation conditions.

The PSA value is first entered into column 1.

If the radiation treatment is external beam radiotherapy, enter the total dose into column 2 and the daily fraction in column 3. Enter a zero into the seed dose column 5 and enter a 1 into the half-life column 6.

If it is brachytherapy only, it is not necessary to enter anything in the EBRT dose column 2 but the column must be clear or contain a zero. The total dose delivered by the seeds is entered into column 5 and the seed half-life in days is entered into column 6. For Iodine 125, the half-life is 60 days and for Palladium 103 it is 16 days.

For radiotherapy consisting of both EBRT and brachytherapy, enter the appropriate details for both treatment arms.

The cell survival fraction columns 4 and 7 show the calculated cell survival fractions for the EBRT component (equation (2)) and the brachytherapy component (equation (3)) respectively.

Finally, column (8) contains the long-term disease free probability calculated from equation (1). In practical terms, this is the disease free survival probability at around to 10 to 15 years. The calculator is set up so that 10 different radiation protocols can be entered into the table. As a check that the calculator has not been corrupted, the reference clinical datum is set up in row 1 with the default values in table 1. It should show a long-term disease free survival probability of 56.8%. The table 2 can be cleared at any time by clicking on the green *Clear Table 2* button.

Finally, it is important to emphasise that this semi-empirical expression is only a guide and the absolute figures should be treated with caution. It also only really applies to low and intermediate risk patients where the probability of seminal vesicle or lymph node involvement is small so that its use should be restricted to PSA levels below about 15 ng/ml. There is no explicit input for the Gleason score or the T-staging as discussed in the review paper 2 but the implied Gleason score is 3+4 or less and t-staging of no more than T2b, say. Although the absolute accuracy is to be treated with caution, it probably gives quite a good indication of the relative effectiveness of different radiation protocols. It also does not include the effect of adjuvant hormone therapies. Generally, hormone therapies should improve the disease free survival but their effect may become less with more aggressive radiation therapies.

One of the interesting exercises is to look at the effects of hypofraction on disease free survival estimates. Compare EBRT only with 70Gy in 2GY fractions with 63Gy in 3Gy fractions!

Les Bradbury
2nd August 2005