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TECHNICAL NOTE

A free program for calculating EUD-based NTCP and TCP in external beam radiotherapy

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Radiotherapy;
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Abstract *Purpose:* Provide a simple research tool that may be used to calculate the NCTP or TCP of a particular treatment plan. Illustrate the implementation of the EUD-based NTCP and TCP models as a research tool.
Methods and materials: A high-level computing language was chosen to implement Niemierko's EUD-based NTCP and TCP mathematical models. The necessary treatment planning software requirements were clearly defined.
Results: The computer code is presented and explained. Six simple examples were created to quickly troubleshoot the reader's code implementation. A table of model parameters based on the Emami data was generated.

Introduction

Over the past decades, there have been many attempts to develop normal tissue complication probability (NTCP) and tumor control probability (TCP) mathematical models [1—16]. The complexity and computer skills required by

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some of these models often alienates clinicians from this area of research. Various NTCP mathematical models based on retrospective data that correlate with clinical outcome exist for specific organs at risk like the rectum [17] and lung [18]. Many of these models have been used primarily as research tools. Unfortunately, the clinical validation and clinical use of most of these mathematical models has been disappointing.

Over the past decade, various software packages implementing other NTCP and TCP models have been created such as BIOPLAN written in Visual Basic [4], a series of Matlab modules by Warkentin et al. [1], and more recently the dose–response explorer system (DREES) also based on Matlab and freely distributed via the web (http://radium.wustl.edu/drees) [19].

Our goal is to provide a simple research tool that may be used to calculate the NCTP or TCP of a particular treatment plan, and ignite further interest in this research area.

Methods and materials

Introduction to the EUD-based NTCP and TCP mathematical models

The EUD-based mathematical model [7,8] is simple because it is based mainly on 2 equations, and versatile because the same model may be used for both TCP and NTCP calculations. The model has an excellent ability in fitting, for example, the Emami et al. normal tissue tolerance values [20] (See Fig. 1). The original definition of the EUD was derived on the basis of a mechanistic formulation using a linear–quadratic cell survival model [21]. Subsequently, Niemierko has suggested a phenomenological model of the form:

$$EUD = \left(\sum_{i=1} \left(v_i D_i^a \right) \right)^{\frac{1}{a}} \tag{1}$$

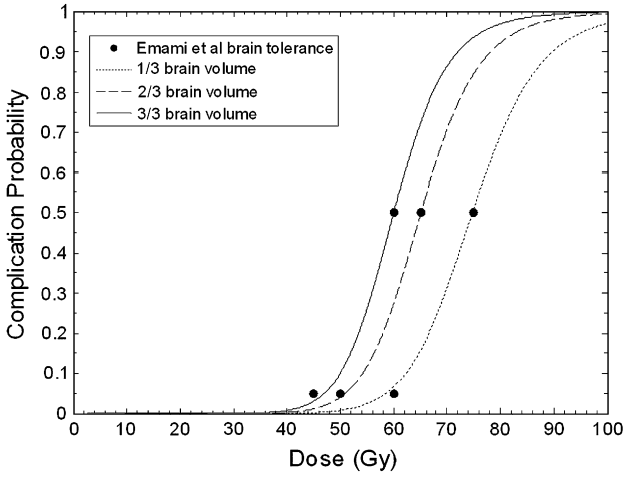

Figure 1 Complication probability vs. dose for the brain. The EUD-based NTCP mathematical model was used to create 3 different brain volume curves to fit the Emami et al. data using the following model parameters: $TD_{50} = 60$ Gy, $a = 5$, and $\gamma_{50} = 3$.

that can be used for both tumors and normal tissues, where a is a unitless model parameter that is specific to the normal structure or tumor of interest, and v_i is unitless and represents the i'th partial volume receiving dose D_i in Gy. Since the relative volume of the whole structure of interest corresponds to 1, the sum of all partial volumes v_i will equal 1. For normal tissues, the *EUD* represents the uniform dose which leads to the same probability of injury as the examined inhomogeneous dose distribution. To illustrate the EUD definition, imagine that you have just calculated the brain's *EUD* for a particular radiotherapy plan. By looking at the whole brain volume curve, the solid line in Fig. 1, you could determine the corresponding *NTCP*. On the other hand, for tumors the *EUD* represents the uniform dose which leads to the same probability of local control as the actual nonuniform dose distribution. The D_i and v_i data pairs are obtained from the differential, not cumulative, dose–volume histogram from a given radiotherapy plan.

The choice of parameter a will determine the behavior of the EUD-based model. For example, as a increases to a large positive number, the *EUD* approaches the maximal dose; as a decreases to a large negative number, the *EUD* approaches the minimal dose; if a equals 1, the *EUD* becomes the dose average; and if a equals 0, the *EUD* equals the geometric mean [21].

The local control of a tumor will likely depend on the volume that received the minimum dose, since this is where the tumor clonogen survival should be highest. Consequently, the *EUD* for tumors will be close to the minimal dose, and the parameter a should be a large negative number.

In normal tissues with a serial or ''links in a chain'' architecture like the spinal cord, breaking one of the links will likely rupture the functional tissue chain. It is the volume or link that receives the maximum dose which will most likely be responsible for breaking the chain. Therefore, the *EUD* for tissues with a serial architecture will be close to the maximal dose, and parameter a will usually be a large positive number.

For normal tissues that exhibit a large volume effect (e.g., liver, parotids, and lungs), the dose–response may be closer to the average dose [21–24]. Consequently, the *EUD* for these tissues will be close to the average dose, and parameter a should be a small and positive number. In summary, the EUD model can mimic the dose–response behavior of the volume of interest through parameter a.

To calculate the EUD-based normal tissue complication probability (*NTCP*), Niemierko proposed parametrization of the dose–response characteristics using the logistic function [8]:

$$NTCP = \frac{1}{1 + \left(\frac{TD_{50}}{EUD} \right)^{4\gamma_{50}}} \tag{2}$$

The TD_{50} is the tolerance dose for a 50% complication rate at a specific time interval (e.g., 5 years in the Emami et al. normal tissue tolerance data [20]) when the whole organ of interest is homogeneously irradiated, and the γ_{50} is a unitless model parameter that is specific to the normal structure or tumor of interest and describes the slope of the

dose–response curve. Parameters a and γ_{50} should be obtained by fitting clinical dose–response data to the EUD-based NTCP or EUD-based TCP model.

Similarly, to calculate the tumor control probability (*TCP*), the *EUD* is substituted in the following equation:

$$TCP = \frac{1}{1 + \left(\frac{TCD_{50}}{EUD}\right)^{4\gamma_{50}}} \quad (3)$$

The TCD_{50} is the tumor dose to control 50% of the tumors when the tumor is homogeneously irradiated. A γ_{50} value of 4 for late effects in Eq. (2), and a value of 2 for tumors in Eq. (3) are reasonable initial estimates in Dr. Niemierko's experience. The values should then be adjusted further to achieve a better fit with the available clinical data.

Treatment planning software requirements for proper implementation of the model

The correct implementation of this model necessitates that the planning software has 3 main features. First, the planning software should be able to convert the dose in each voxel, or volume element, to a biologic equivalent dose (*BED*) so that hot spots and cold spots are more accurately accounted for radiobiologically. The biologic equivalent dose (*BED*) may be calculated using the linear–quadratic formula or any of its variants. For example, if the model's a, γ_{50}, TCD_{50} and/or TD_{50} parameters are based on the Emami data, calculating the *BED* in 1.8–2 Gy/fraction for each voxel is necessary because the tolerance data was based on treatments using 1.8–2 Gy/day, 5 days a week [20]. The ultimate choice of 1.8 Gy or 2 Gy becomes purely arbitrary, and should have an insignificant impact in most cases. Ideally, these parameters should be based on prospective clinical data where the dose distribution and follow-up results of each patient are available.

Second, the software should allow different α/β ratios to be assigned to each of the contoured structures for *BED* calculation purposes. Unfortunately, at present there is a great degree of uncertainty when choosing an appropriate alpha–beta ratio for many normal tissues and tumors.

Third, if the patient is treated with different plans (for example, an initial plan and a boost plan) the planning software should be able to individually add the *BED* in each corresponding voxel in the different plans. These 3 software requirements will generate the most representative DVHs of the entire treatment plan.

Choice of normal tissue tolerance values

Although for simplicity we will mainly use the Emami normal tissue tolerance values to illustrate the potential of radiobiological modeling, there are numerous more recent publications addressing the normal tissue tolerance values for specific organs; seminars in Radiation Oncology (volume 11, issue 3, July 2001) has an excellent overview.

Choice of programming language

Of the multiple high-level computer programming languages commercially available, Matlab (www.mathworks.com) was chosen to implement the models. Matlab is a high-level technical computing language and interactive environment. It is a language that is easy to learn, is available for the Microsoft Windows, Macintosh, UNIX, and Linux operating systems, and is also available in many academic institutions. We obtained the Matlab and Simulink Student Version (Version 7.0.0.27) Release 14 for the implementation of the models.

Results

Appendix 1 shows the program's code in Matlab and includes comments explaining the different sections of the code. The program may be downloaded from: http://www.ecu.edu/radiationoncology/downloads.htm or save the code in Appendix 1 as a Matlab function named eudmodel.m. The square brackets, ''['' and '']'', used in this section are used in Matlab to define matrices. To test the code go to the *Command Window* and at the command prompt type *dvh = [ ]* to create the variable *dvh*. The matrix *dvh* which represents the cumulative, not differential, DVH, and its structure is as follows: the first column corresponds to increasing absolute dose or percentage dose values, and the second column to the corresponding absolute or relative volume values. The software internally converts the cumulative DVH to the differential DVH required by the mathematical model. We chose the cumulative DVH as the software's input because commercial planning systems commonly use cumulative DVHs instead of the differential DVH.

The next 6 cumulative DVHs are provided to quickly verify the correctness of their EUD-based program implementation in Matlab or any other program:

- Example 1: dvh = [0 100; 200 0]
- Example 2: dvh = [0 100; 12000 0]
- Example 3: dvh = [0 100; 80 0]
- Example 4: dvh = [0 100; 150 0]
- Example 5: dvh = [0 100; 14000 0]
- Example 6: dvh = [0 100; 90 0]

To test example 1 type in the *Command Window*:

dvh = [0 100; 200 0]

followed by:

eudmodel(dvh)

and enter the corresponding parameters in Table 1. Running the 6 examples should test the software's different features and help identify coding errors. Table 2 lists some sample parameters based on the Emami data for experimenting with the program.

Discussion

One potential limitation of the EUD-based models is that an infinite number of different spatial dose distributions may

Table 1 Results of the Matlab EUD-based program test examples

Example	Dose format	Dose unit	Volume type	100% dose	# f	a	γ_{50}	TD_{50} (Gy)	dpf (Gy)	α/β (Gy)	[a]EUD (Gy)	[a]$NTCP$
1	Percentage	—	Normal	2	30	6	3	65	2	5	60	27.68%
2	Absolute	cGy	Normal	—	30	4	4	60	2	3	60	50.00%
3	Absolute	Gy	Normal	—	20	25	3	65	3	4	34.29	0.046%
								TCD_{50}				[a]TCP
4	Percentage	—	Tumor	5	20	−10	2	70	2	10	85.94	83.77%
5	Absolute	cGy	Tumor	—	40	−8	2	80	2	7	68.06	21.52%
6	Absolute	Gy	Tumor	—	30	−12	2	60	3	8	38.86	3.01%

Abbreviations: # f = number of fractions; α/β=alpha—beta ratio; and dpf = parameters' source data's dose per fraction.
[a] Even though 2 or less significant figures should be used due to the EUD-based model's uncertainty, these results have up to 4 significant figures only for the purpose of verifying the calculations.

result in the same DVH and consequently in the same DVH-based NTCP or TCP estimates. Nevertheless, at present there is no solid clinical evidence that these different spatial distributions with identical DVHs correspond to different clinical outcomes.

Optimization of intensity-modulated radiotherapy plans can be based on the EUD-based models, and has been described in detail by Wu et al. [25]. Eqs. (2) and (3) in this paper can be used as the IMRT optimization objective functions for the organs at risk and tumors, respectively. Optimized IMRT plans using EUD-based models tend to have a greater degree of dose inhomogeneity within the tumor target requiring additional dose constraints to minimize this effect [25]. Of note, Wu et al. did not obtain the corresponding BED in 1.8 or 2 Gy fractions for each dose from the differential DVH prior to calculating the result of the objective function. This may be acceptable for treatment plans with a small degree of dose inhomogeneity using standard doses per fraction. However, if treatment plans do not meet these criteria, as in the case of hypofractionated lung radiosurgery using large doses per fraction the dose bins should be modified using the linear—quadratic model to calculate the BED in standard fractions prior to calculating the objective function. Otherwise, the complication or tumor control results could be grossly underestimated.

A simpler and attractive use of a modified version of this software is the dose per fraction optimization of a given treatment plan. This mandates the use of the linear—quadratic model and prospectively obtained α/β ratios for both tumors and normal tissue. Once the minimum TCP and maximum NTCP are defined, the program could generate a table of the number of fractions (for example, 1—40), the dose per fraction that optimally satisfies the criteria, and the corresponding NTCP and TCP. The physician could then select, for example, the treatment that most closely satisfies the NTCP and TCP criteria in the fewest fractions. This could be of great benefit in countries with limited external beam radiotherapy facilities. The site best suited for testing this concept would be breast, since alpha/beta ratios based on prospective data are available for both tumor control [26] and various normal tissue late adverse effects [27].

One area where validated NTCP and TCP models could be extremely useful is lung hypofractionated lung radiosurgery. The large doses per fraction employed challenge our current normal tissue complication and tumor control knowledge based on standard fractions. Clinicians can no longer rely on their acquired clinical intuition based on standard fractions. Validated models could assist the clinician in choosing safer and more effective treatment plans.

Table 2 Normal tissue parameters based on the Emami et al. normal tissue tolerance when radiation is given in 1.8—2 Gy fractions

Structure	Endpoint	a	γ_{50}	TD_{50} (Gy)
Brain	Necrosis	5	3	60
Brainstem	Necrosis	7	3	65
Optic chiasm	Blindness	25	3	65
Colon	Obstruction/perforation	6	4	55
Ear (mid/ext)	Acute serous otitis	31	3	40
Ear (mid/ext)	Chronic serous otitis	31	4	65
Esophagus	Perforation	19	4	68
Heart	Pericarditis	3	3	50
Kidney	Nephritis	1	3	28
Lens	Cataract	3	1	18
Liver	Liver failure	3	3	40
Lung	Pneumonitis	1	2	24.5
Optic nerve	Blindness	25	3	65
Retina	Blindness	15	2	65

Appendix 1
Matlab program code

The sample EUD model parameters included in the program code are based on Refs. 20, 24, 28—33.

```
%Save this file in Matlab as eudmodel.m
%EUDMODEL(DVH), where DVH is a 2 column matrix corresponding to the cumulative, not
%differential, dose volume histogram. The 1st column corresponds to increasing absolute dose or
%percentage dose values, and the 2nd column to the corresponding absolute or relative volume value.
%The matrix must have a minimum of two rows, and both columns must be of equal length.
function probability = eudmodel(dvh)
%user input section
clc; disp('Welcome to the Equivalent Uniform Dose (EUD)-Based Model Program'); disp(' ');
disp('Please note that: 1) the variable dvh should be a CUMULATIVE, not differential, DVH');
disp('                  2) the program assumes that all treatment fractions are equal');
disp(' '); disp(' ');
%end of user input section


%verifying that the cumulative DVH has at least 2 rows and columns
 [nb,N]=size(dvh);
if (nb < 2)
   disp('Error: Cumulative dvh must have at least 2 rows.'); return;
end
if (N < 2)
   disp('Error: Cumulative dvh must have at least 2 columns.'); return;
end
%verifying that the cumulative DVH has no negative numbers in the dose or volume columns
for i=1:nb
   if (dvh(i,1) < 0)
      message = sprintf('Error: Dose data error. dvh column 1, row %g is negative',i);
      disp(message); return;
end
if (dvh(i,2) < 0)
   message = sprintf('Error: Volume data error. dvh column 2, row %g is negative',i);
   disp(message); return;
end
end
% Converting cumulative DVH to differential DVH, and checking for DVH errors
for i=2:nb
```

```
    dvh(i-1,1)=dvh(i-1,1)+(dvh(i,1)-dvh(i-1,1))/2;
    if (dvh(i,1)-dvh(i-1,1) <= 0)
       message = sprintf('Error: Dose data error. dvh column 1, row %g <= dvh column 1, row %g',i,i-1);
       disp(message); return;
    end
    dvh(i-1,2)=(dvh(i-1,2)-dvh(i,2));
    if (dvh(i-1,2) < 0)
       message = sprintf('Error: Volume bin < 0. Verify dvh column 2, rows %g and %g',i-1,i);
       disp(message); return;
    end
  end
  dvh(nb,:)=[];
  [nb,N]=size(dvh);
  nf=input('Enter the number of treatment fractions: '); disp(' '); disp(' ');
  disp('Is the DVH dose data in: ');
  disp('    1. percentage dose format');
  disp('    2. absolute dose format');
  dose_type=input('Enter 1 or 2: '); disp(' '); disp(' ');
  %if DVH dose data is in percentage dose format
  if (dose_type==1)
    normalized_fraction=input('Enter the dose in Gy (not cGy) corresponding to the 100% dose for ONE fraction: ');
    disp(' '); disp(' ');
   %converting percentage dose bins into absolute dose bins
    for i=1:nb
      dvh(i,1)=dvh(i,1)*nf*normalized_fraction/100;
  end
  message = sprintf('The maximum dose was %g Gy. Is this number reasonable?',dvh(nb,1));
  disp(message);
  disp('    1. yes');
  disp('    2. no');
  answer=input('Enter 1 or 2: '); disp(' '); disp(' ');
%if DVH dose data is in absolute dose format
  if (answer == 2 )
```

```
        disp('Error: if the maximum dose was too high: ');
        disp('        1) the dose data could be in ABSOLUTE, not percentage, dose format.');
        disp('        2) the 100% dose entered was for more than 1 fraction.'); return;
    elseif (answer == 1)
    else
        disp('Error: Invalid choice. Exiting program.'); return;
    end
elseif (dose_type==2)
    disp('Is the DVH absolute dose data in: ');
    disp('     1. Gy');
    disp('     2. cGy');
    answer2 = input('Enter 1 or 2: ');
%if DVH dose data is in cGy it is converted to Gy
    if (answer2 == 2)
        for i=1:nb
            dvh(i,1)=dvh(i,1)/100;
        end
    elseif (answer2 == 1)
    else
        disp('Error: Invalid choice. Exiting program.'); return;
    end
else
    disp('Error: Invalid choice. Exiting program.'); return;
end
%EUD mathematical model parameters input section
        clc; disp('Does the DVH correspond to:');
        disp('     1. tumor target');
        disp('     2. normal tissue')
        tissue_type=input('Enter 1 or 2: '); disp(' ');
        if (tissue_type==1)
            clc
            disp('Structure (Source)              End-point          a*'); disp(' ');
            disp('Breast (Brenner[28])              Local control       -7.2');
            disp('Melanoma (Brenner[28])            Local control       -10');
```

```
    disp('Squamous cc (Brenner[28])              Local control       -13');
    disp('* = Niemierko'); disp(' ');
    a=input('Enter the value of parameter a: ' );
    gamma50=input('Enter the value of parameter gamma50 (recommend 2 if unknown): ' );
    tcd50=input('Enter the TCD50 (Gy): ');
    standard_fractionation=input('Enter the source data"s dose per fraction (Gy): ');
    ab=input('Enter the tumor alpha/beta ratio (Gy): ');
elseif (tissue_type==2)
    clc
    disp('Normal tissue EUD Parameters:'); disp(' ');
    disp('Structure (Source)    End-point                a* / a**  g50**  TD50***  DPF****');
    disp(' ');
    disp('BRAIN (Emami[20])         Necrosis                /  5    3      60      1.8 - 2');
    disp('Brainstem (Emami[20])         Necrosis            /  7    3      65      1.8 - 2');
    disp('Optic chiasm (Emami[20])    Blindness             / 25    3      65      1.8 - 2');
    disp('Colon (Emami[20])       Obstruction/perforation     /  6    4      55      1.8 - 2');
    disp('Ear(mid/ext) (Emami[20]) Acute serous otitis       / 31    3      40      1.8 - 2');
    disp('Ear(mid/ext) (Emami[20]) Chronic serous otitis     / 31    4      65      1.8 - 2');
    disp('Esophagus (Emami[20])    Perforation               / 19    4      68      1.8 - 2');
    disp('Heart (Emami[20])       Pericarditis             /  3    3      50      1.8 - 2');
    disp('Kidney (Emami[20])      Nephritis                /  1    3      28      1.8 - 2');
    disp('Lens (Emami[20])        Cataract                 /  3    1      18      1.8 - 2');
    disp('Liver (Dawson[29])         Liver failure          0.9 /');
    disp('Liver (Emami[20])       Liver failure            /  3    3      40      1.8 - 2');
    disp('Liver (Lawrence[30])       Liver failure          0.6 /');
    disp('Lung (Emami[20])        Pneumonitis              /  1    2    24.5      1.8 - 2');
    disp('Lung (Kwa[31])            Pneumonitis            1.0 /');
    disp('Optic nerve (Emami[20])     Blindness            / 25    3      65      1.8 - 2');
    disp('Parotids (Chao[32])       Salivary function (<25%)    0.5 /');
    disp('Parotids (Eisbruch[24])   Salivary function (<25%)   <0.5 /');
    disp('Retina (Emami[20])         Blindness               / 15    2      65      1.8 - 2');
    disp('Spinal cord (Powers[33])  White matter necrosis        13 /');
    disp('* = Niemierko / ** = Gay  / ***= Emami / **** = dose per fraction'); disp(' ');
    a=input('Enter the value of parameter a: ' );
```

```
    gamma50=input('Enter the value of parameter gamma50 (recommend 4 if unknown): ' );
    td50=input('Enter the TD50 (Gy): ');
    standard_fractionation=input('Enter the source data"s dose per fraction (Gy): ');
    ab=input('Enter the normal tissue alpha/beta ratio (Gy): ');
else
    disp('Error: Invalid choice. Exiting program.'); return;
end
%end of EUD mathematical model parameters input section
total_volume=0;
%calculating the biologically equivalent dose and the total volume
for i=1:nb
    bndvh(i,1)=dvh(i,1)*((ab+dvh(i,1)/nf))/(ab+standard_fractionation);
    total_volume=dvh(i,2)+total_volume;
end
%normalizing volume data to 1 (therefore, total volume corresponds to 1)
for i=1:nb
    dvh(i,2)=dvh(i,2)/total_volume;
    bndvh(i,2)=dvh(i,2);
end
eud=0;
%calculating the EUD
for i=1:nb
    eud=eud+(bndvh(i,2))*(bndvh(i,1))^a;
end
eud=eud^(1/a);
disp(' '); disp(' ');
message = sprintf('The equivalent uniform dose = %g Gy',eud);
disp(message); disp(' ');
%Results section
if (tissue_type==1)
    %calculating tumor contol probability
    tcp=1/(1+((tcd50/eud)^(4*gamma50)));
    tcp=tcp*100;
    message = sprintf('The tumor control probability = %10.10f %%',tcp);
```

```
    disp(message); disp(' ');
elseif (tissue_type==2)
    %calculating normal tissue complication probability
    ntcp=1/(1+((td50/eud)^(4*gamma50)));
    ntcp=ntcp*100;
    message = sprintf('The normal tissue complication probability = %10.10f %%',ntcp);
    disp(message); disp(' ');
end
%end of results section
```

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