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Original Research

Microsoft Excel Based Estimation of Radiobiological Parameters In Radiotherapy: A User Friendly Computational Tool

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ABSTRACT
Introduction: The purpose of the present study was to compute the radiobiological parameters i.e Tumor Control Probability (TCP) and Normal Tissue Complication Probability (NTCP) help in assessing the quality of radiotherapy treatment plans for both External Beam Radiotherapy (EBRT) and Brachytherapy using Microsoft Excel software. **Material and Methods:** An evaluation sheet in Mircosoft Excel was constructed to compute TCP and NTCP from Dose Volume Histograms (DVHs) of treatment plan. The computation module i.e. in house developed Microsoft Excel sheet was employed to estimate probabilities of tumor control and normal tissue complications for 150 patients of breast cancer in EBRT and for 150 patients of cervical cancer in Brachytherapy. **Results:** For all the patients TCP of cervix and breast cancer was calculated with this program. TCPs of breast and cervix were evaluated with this computational tool along with NTCPs of contralatetral breast, bladder and rectum. **Conclusion:** This tool has been found useful for TCP/NTCP calculation with the advantage of being simple and user friendly as compared to the technically complex and complicated for non-computer savvy researchers.

Keywords- Microsoft Excel; TCP; NTCP; Breast; Cervix.

INTRODUCTION

Radiotherapy plan evaluation is one of the vital steps of conformal treatment planning process which can be done using various dosimetric and radiobiological parameters along with slice by slice isodose distribution analysis. Dosimetric evaluation can be done through differential or cumulative DVH where as radiobiological evaluation can be done using TCP and NTCP which makes use of radiobiological models. Various radiobiological models have been developed in the past decades with some complexities in their implementation and are being used as research tools [1]. However, the lack of accurate knowledge of these models restricts them to be used in clinical practice. A number of software tools have been developed in the past for the assessment of radiobiological parameters for radiotherapy plans like BIOPLAN based on Poisson, Zaider Minnerbo, Linear Quadratic (LQ), Critical Volume (CV) and Sigmoidal Dose Response (SDR) models; CERR tool; TCP & NTCP_calc tool based on CV and SDR models ; DREES and EUCLID MATLAB-based calculation programs ; Equivalent Uniform Dose (EUD) Model based MATLAB code ; Histogram Analysis in Radiation Therapy (HART) based on Lyman model for NTCP and the Poisson model for TCP; MATLAB platform “SABER” (Spatial And Biological Evaluation of Radiotherapy) ; BIOSUITE etc.[2-10] . These software tools are being used to calculate TCP/NTCP for EBRT.

Many of TCP calculation tools are based on the LQ model and Niemierko Model while for NTCP calculation usually, Lyman-Kutcher-Burman (LKB) model and Niemierko model are used for most of the organ at risk. But for some structures, the data used in these models are not available in literature like for normal breast. In this study an attempt was made to calculate the NTCP of these unusual structures in EBRT.

As Brachytherapy is a vital part of radiotherapy treatment followed by EBRT but there is no special tool to radiobiologically evaluate Brachytherapy treatment plan on the basis of TCP and NTCP values. Also various commercially available treatment

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planning systems (TPSs) do not offer option for calculating the radiobiological outcomes from a Brachytherapy treatment plan. The novelty of the present study is to compute the radiobiological parameters for both EBRT and Brachytherapy using user friendly Microsoft Excel software which has not been discussed in the literature yet. The calculations of TCP & NTCP are not routinely used because of very complex calculations for the same but proposed tool in the present study will help the researchers and radiotherapy professionals.

MATERIAL AND METHODS

For the purpose of radiobiological evaluation of treatment plans, TCP and NTCP were calculated in the present study using LQ model and Niemeirko model. The computation module i.e. in house developed Microsoft excel sheet was employed to estimate probabilities of tumor control and normal tissue complications for 150 patients of breast cancer in EBRT and for 150 patients of cervical cancer in Brachytherapy.

Tumor Control Probability

External Beam Radiotherapy: TCP for target volume was calculated using Niemierko's Model in EBRT. As per the Niemierko's Model, TCP can be calculated using equation (2) which makes use of various parameters [11]. The description of parameters is as follows:

- **"a"** describes the response of the structure or organ in relation to the irradiated volume **a<0** for tumour (large negative value) where cold spots are unwanted.
- **EUD** is equivalent uniform dose which summarize the heterogeneous dose distribution within an irradiated volume into a single value that represents the "equivalent" uniform dose. It can be calculated using equation (1) where D_i and V_i are the dose and volume of i^{th} voxel of target volume.
- **"TCD_{50}"** is the radiation dose that yields local control of half of the irradiated tumors.
- **"γ_{50}"** describes the slope of sigmoid dose response curve specific to the tumor of interest /normal tissue at 50% control/complication probability.
- Formulae used for EUD, TCP and NTCP calculation are as follows

$$EUD = \left(\sum V_i D_i^{a}\right)^{\frac{1}{a}} \quad (1)$$

$$TCP = \frac{1}{1+\left(\frac{TCD_{50}}{EUD}\right)^{4\gamma}} \quad (2)$$

Steps to roll out the computational tool in MS Excel: Using Niemierko's formalism, TCP was calculated with the help of Microsoft (MS) Excel for each patient. For the computation of TCP in EBRT, following steps was done in Microsoft Excel.

a) Enter cDVH (Dose and Volume separately) of each bin in specified cells viz Dose in A2 and adjacent row cells (A3,A4…) and Volume in B2 and adjacent row cells (B3,B4…)
b) Calculate Diff Di in cell next to Volume (*viz C2*) using formula *=(A2+(A3-A2)/2)*
c) Calculate Vi adjacent to Diff Di *(viz D2)* using formula *=0.01*(B2-B3)*.
d) Summation of Vi*Di^a was calculated *(viz H2)*
e) EUD was calculated *(viz H3)* using *=POWER(H2, -0.14)*
f) Finally, TCP was calculating *(viz G4)* using *=1/(1+POWER((39.3/H3),4*1.7))*

2. Brachytherapy: LQ model was used for the calculation of TCP of uniform dose distribution within the target volume as follows [12] :

$$TCP = \exp\left[-\rho V \exp\left(-\alpha BED_t\right)\right] \quad (3)$$

where ρ, V, α, and BED_t are the clonogenic cell density, target volume, coefficient of lethal damage (radio-sensitivity of lethal damage), and BED_t (Biologically Effective Dose) for the target, respectively.

The dose distribution within the target in Brachytherapy is highly non-uniform, so equation (3) cannot be applied directly to compute TCP. Therefore, the target volume was divided into four different regions as shown in figure 1 and TCP (ICBT) was calculated individually for each region as per equations 4,5,6,7.

$$TCP_1 = \exp[-\rho TV_{Dref}\{(1-CI)/CI\}\exp(-\alpha BEEUD_1)] \quad (4)$$

$$TCP_2 = \exp[-\rho TV_{Dref}.DHI \exp(-\alpha BEEUD_2)] \quad (5)$$

$$TCP_3 = \exp[-\rho TV_{Dref}(DNR-ODI)\exp(-\alpha\ BEEUD_3)] \quad (6)$$

$$TCP_4 = \exp[-\rho TV_{Dref}.ODI \exp(-\alpha BEEUD_4)] \quad (7)$$

Finally, total TCP was calculated using equation (8) as suggested by T. S. Kehwar et al. in 2008, Surega Anbumani et al. 2014 and Kaur G et al.2022 [13,14,15,16] :

$$TCP\ (ICBT) = \exp[-\rho TV_{Dref}\{[(1-CI)/CI]\ \exp(-\alpha BEEUD_1) + DHI\ \exp(-\alpha BEEUD_2) + (DNR-ODI)\exp(-\alpha BEEUD_3) + ODI \exp(-\alpha BEEUD_4)\}] \quad (8)$$

where:

- TV_{Dref} is target volume that received reference dose
- CI is the coverage index
- DHI is the relative dose homogeneity index
- DNR is dose non-uniformity ratio
- ODI is overdose volume index
- BEEUD is Biologically Effective Equivalent Uniform Dose (As a future perspective, the radiobiological indices computed from BEEUD concept may be used as objective function get optimal plan)

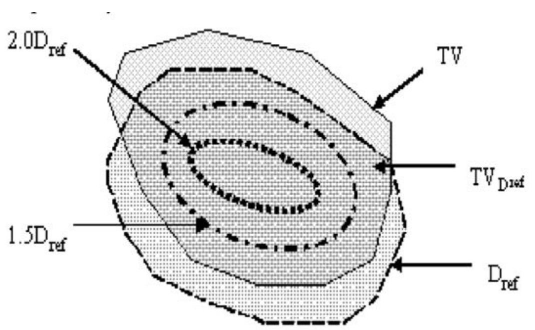

Figure 1: **Drawing Showing Target Volume With Different Regions**

Above said parameters were calculated as per the formula given by Kaur G et al. in 2022[16].The assumption was also made that for EBRT uniform dose has been delivered throughout the target volume for all the patients. V_{95} and D_{95} in EBRT were assumed to be 1945cc and 43.7Gy, respectively. TCP for EBRT was calculated using LQ model equation .Total TCP for EBRT and ICBT was calculated as follow:

Total TCP = *TCP (EBRT) x TCP (ICBT)* (5)

Steps to roll out the computational tool in MS Excel: Formulas for the computation of total TCP is as under

a) Enter cDVH (Dose and Volume separately) of each bin in specified cells *viz* Dose in B2 and adjacent row cells (B3,B4…) and Volume in C2 and adjacent row cells (C3,C4…)
b) The DVH are divided in four groups and entered with different color coding. The Groups ranges from 1-50 (G1), 51-76 (G2), 77-101 (G3), 102-199 (G4) in our reference sheet.
c) Calculate Diff Di in cell next to Volume *(viz D2)* using formula *=(B2+(B3-B2)/2)*
d) Calculate Vi adjacent to Diff Di *(viz E2)* using formula *=0.01*(C3-C4)*
e) Enter TV,TVDref,TV1.5Dref,TV2Dref in next column adjacent cells *(viz F2,G2,H2 and I2)*
f) Calculate BED1,BED2,BED3 and BED4 in next adjacent column cells *(viz J2,K2,L2 and M2)* using following formulas with prescribed dose (9.5Gy per fraction in present study)

BED1 *= 9.5*(1+D2*0.01/10)*
BED2 *=9.5*(1+D51*0.01/10)*
BED3 *=9.5*(1+D51*0.01/10)*
BED4 *=9.5*(1+D77*0.01/10)*

a) Enter RHO(million/cc) in next column adjacent cell *(viz N2)*
b) Calculate Cl in next column adjacent cell *(viz O2)* using formula *=G2/F2*
c) Calculate DHI in next column adjacent cell *(viz P2)* using formula *=(G2-H2)/G2*
d) Calculate DNR in next column adjacent cell *(viz Q2)* using formula *=H2/G2*
e) Calculate ODI in next column adjacent cell *(viz R2)* using formula *=I2/G2*
f) Calculate BEEUD1, BEEUD2, BEEUD3 and BEEUD4 in next columns adjacent cells with reference to different groups as specified in b) above using the following formulas

BEEUD1
*=(1/0.35)*LN((1/F2)*SUM(E2:E50)*EXP(-0.35*AVERAGE(J2:J50)))*
BEEUD2
*=1/0.35)*LN((1/F2)*SUM(E51:E76)*EXP(0.35*AVERAGE(K2:K27)))*
BEEUD3
*=(1/0.35)*LN((1/F2)*SUM(E77:E101)*EXP(0.35*AVERAGE(L2:L26)))*
BEEUD4
*=(1/0.35)*LN((1/F2)*SUM(E102:E199)*EXP(0.35*AVERAGE(M2:M99)))*

g) Calculate TCP1, TCP2, TCP3 and TCP4 and TCP in appropriate cells (O9,P9,Q9,R9 and T9 in reference sheet) and calculate using the following formulas

TCP1*=EXP(-N2*G2*((1-O2)/O2)*(EXP(-0.35*S2)))*
TCP2*=EXP(-N2*G2*P2*(EXP(-0.35*T2)))*
TCP3*=EXP(-N2*G2*(Q2-R2)*EXP(-0.35*U2))*
TCP4*=EXP(-N2*G2*R2*EXP(-0.35*V2))*
TCP (ICBT)*=O9*P9*Q9*R9*

h) Calculate TCP (for 2 fraction in the present study) and EBRT (46Gy/23#) in appropriate cells (R15 and R16 in reference sheet) and calculate using the following formula

TCP_2# *=POWER(T9,2)*
EBRT*=EXP((-100*1945)*EXP(-0.35*55.2))*

i) Calculate Total TCP(EBRT+ICBT) in appropriate cell (R21 in reference sheet) and calculate using the following formula

Total TCP (EBRT+ICBT) *=R16*R15*

Table 1 shows the values of the various parameters used for TCP calculation in the present study. The parameter values used for TCP calculation of ca breast are taken from the study done on radiation response on human tumours by okunieff et al in 1995[17].

TABLE 1: PARAMETER VALUES USED FOR TCP CALCULATION

Site	Radiobiological Models	Parameter values	
Breast	Niemeirko Model	a	-7.2
		γ50	1.7
		TCD_{50}	39.3
Cervix	LQ Model	ρ	10^7 cells/cc
		α	0.35 Gy^{-1}
		α/ß	10 y

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A. Normal Tissue Complication Probability

1. **External Beam Radiotherapy:** NTCP for contralateral breast was calculated in this study using the Niemierko model. The model was proposed by Andzej Niemierko in 1993 and was based on a generalization of Lyman-Kutcher-Burman (LKB) model [18]. This model considers both volume effect and dose response to estimate the complication probability in OARs which requires specific tissues parameters and clinical data for its accurate prediction. Using equation (1) and (7), NTCP was calculated for contralateral breast in this study.
2. **Brachytherapy:** NTCP for bladder and rectum was calculated in this study using the Niemierko model. In case of Brachytherapy, the dose per fraction is not equal to 2Gy per fraction so there was a need to convert doses of each voxel of organ at risk into its EQD_2 (equivalent doses in 2Gy fractions). EBRT doses were also added into this EQD_2 to get the total EQD_2. Then this EQD_2 was used to calculate EUD. DVH raw data of OAR was converted into the whole volume of organ (Vi). Using equation (6), the DVH reduction method as proposed by Kutcher et. al. in 1991, EUD was calculated [19].

$$EUD = [\sum_{i=1}^{N}(Vi).(EQD2i)^{a}] \quad (6)$$

where $EQD_{2i} = EQD_2\ (EBRT) + EQD_2\ (ICBT)$

'a' is a parameter describing the response of organ in relation to the irradiated volume; a>0 for normal tissues (large and small +ve value for small & large volume effect) where hotspots are undesirable. Using equation (6) and (7) NTCP was calculated for rectum & bladder in this study.

NTCP is determined using a following formula for both EBRT and Brachytherapy:

$$NTCP = \frac{1}{1+[TD50/EUD]^{4\gamma 50}} \quad (7)$$

where γ50 is the slope of sigmoid dose response curve of normal tissue at 50% complication probability and TD_{50} is the dose required to produce a toxic effect in 50% of the population. Parameter values used for NTCP calculation of OARs according to Niemierko Model are shown in Table 2.

Table 2: Parameter Values Used For Ntcp Calculations

OAR	a	γ50	TD_{50} (Gy)	End Point
Bladder	2	4	80	Bladder contracture / volume loss
Rectum	8.33	4	80	Severe proctitis/necrosis/stenosis/fistula
Contralateral Breast	0.78	1.47	62.4	Breast Fibrosis

Steps to roll out the computational tool in MS Excel: For the computation of NTCP, Using Niemierko's formalism, NTCP was calculated with the help of Microsoft (MS) Excel for each patient.

a. Enter cDVH (Dose and Volume separately) of each bin in specified cells *viz* Dose in B2 and adjacent row cells (B3,B4…) and Volume in C2 and adjacent row cells (C3,C4…)
b. Calculate Diff Di in cell next to Volume *(viz D2)* using formula *=(B2+(B3-B2)/2)*
c. Calculate Vi adjacent to Diff Di *(viz E2)* using formula *=0.01*(C3-C4)*
d. Calculate BED *(viz F)* cell with prescribed dose (9.5Gy per fraction in present study) using formula *=9.5*((1+(D2*0.01)/3))*
e. Calculate EQD_2 *(viz G)* cell using formula *=(F3/1.2)*2*
f. Total EQD_2 was calculated *(viz H)* which was further used to calculate EUD.
g. Summation of Vi*EQD2i^a was calculated *(viz K1)*
h. Summation of Vi*Di^a was calculated in case of EBRT
i. EUD was calculated *(viz K2)* using *=POWER(K1,1/2)*

Finally, NTCP was calculating *(viz K3)* using *=1/(1+POWER((80/K2),4*4))*

(steps d,e,f & g were used in case of Brachytherapy only) *

RESULTS

The computation module i.e. in house developed Microsoft excel sheet was employed to estimate probabilities of tumor control and normal tissue complications in 150 patients of cervix cancer and 150 of breast cancer. For all the patients TCP of cervix and breast cancer was calculated with this program. Median TCP from EBRT plans of 150 breast cancer patients and ICBT plans of cervix cancer patients was found to be 0.88 and 0.98 respectively. NTCP for contralateral breast in EBRT; bladder and rectum in Brachytherapy was found to be 1.029E-0.08; 0.01 and 0.25, respectively. The values of TCP and NTCP are shown in table 3.

Table 3: Median Values Of Tcp And Ntcp For Ebrt And Icbt

Treatment Modality	TCP		NTCP		
	Breast	Cervix	Contralateral breast	Bladder	Rectum
EBRT	0.88	-	1.029E-0.08	-	-
ICBT	-	0.98	-	0.01	0.25

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DISCUSSION

Many of the commercially used treatment planning system have in-built function to calculate radiobiological parameters based upon literature data. Some TPSs have limitation of availability of such biological evaluation tool due to inadequate clinical data related to the parameters required for calculating TCP/NTCP. So, in this perspective, various independent tools have been developed by the researchers using various computer based programs (C++, Matlab etc.) for radiobiological evaluations of treatment plans in EBRT and Brachytherapy. For example, BIOPLAN was developed in 2000 by Sanchez-Nieto and Nahum which calculates dose response based on Poisson, Zaider Minnerbo, Linear Quadratic (LQ), critical volume (CV) and sigmoidal dose response (SDR) models[2]. A computational environment for radiotherapy research was developed by Deasy et al. in 2003 [3]. Warkentin et al. in 2004 have developed a TCP, NTCP_ calc tool based on CV and SDR models [4]. MATLAB-based calculation programs namely DREES and EUCLID which model the clinical outcomes using multivariate analysis structure were developed in 2006 and 2007[5,6]. A MATLAB code was developed in 2007, calculates the TCP and NTCP with a unified formula based on Equivalent Uniform Dose (EUD) Model [7]. Lyman model for NTCP and the Poisson model for TCP models were used in the Histogram Analysis in Radiation Therapy (HART) analysis in 2010 [8]. Dose convolution factor and P+ were calculated in MATLAB platform with SABER (Spatial And Biological Evaluation of Radiotherapy) program which uses the spatial DVH concept [9]. BIOSUITE was developed by Uzan J and Nahum A E in 2012 that includes several tumor and normal tissue dose response models. It takes DVHs as input and computes the best combination of number of fractions and fraction size to achieve the highest TCP without exceeding NTCP constraints set by the operator [10]. The software tools listed so far are used to calculate TCP/NTCP for EBRT. Many of TCP calculation tools are based on the LQ model and Niemierko Model while for NTCP calculation usually, Lyman-Kutcher-Burman (LKB) model and Niemierko model are used for most of the organ at risk. But for some structures the data used in these models are not available in literature like for contralateral breast in case of breast cancer patients. In this study an attempt was made to calculate the NTCP of these unusual structures in EBRT.

In the present study, an attempt was made to do such big calculations on Microsoft Excel which is easily available and relatively simple to understand as compared to C++ or other computer languages. For the treatment of certain malignancies like ca cervix, ca breast where combination of EBRT and Brachytherapy is used, there arises a need to calculate TCP/NTCP from the entire treatment. So, in this context, formalism in Microsoft Excel has been prepared in the present study to calculate TCP and NTCP for both EBRT and ICBT individually and collectively. Also the results obtained using this tool is in accordance to the expected values for a particular parameter like TCP near to 1 or 100% (as high as possible) and lesser NTCP (as low as possible).

CONCLUSION

From this study, Microsoft Excel tool has been found useful for TCP/NTCP calculation with the advantage of being simple and user friendly as compared to the technically complex and complicated for non-computer savvy researchers. TCP/NTCP should be used only for radiobiological comparison of different plans generated for same patient. Due to uncertainty involved in the parameter values which are taken from literature, it is not recommended to consider absolute values of the calculated NTCP for the clinical evaluation of the treatment plans. Radiobiological parameters are helpful in evaluating treatment plans in addition to dosimetric and slice by slice analysis.

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