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The use of the normal tissue non-complication probability (NTCP0) methodology as a new alternative of assessing side-effects in brachytherapy treatments

Terman Frometa-Castillo[1], Anil Pyakuryal[2], Ganesh Narayanasamy[3], Asghar Mesbahi[4], Amadeo Wals-Zurita[5]

[1]Owner at Statistical models project, LLC, Chicago, IL, United States
[2]University of District of Columbia, Division of Science and Mathematics, Washington, DC, United States
[3]University of Arkansas for Medical Sciences, Little Rock, United States
[4]Tabriz University of Medical Sciences, Tabriz, Iran
[5]Hospital Universitario Virgen Macarena, Sevilla, Spain

ABSTRACT

Background: The NTCP methodology evaluating side-effects (S-Es) was initially used in radiotherapy (RT), and later was extended to brachytherapy (BT). The NTCP0 methodology has been recently introduced in RT. Given the advantages, this methodology could replace NTCP.

Materials and methods: Revisions of studies related to use of NTCP in the evaluations of S-Es in BT. Development of the first versions of two Matlab applications of the NTCP0 methodology. These applications have three options. Two of them employ the well-known aspects of a phenomenological model, or the probabilistic relationship between NTCP0 and total NTCP (TNTCP) that is the *sum(NTCP(x_i)) i: i^{th} complication i:1..nc*: Number of complications; where NTCP0 = 100% — TNTCP; and the third option assumes a NTCP(x_i) discrete probabilistic distribution generated by the binomial distribution, where one of its parameters is automatically obtained from a databased of the Disease locations Vs. Late complications.

Results: The NTCP0cal and NTCP0calDr Matlab applications have been developed, and respectively used for fractional continuous low dose-rate BT.

Conclusions: NTCP0 is defined as the ratio of the number of patients without acute/late complications and total of them, and also can be obtained using our Matlab applications. NTCP0 works do not disregard the last 10–15 years of NTCP research; but NTCP0 was not considered during these years. A generic example was used for showing the variations of the late complications and NTCP0 for a BT treatment of a constant number of fractions and six different dose per fraction values.

Key words: NTCP; binomial distribution; LKB NTCP model; side-effect; brachytherapy

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Introduction

The safety of treatments with drugs is an aspect that must be evaluated in the pre-clinical phases of development of a drug before using it in humans; and must be reported during the clinical treatments. As a widely used drug treatment, BT has probabilistic levels of cure and side-effects (S-Es). The normal tissue complication probability (NTCP) is a way of evaluating S-E in radiation

Address for correspondence: Terman Frometa-Castillo, Statistical models project, LLC, Chicago, IL, United States, tel: 312-687-6422; e-mail: terman.frometa@gmail.com

treatments. Regardless of the level of toxicity of any treatment, there is a probabilistic level of safety, which is a complement of the global toxicity; i.e., total NTCP (TNTCP) that is the *sum(NTCP(x_i)) i: i^{th} complication i:1..nc*: Number of complications.

Whatever specific BT treatment given to a homogenous population with specific patients having a specific tumor has its own NTCP(x_i) discrete probabilistic distribution (DPD), where NTCP0 = NTCP(0).

Individual NTCP(x_i) has been modeled with complex analytical models, like Lyman-Kutcher-Burman (LKB) NTCP model, as shown in [1–2]; function of an independent variable (IV), then it was necessary to formulate analytical expressions for these IVs in order to determine an equivalent uniform dose (EUD) or an effective dose (Deff).

As a result of a radiation treatment, the volume of an organ at risk (OAR) generally receives a heterogenous distribution of dose. Based on this distribution, some NTCP models have been developed, such as the LKB and Relative seriality of [3].

NTCP0 is a metric associated to safety, which is the ratio between the number of patients without acute/late complications and the total number of them given a radiation treatment, well-characterized by its variables and factors. This is not associated with OARs, but non-complications. The NTCP0 phenomenological model of [4], the SMp NTCP0(D), is a function of the prescribed dose (*Dpres or D=n*d*). This model should be used for a constant number of fractions (n) and a range of dose per fraction (d), or vice versa.

NTCP0 value can be determined from experimental/observational data; or from assuming a determined NTCP(x_i) DPD. There are developed methodologies that mathematically generate DPDs, as described in [5] and [6]. Introducing NTCP0 and its phenomenological SMp models in the BT will be advantageous compared to the current NTCP methodologies.

The SMp NTCP0(D) and SMp NTCP0(R0) phenomenological models, where R0 is the initial dose-rate, are simple and not dose-volume histogram (DVH)-based; i.e., the DVHs of the OARs are irrelevant for these models. In other words, the new NTCP0 methodologies of evaluating S-E will not require the current DVH calculations for the OARs. NTCP0 is a new alternative of evaluating S-Es, instead of the habitual NTCP methodologies.

Given inherent probabilistic aspects of a specific stochastic process (SP) with more than one outcome, like normal complications in a BT treatment given to a specific population under specific circumstances; then:

- whatever specific BT treatment is associated with NTCP(x_i) DPD;
- NTCP0 = NTCP(0), and NTCP0 = 100% – TNTCP;
- as a SP, the normal complications have their deterministic and stochastic regions. The SMp NTCP0 parameters (*TDmin, TDmax, R0min and R0max*) are respectively the lower and upper limits of the stochastic region.

NTCP0cal and NTCP0calDr applications calculate NTCP0 using three options. The first of them is related to phenomenological models, in particular SMp NTCP0(D) and SMp NTCP0(R0) that are probabilistic-decreasing functions, and appropriate for describing the mean radiobiological behavior of NTCP0 in the function of D and R0, respectively. The second option is based on the probabilistic relationship between NTCP0 and TNTCP like NTCP0 = 100% – TNTCP.

Contrary to TCP calculations that can be done with computational simulations, for NTCP0 it is very difficult or impossible due to numerous parameters and variables involved; for this reason, the second and third options use an assumed or known NTCP(x_i) DPDs. In the third, we employ the binomial distribution (BD). As described in [5], the BD is an excellent-mathematical generator of these kind distributions

Results

The NTCP0cal application

This application provides three options, two of them employ the well-known aspects of a phenomenological model, or the relationship with TNTCP; and the third option determines NTCP0 from an assumed NTCP(x_i) DPD generated from the BD, where one of its parameters is automatically defined from a databased of the Disease locations Vs. Late complications. Figure 1 is the flow chart for determining NTCP0 in a fractionated BT treatment with *Dpres*.

The steps for executing the NTCP0cal are:

- select one of the three panels pressing the "Use" button of the desired panel;

  If the selection is Panel 1 "Using the SMp NTCP0 parameters"; introduce *d* of the *Dpres*,

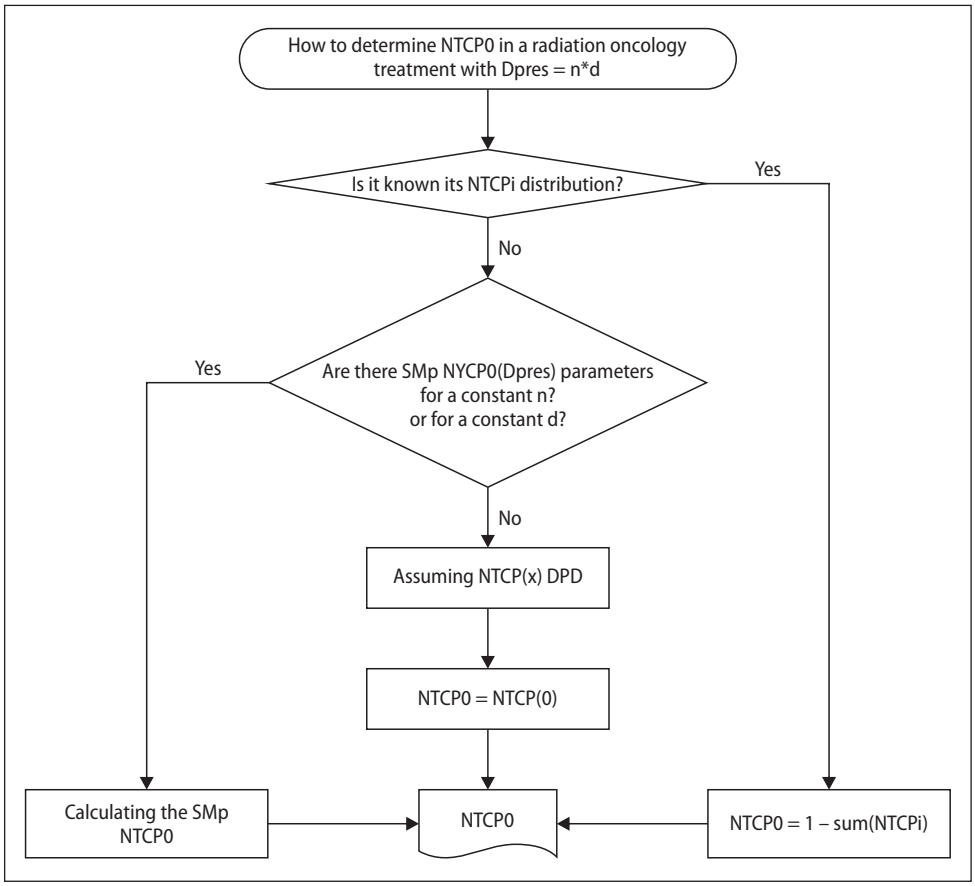

Figure 1. Diagram of procedures for determining NTCP0 in a fractional BT treatment. Dpres — prescribed dose; NTCPi — NTCP for the ith complication; i — 1... nc, nc number of complications; DPD — discrete probabilistic distribution; SMp — statistical model project

and the SMp NTCP0 parameters (*TDmin, TDmax* and *pN0*).

If the selection is Panel 2 "Using an assuming NTCP(x) DPD"; select the disease location, and introduce the BD parameter *p*.

If the selection is Panel 3 "Using a known/assumed NTCPi DPD"; introduce the values of probabilities (VPs) for each complication Ci (I = 1..7), and introduce the VP for Other complications *OCs*;

- if the selection is "Using an assuming NTCP(x) DPD", one can define the legend of the numerical and graphical information. Each disease location has its number of possible cases (Xmax). Xmax is equal to BD parameter *n*;
- by pressing the "Finish" button of the selected panel you return to the main screen.

The NTCP0calDr application

The essential difference between this application and NTCP0cal is given in Panel 1, where SMp NTCP0 is in the function of R0, instead of D, and expressed as

$$SMp\ NTCP0(R0) = [\frac{TR0max - R0}{TR0max - TR0min}]^{pN0} \quad (1)$$

TR0min — maximum value of *R0* for *NTCP0* = 100%. (*TR0min* ≥ *0); TR0max* — minimum value of *R0* for *NTCP0* = 0%; *pN0* — Power in this model. *pN0>0.*

In *R0* < *TR0min* and *R0* > *TR0max*, SMp *NTCP0(R0)* is respectively equal to 100% and 0%.

The flow chart for determining NTCP0 in a CDLR treatment is similar to a fractionated one with Dpres; and they differ in their respective SMp NTCP0 models.

The steps for executing the NTCP0 calculation are:

- select one of the three panels pressing the "Use" button of the desired panel.

If the selection is Panel 1"Using the SMp NTCP0 parameters"; select the radionuclide used, intro-

duce the initial dose-rate R0 in Gy/h, and introduce the SMp NTCP0 parameters (*TR0min, TR0max* and *pN0*).

If the selection is Panel 2 "Using an assuming NTCP(x) DPD (Discrete probabilistic distribution)"; select the disease location, and introduce the BD parameter *p*.

If the selection is Panel 3 "Using a known NTCPi DPD"; introduce the values of probabilities for each complication Ci (i = 1..7), and introduce the value of probability for other complications *OCs*;

- press the "For calculating NTCP0" button for obtaining the result of NTCP0;
- if the selection is "Using an assuming NTCP(x) DPD", one can define the legend of the numerical and graphical information. Each disease location has its number of possible cases (Xmax). Xmax is equal to BD parameter *n*;
- by pressing the "Finish" button of the selected panel you return to the main screen.

Discussion

The SMp NTCP0 models

The SMp(x) function of [6] was derived from the well-known Triangular model (TM), as a result of including powers p1 and p2 (*p1* and *p2* ≥0).

$$TM = \begin{cases} f1(x;a,b,c) * MaxTM \\ f2(x;a,b,c) * MaxTM \end{cases} \quad (2)$$

$$SMp = \begin{cases} f1(x;a,b,c)^{p1} * MaxSMp \\ f2(x;a,b,c)^{p2} * MaxSMp \end{cases} \quad (3)$$

where *a, b* and *c* are TM and SMp parameters, and *MaxTM* and *MaxSMp* are the respective maximum values of the TM and SMp models.

The SMp(x) can play the role of some probability density functions and DPDs, such as normal distribution and BD. Also, this can generate the three types: SMp1, SMp2 and SMp3. For example, NTCP0 Vs. D model of [4] is a type SMp3, which has a 100%-deterministic region, a stochastic and a 0%-deterministic, respectively defined by the parameters *TDmin* ≥ 0 and *TDmax* as

$$SMp\ NTCP0(D) = [\frac{TDmax - D}{TDmax - TDmin}]^{pN0} \quad (4)$$

TDmin — maximum value of *D* for *NTCP0* = 100%. (*TDmin* ≥ *0); TDmax* — minimum value of *D* for *NTCP0* = 0%; *pN0* — power in this model. *pN0* > *0; D* — *Dpres* function of *d* for a constant *n*; or function of *n* for a constant *d*. In *D* < *TDmin* and *D* > *TDmax*, SMp *NTCP0(D)* is respectively equal to 100% and 0%.

The current NTCP models provide approaches of this metric; i.e., NTCP estimations. An experienced radiation team will be able to assume good NTCP (x_i) distributions. This implies good NTCP0 estimations, too.

The NTCP(x_i) DPD assumed

The tumor control probability (TCP) is a metric related to cell kill in a determined tumor tissue. For this reason, one can estimate its value using a computational simulation based on its own probabilistic concept, as has been developed in [7]. Contrary to simulated TCP calculations, nowadays, the determination of NTCP0 by means of mathematical models or computational simulations for treatments with few or no data is very complicated or almost impossible. For this reason, there is an option of assuming NTCP(x_i) distributions using generators of DPDs, like BD. For choosing the BD parameter *p*, one should consider that:

1 — if p << 0.5, the NTCP0 is the event with maximum probability (EwMP);
2 — if p < 0.5, one of the complications is the EwMP, and NTCP0 >> 0%; if p ≈ 0.5, one of the complications is the EwMP, and NTCP0 >0%;
3 — if p > 0.5, one of the complications is the EwMP, and NTCP0 0%.

The Figure 2 illustrates a hypothetical example of a NTCP(x_i) DPD for describing or assuming the probabilities of late complications discussed in [8], and associated to BT treatment for prostate cancer. The NTCP0 = NTCP(0) = 24%. This value increases if *D* or *R0* decreases, and vice versa, as a result of variations of *d* for a treatment with a constant *n;* or variations of *n* for a constant *d;* or variation of R0.

Figure 3 shows an example of an option of the Matlab application for an assumed NTCP distribution generated by the BD expression: BD(x;0.4,6) for a head & neck disease location.

For selecting NTCP(x_i) and its correspondent x_i, the aspect contained in the Table 1, sub-region of the disease and other clinical and physical factors should be considered. The table is based on some QUANTEC studies.

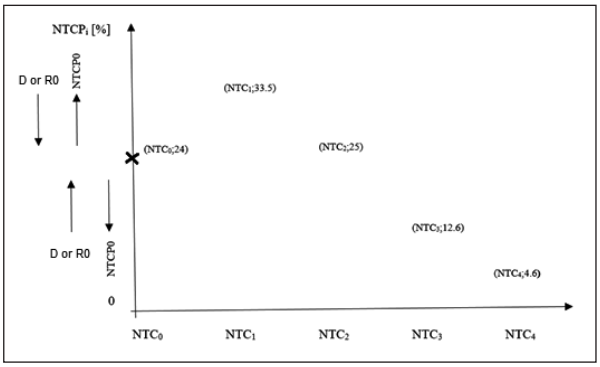

Figure 2. Hypothetical example of a NTCP(x_i) discrete probabilistic distribution for describing or assuming the probabilities of late complications associated with a BT treatment for prostate cancer. D — prescribed dose; NTC_0 — no complication; NTC_1 — leakage of urine; NTC_2 — cancer of the bladder; NTC_3 — cancer of the lower bowel; NTC_4 — erection problems (impotence). The NTCP0 = $NTCP_0$ = 24% is represented by a x; and its value increases if D or R0 decreases, and vice versa, as is shown by the four arrows on the right side of the y-axis

Other aspects

From revisions of studies related to use of NTCP in the evaluations of S-Es of the BT, we can say that:

- the majority of current NTCP models are DVH-based;
- the risk of toxicity is the way of evaluating the S-Es of radiation oncology treatments;
- NTCP is used mainly for evaluations of individual or principal complications or Endpoints of radiation treatments.

Nowadays, as described in [10], [17] and [24], the NTCP studies have been focused on separated OARs, or the principal late complications of a radiation treatment of an OAR; however, these treatments have various normal tissue complications; in other words, they have their own associated NTCP(x_i) DPDs.

The fractional radiation treatment has two independent variables: 1 — Number of fractions (n); and 2 — Dose per fraction (d). For this reason, the SMp NTCP0(D) could be expressed as SMp NTCP0(d) for a constant n; or as SMp NTCP0(n) for a constant d.

Because of the difficulty of obtaining NTCP model parameters for different combinations of *n* and *d*, the equivalent dose of 2 Gy per fraction (EQD_2) was derived. But it is very important to consider that EQD_2 establishes a cellular radiosensitivity equivalence, not a normal complication one.

As shown in the Figure 1, if SMp NTCP0(D) model parameters are not known for a determined

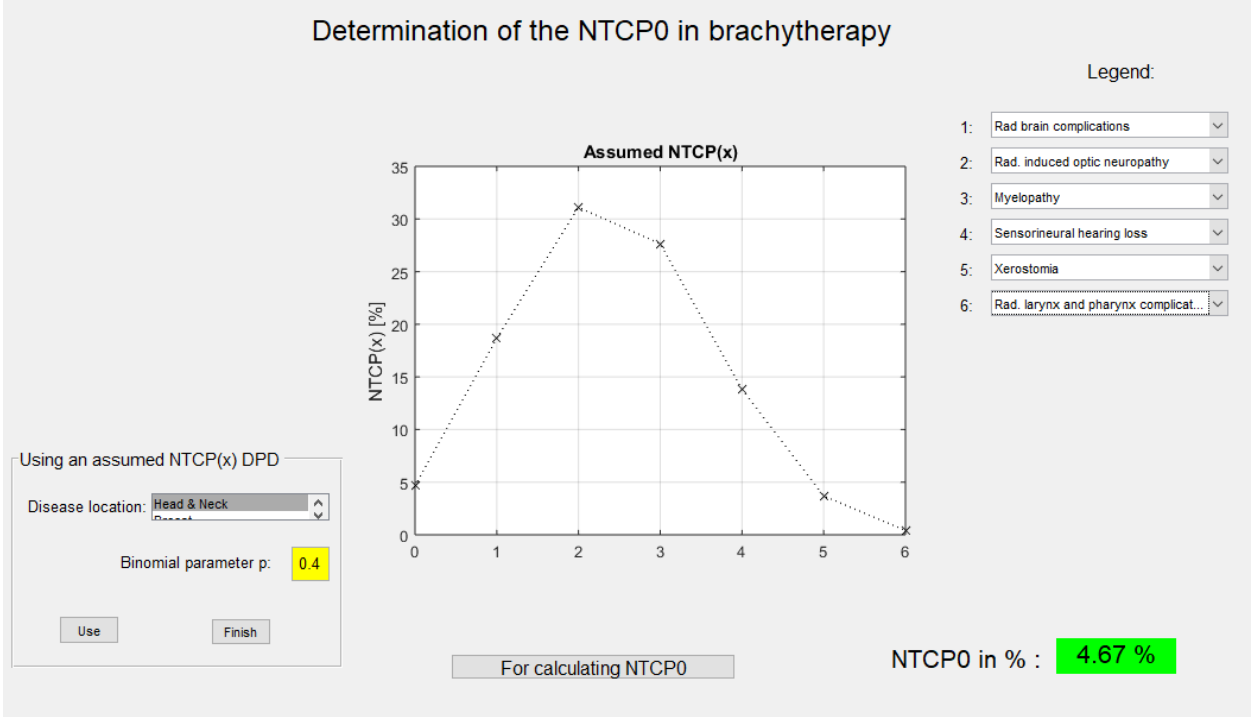

Figure 3. An example of the third option of the NTCP0cal/NTCP0CalDr application for an assumed NTCP distribution generated by the BD expression: BD(x;0.4,6) for a head & neck disease location

Table 1. Late complications of the BT treatments for their correspondent disease location

Late complications	Disease location				
	Head and Neck	Breast	Chest	Abdomen	Pelvis
Radiation (Rad.) brain	[9]				
Rad. induced optic neuropathy	[10]				
Myelopathy	[11]	[11]	[11]	[11]	[11]
Sensorineural hearing loss	[12]				
Xerostomia	[13]				
Rad. larynx and pharynx complications	[14]				
Rad. lung		[15]	[15]		
Rad. heart		[16]	[16]		
Rad. esophagus		[17]	[17]	[17]	
Liver dysfunction		[18]	[18]	[18]	
Rad. stomach and small bowel				[19]	[19]
Rad. kidney				[20]	[20]
Genitourinary				[21]	[21]
Rad. rectal				[22]	[22]
Rad. penile bulb				[23]	[23]

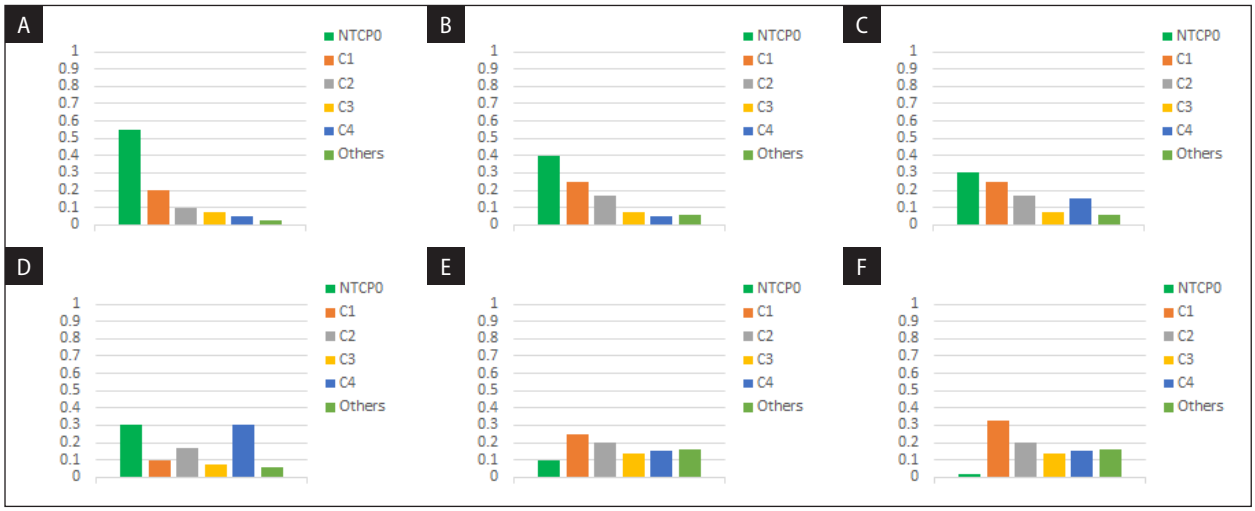

Figure 4. Illustrations of a generic example of a BT treatment with a constant number of fractions (n) dose per fractions, and (**A**): for dose per fraction d1; (**B**): d2; (**C**): d3; (**D**): d4; (**E**): d5 and (**F**): d6; where < d2 < d3 < d4 < d5 and < d6. The treatment has associated five late complications (C1, C2, C3, C4 and Others). We graphically and numerically show the independent variations of each late complications, and NTCP0

combination of *n* and *d*, we suggest that a NTCP(x_i) DPD should be assumed using a binomial distribution. For example, in Figure 4 (f) the BD(x;5,0.54) can be assumed for describing the NTCP DPD of this figure.

Figure 4 illustrates a generic example for showing variations of the late complications and NTCP0 for a BT treatment of a constant number of fractions and six different dose per fraction values. We want to show with this figure that:

1 — Any specific BT treatment given to an homogeneous patient populations has an associated acute/late NTCP(x_i) DPD, where *i=0:nc* and *nc*: Number of complications; NTCP0 = NTCP(0) and TNTCP = 100% – NTCP0;

2 — For a treatment with a constant *n*, if *d* increases TNTCP increases, and NTCP0 decreases; i.e.

the number of patients with late complications increases, and the number of those without complications decrease;

3 — Each NTCP(x_i) complication (I > 0) has an independent behavior when *d* increases. For example: C1 decreases when d increases in CD; C3 keeps its value in A–D; and C2 increases in AB; and when D increases as a result of increases of d, the NTCP(x_i) cannot be described with increasing functions, but these can describe TNTCP; and of course the decreasing functions of NTCP0.

The SMp NTCP0(D) model does not require DVH values of the OARs, nor their derivations, such as the EUD ; but the prescribed dose. Contrary to our models, the widely used LKB, and relative seriality model are DVH-based.

Implementing NCTP0 in the BT will represent the following advantages compared to the current S-E evaluations:

- the SMp NTCP0(D) and SMp NTCP0(R0) models are mathematically less complex than the LKB NTCP(Deff), where *Deff*: Effective dose;
- contrary to other NTCP models, these models do not involve OARs nor complications with different grade of severity. According to the type of OAR, one should use the LKB or relative seriality;
- given these models are not DVH-based, calculations of: EUD, Deff, or Maximum dose (Dmax) are not required. This model uses only information of the treatment.

Some previously discussed aspects and others of [7] are probabilistic foundations of our NTCP0 applications, and show why its validation is a priori. The validation of the NTCP0 methodologies is a priori because these are wholly based on strong probabilistic foundations, such as the normal complications of the specific radiation oncology treatments, as stochastic processes of more than outcome, have their own NTCP(x_i) DPDs, where NTCP0 = NTCP(0).

Conclusions

The LKB NTCP(Deff) model is the normal cumulative distribution function (NCDF). As a cumulative distribution function, the NCDF has a sigmoidal shape and should be used for calculating the probability *P(Deff<=x)* if Deff follows a normal distribution. For this reason, its use is not wholly appropriated as a NTCP model.

The current NTCP models used for evaluating S-Es in the radiation treatments provide NTCP approaches. An experienced radiation oncology team can assume a good NTCP(x_i) DPD based on database. Although an NTCP distribution is generated, the team should be interested only in one value, NTCP0. The NTCP0 estimations will be corrected in the future when a major data are available.

Concerning the mathematical correlations, the NTCP0(D) and NTCP0(R0) models are three-parameter phenomenological, and given the number of parameters and type, it is very easy to fit whatever real data NTCP0 Vs. D or R0, whose radiobiological mean behaviors should be described with decreasing functions aimed at acceptable estimations of S-Es.

Given gathering a data that lets us reproduce real graphical representations is too difficult or impossible; we have developed a generic example based on strong radiobiological and probabilistic foundations.

Conflict of interest

None declared.

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