A treatment planning system with new paradigms in the effectiveness and side-effect evaluation sections

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Abstract

Aim

Academic dissemination of the “SMp treatment planning system (TPS)” for external beam radiotherapy, which has been developed as a software function that could meet the definition of a device with an entirely new intended use. This system will have new paradigms in the effectiveness and side-effect (S-E) evaluation sections, where tumor control probability (TCP) is calculated with computational simulations instead of current analytical TCP models; and S-E is evaluated with the normal tissue non-complication probability (NTCP0) methodology instead of standard NTCP one.

Methods

Use of probabilistic foundations in the NTCP0 methodologies; and computational simulations of the interactions of ionizing radiation with the tumor tissues in the radiation oncology treatments for the TCP calculations.

Results

The "TCPsim" and “NTCP0cal” calculation modules of the SMp TPS, which calculate respectively TCP and NTCP0.

Conclusions

While the "NTCP0cal" application has unquestionable probabilistic foundations associated to normal tissue complications as a stochastic process with more than one outcome; the "TCPsim" is based on proper approaches that are result of the computational simulations that follow logic-probabilistic procedures, and probabilistic aspects, like the relationship between TCP and linear-quadratic cell survival model for a fraction with dose *d*.

1. Introduction

This work is aimed to disseminate the first treatment planning system (TPS) that uses normal tissue non-complication probability (NTCP0) as a new alternative of evaluating side-effects (S-Es) without requiring of the current organ at risk dose-volume histograms (OAR DVHs). Also, the “TCPsim” is the application of this TPS that calculates tumor control probability (TCP), and represents a significant advance in radiotherapy, where they only calculate TCP based on analytical models, while us do it based on computational simulations. The TCPsim methodology could replace the current ones employing analytical models.

Our application aims to develop a TCP\NTCP0 based TPS, where contrary to current systems using TCP

l simulation for determining TCP and NTCP0 as a

new alternative of evaluating S-Es of the radiation treatments.

The “TCPsim” will represent a big contribution due to one potential innovation is that rather than evaluating TCP by analytically calculating, this is calculated based on its own probabilistic definition; and can be considered an extension of the Monte Carlo, where outcomes of the radiation interactions with three possible types of tumor cells are analyzed, instead of the DNA damages.

Given inherent probabilistic aspects of a specific stochastic process (SP) with more than outcome, like normal tissue complications in a radiation treatment given to a specific population under specific circumstances, this has own discrete probabilistic distribution (DPD). Then, a) Whatever specific radiation oncology treatment has associated a NTCP(x_i) DPD; b) NTCP0 = NTCP(0), total NTCP (TNTCP = sum(NTCP(x_i)) where x_i is the i^{th} complication, *i = 1..nc*, and *nc*: Number of complications); and c) As a SP, the normal complications have their deterministic and stochastic regions. The SMp NTCP0 parameters *TDmin* and *TDmax* are respectively the lower and upper limits of the stochastic region. “NTCP0cal” application calculates/estimates NTCP0 using three options. The first of them is related with the well-known phenomenological models, in particular SMp NTCP0(D) is a probabilistic-decreasing function, and appropriate for describing the mean radiobiological behavior of NTCP0 in function of D. 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 is very difficult or impossible due to numerous parameters and variables involved. The second and third option can be used for assuming the NTCP(x_i) DPDs. In the third, we employ the binomial distribution (BD) as an excellent-mathematical generator of these distributions.

The “TCPsim” is a better computational simulator as compared to its previous version of (1) and calculates the TCP as a function of minimum dose per fraction (*dmin*) in the tumor region with the total minimum dose (*Dmin*) and number of fractions (*n*). The simulator is based on strong probabilistic-radiobiological foundations and knowledge/estimation of some radiobiological and tissue parameters, such as α, α/β, cell repair and cell sub-lethal damage. The “NTCP0cal” is a tool that calculates/estimates NTCP0, which is a new alternative of evaluating side-effects (S-Es).

The radiation oncology treatments have their own NTCP(xi) discrete probabilistic distributions (DPDs), where NTCP0 = NTCP(0). For this reason, NTCP0 is not a creation, such as the complication-free cure (P+) and uncomplicated TCP (UTCP); but an inherent concept of the stochastic processes. Our NTCP0 studies do not disregard the last 10–15 years of research; but NTCP0 was not considered in the radiation treatments during those last 10–15 years.

Our SMp TPS is based on new probabilistic knowledge about BD and Poisson distribution, like the incoherently derived Poisson-based TCP model, all described in (2).

The new SMp terms introduced in (3) are: 1) NTCP0 that corrected to P + and UTCP; and 2) Total NTCP (TNTCP) that corrected to tNTCP (The current NTCP for multiple OARs of (4)), and is determined as TNTCP = sum(NTCP(xi)) i = 1:nc, nc: Number of complications.

According to the section VI of (4) “Vision of TG-166 for future development of biologically based treatment planning (BBTP)”, the final evolution stage (No. 3) for the Plan Optimization/Evaluation Strategy are the Absolute values of TCP/NTCP/UTCP. While for our research team, the final evolution stage will be associated with the absolute values of TCP and NTCP0 determined with our proposed TPS. In the following table we establish comparisons among the current BBTPs and ours.

Table 1
Comparisons among the current biologically based treatment planning systems (BBTPSs) and our TPS.

No.	Aspects	Current BBTPs	SMp TPS
1	Numerical and graphical information about the OAR DVHs	It is used	Does not use it
2	Numerical and graphical information about the tumor DVH	It is used	Only the tumor Dmin is used
3	Phenomenological models for S-E evaluations	DVH-based and complex NTCP ones	NTCP0(D) that is not DVH-based
4	TCP calculation	Use of analytical models	Uses computational simulations
5	P+, UTCP, tNTCP, BED, and EUD	It is used	Does not use it
6	Tumor DVH calculation	Have it	Should include it

2. The "tcpism" Module

Some variables used in this module

S1: The linear-quadratic cell survival (S) for one fraction with dose dmin; the LQ S1(dmin), where K1 = 1-S1.

K1: Probability of the cell kill for each healthy cell of a tissue volume (Vol) irradiated with dmin.

dmin: Dose per fraction that receives a tumor in its region with Dmin.

Dmin: Minimum dose of the dose-volume histogram (DVH) tumor.

Alfa: Parameter α of the LQ S(d) model for one fraction.

AlfaBeta: Parameter α/β of the LQ S(d).

NTC: Number total of cell in a volume Vol with cellular density Cden.

nvs: Number of virtual simulations.

nkc: Number of killed cells.

nslc1: Number of sub-lethally damaged cells in the first fraction.

nrc: Number of repaired cells.

CR: Probability of the cell repair for the sub-lethally damaged cells.

nslcj: Number of sub-lethally damaged cells in the j^{th} fraction.

nudc: Number of undamaged cells.

gnum, gnum1 and gnum2: Randomly generated numbers

KSL: Maximum number between the gnum1 and (1-gnum1).

NKC: Number total of killed cells.

NSLC: Number total of sub-lethally damaged cells.

TC: Counter of the condition of tumor control.

TCOK: Number of times that nkc ≥ NTC; i.e. Total cell kill (K) is equal to 100%

The proposed TPS will let to the radiation oncologists to decide the selection of the determined treatment parameters: *dmin* and *n* as part of the optimization/evaluation processes.

The selected DVH tumor must satisfy the condition: *Dim/n = dmin*. Our TCP methodology only involves Dmin.

When a living tissue tumor is irradiated in a fractionated treatment, the final result of this irradiation may be:1) All tumor cells are wholly killed; or 2) There is an amount of survived tumor cells. Due to these two possibilities, the effectiveness (Point 1) of the radiation oncology treatments is evaluated with TCP, which evaluates how likely a tumor control is to occur.

As is shown in the diagram of the Fig. 1, for simulating a fractioned treatment, one should consider:

- The first fraction generates a mean *nkc* killed cells, *nslc* sub-lethally damaged cells, and *nudc* undamaged cells.
- For the second and successive fractions, the three kinds of cells are analyzed in their possible final outcomes in each fraction.
- The Matlab function *rand* is used for generating a random number *gnum* < = 1. The probability of meeting a killed cell (*PMKC*) is calculated as *nkc/NTC*, then if *gnum < PMKC*, the analyzed cell is died, but this is survived.
- For a killed cell, the simulator will analyze a new cell; but for a survived cell, there are two possibilities: the cell is undamaged or sub-lethally damaged. The probability of meeting a sub-lethally damaged cell is defined with a new *gnum > nslc/(nslc + nudc).*
- For an undamaged cell, if a new *gnum* < probability for K, this cell will die, but if *gnum* < = K + maged.

- For a sub-lethally damaged cell (SLDC) there is a range of damage degree. Two new random numbers *gnum1* and *gnum2* are generated, and let us defining *KSL = max(gnum1;1-gnum1).* If *gnum2 < = KSL*, the cell will die, but is kept as a sub-lethally damaged. The previous condition is associated to a major probability of killing the SLDC.
- While the number of fractions increases, *nkc* increases, and *nudc* decreases. The *nslc* increases after the first fractions, and can increase or decrease and finally decreases after the second or successive fractions.
- The cell repair is a temporal-cellular process; and the number of repaired cells is determined after each fraction as: *nrc = nslcj-nslcj*CR*.
- If *nkc* $\geq$ *NTC* after *n* fractions, there is tumor control. The TCP is calculated as: *TCP = TCOK/nvs*.

As responsible of the radiation treatments, the radiation oncologists with collaboration of the medical radiation physicists will choose or estimate the values of the radiobiological and tissue parameters.

The steps for executing the simulator are:

a) Introduce for a tumor non-homogeneously irradiated:

- *dmin* in Gy.
-
- α in Gy^{-1}
-
- α/β in Gy
-
- SL in %
-
- CR of the SLDCs during interfractions in %:
-
- Vol in mm^3 (It is suggested using always values greater or equal than $1mm^3$)
-
- Cden in cells/cm^3

b) Introduce for the virtual simulations:

- nvs (It is suggested using always values $\geq$ 30)
- n

c) Press the “For calculating” button for obtaining the simulated TCP

Given the tumor region with *dmin* has the maximum *S*, i.e. minimum cell kill (K), the simulations should be done only in this region, where radiation has the lowest probability of killing tumor cells. The Fig. 2 provides explanations about that.

The current radiosensitivity studies are described with S, which probabilistically is related with K, cell sub-lethal damage (SL) and cell undamaged (U) as $K + SL + U = 1\ (100\%)$, where $S = SL + U$. Due to little available information of the SL, in many cases the SL values should be assumed taking into account that $SL \leq S$. The TCPsim reports the LQ S(dmin) for being compared with the assumed value of the SL, which should be ≤ S.

The Table 2 and Table 3 show TCP reported in some references, and obtained with the TCPsim.

Table 2
Simulated mean TCP results and TCP values reported in their respective references. Abbreviations: **ρ** Cden; and **Ref.** Reference.

No.	*dmin* [Gy]	*α* [Gy^{-1}]	*α/β* [Gy]	*ρ*10^7* [cell/cm^3]	SL [%]	CR [%]	*n*	Ref.	TCP reported [%]	TCP simulated [%]	Obs.
1	2	0.262	7	1	10	40	35	(5)	70	72	TCP reported for α/β = 10 Gy
2	3.1	0.307	10	1	25	40	20	(6)	80	85	
3	18	0.06	5	0.01	1	10	3	(7)	85	80	

Table 3
Simulated TCP in % for tumor characterized with α and α/β (0.307 Gy^{-1} and 10 Gy respectively of (6); Cden = 10^7 cell/cm^3; SL = 25%-30%; and CR = 40%.

dmin [Gy] *n*	10	15	20	25	30
1	0	0	0	3	10
1.8	0	2	50	67	92
2	0	7	57	82	97
2.5	0	13	61	85	99
3.1	0	15	85	97	100
3.5	0	56	88	99	100

3. The Ntcp0cal Module

As is shown in the Fig. 3, the final decision for a radiation treatment one should conjugate TCP and criteria of the S-Es.

This module 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 binomial distribution (BD), where one of its parameters is automatically defined from a databased of the Disease locations Vs. Late complications. The Fig. 4 is the diagram of procedures of the NTCP0cal.

The steps for executing the NTCP0 calculation are:

d) Select one of three panels pressing the “Use” button of the desired panel.

If the selection is “Using the SMp NTCP0 parameters”.

- Introduce *d* of the *Dpres*.
- Introduce the SMp NTCP0 parameters (*TDmin, TDmax* and *pN0*).

If the selection is “Using an assuming NTCP(x) DPD”.

- Select the disease location.
- Introduce the BD parameter *p*.

If the selection is “Using a known/assumed NTCPi DPD”.

- Introduce the values of probabilities (VPs) for each complication Ci (i = 1..7).
- Introduce the VP for Other complications *OCs*.

e) Press the “For calculating NTCP0” button for obtaining the result of NTCP0.

f) 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*.

g) Pressing the “Finish” button of the selected panel you return to main screen.

3.1 The SMp NTCP0(D)

The SMp(x) function of (8) was derived from the well-known Triangular model (TM), as a result of including powers p1 and p2 (*p1* and *p2* ≥ 0).

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

1

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

2

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 (ND) and BD. Also, this can generate the three types: SMp1, SMp2 and SMp3. For example, NTCP0 Vs. D model of (3) is a type SMp3, which may have one 100%-deterministic region, has one stochastic and one 0%-deterministic, respectively defined by the parameters *TDmin* > = 0 and *TDmax* as

$$SMpNTCP0(D) = \left[\frac{TDmax - D}{TDmax - TDmin} \right]^{pN0}$$

3

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 SMp NTCP0(D) is not a DVH-based model, and does not evaluate complications in specific organs at risk (OARs), but S-Es of the treatments.

The Lyman-Kutcher-Burman (LKB) NTCP (Deff) of (4) is widely used for evaluating S-Es in the radiation treatments. LKB is the normal cumulative distribution function (NCDF), where *Deff*: Effective dose. 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 ND. Given the NCDF is an increasing function, they have used this complex probabilistic function for correlating NTCP with Deff. The widely used LKB NTCP model is more mathematically complex than the SMp NTCP0, and is DVH-based.

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.

3.2 The NTCP(x_i) DPD assumed

While the TCP is obtained with simulated calculations analyzing an irradiated tumor volume, the simulations for obtaining the NTCP0 are difficult or almost impossible due to lot of variables and parameters involved. Contrary to the TCP calculations, nowadays, the determination of NTCP0 by means of mathematical and mechanistic models or computational simulation for treatments with few or none data is [illegible] iculties, 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 $p \approx 0.5$, one of the complications is the EwMP, and $NTCP0 > 0\%$; and 3) if $p > 0.5$, one of the complications is the EwMP, and $NTCP0 \approx 0\%$.

For selecting NTCP(x_i) and its correspondent x_i, the aspect described in the Table 4, sub-region of the disease and other clinical and physical factors should be considered.

Table 4
Late complications of the radiation treatments for their correspondent disease location

	Disease location						
Late complications	Head & Neck	Breast	Chest	Abdomen	Pelvis	Total body (TB) in female	TB in male
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)		(18)	(18)
Encephalopathy		(18)	(18)	(18)		(18)	(18)
Death		(18)	(18)	(17) (18)		(18)	(18)
Rad. stomach and small bowel				(19)	(19)		
Rad. kidney				(20)	(20)	(20)	(20)
Hypertension				(20)	(20)	(20)	(20)
Genitorinary				(21)	(21)		
Rad. rectal				(22)	(22)		
Rad. penile bulb				(23)	(23)		(23)

4. Conclusions

The future researches related with our simulator should be aimed to obtaining better values or ranges of its parameters.

If we include a module for tumor DVH calculations, our system can be built stand-alone.

Our simulator will represent a big contribution due to one potential innovation is that rather than evaluating TCP by analytically calculating, this is calculated based on its own probabilistic definition.

TCPsim is an extension of the MC that analyzes outcomes of the radiation interactions with three possible types of tumor cells, instead of the DNA damages.

Our NTCP0 work does not disregard the last 10–15 years of research, but we encourage the medical physicist communities to use the NTCP0 methodologies. Actually, NTCP0 was not considered during those last 10–15 years.

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

The NTCP0 methodologies of evaluating S-Es in the radiation treatments could be extended to whatever hazard activity.

The probabilistic aspects NTCP0cal application discussed in this work, and others of the [2] show why its validation is a priori; i.e., its foundations are based on knowledge considered to be true without being based on previous experience or observation.

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. Despite a NTCP DPD is generated, the team should be interested only for one value, NTCP0. The NTCP0 estimations will be corrected in the future when a major data will be available.

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Code availability: Not applicable

Authors' contributions: Not applicable

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Figures

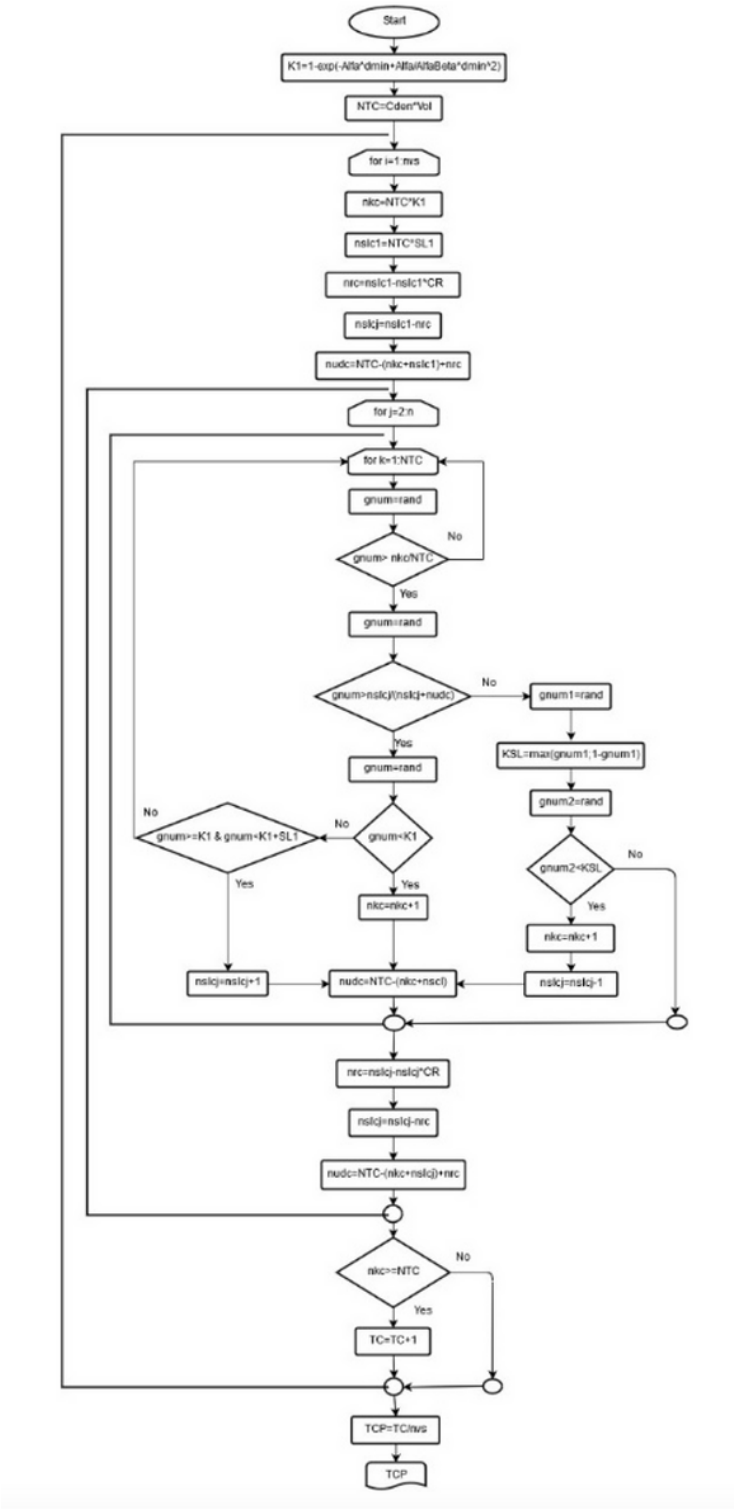

Figure 1

Diagram of the “TCPsim”

Given dmin<d1<d2.....<d5; then

LQ S(dmin)> LQ S(d1)> LQ S(d2).....> LQ S(d5); or

K(dmin)< K(d1)< K(d2)..... <K(d5)

Given there is tumor control (TC) when total K=100%; then

TCP(dmin)<TCP(d1)<TCP(d2)..... <TCP(d5) ; and

Given TCP=min(TCPi); then

TCP=TCP(dmin)

Figure 2

A non-homogenous distribution of dose di in a tumor with minimum dose dmin, and explanations of why TCP should be determined with the dmin.

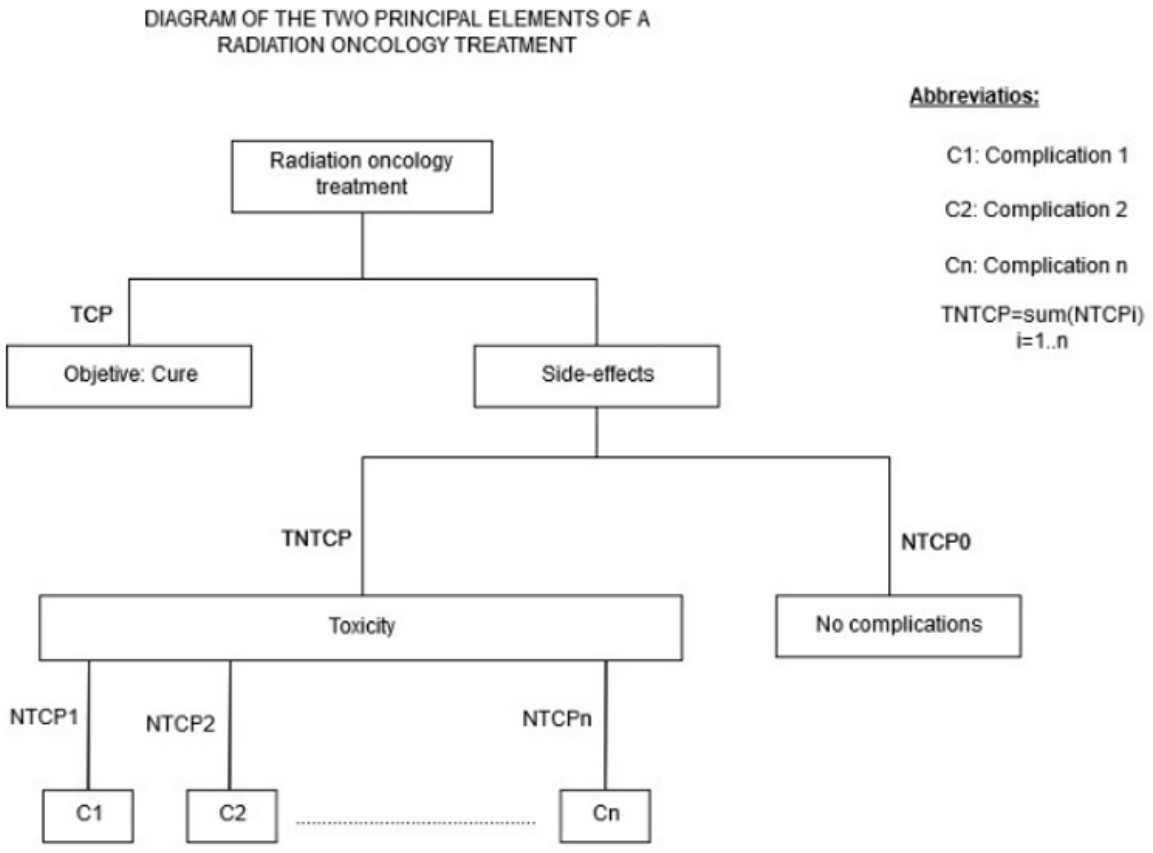

Figure 3

The two principal elements of a radiation treatment.

Figure 4

Diagram of procedures for determining NTCP0 in a radiation treatment.