Breast cancer normal tissue complication modelling and parameter uncertainties

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Abstract

External radiation treatment (ERT) is one of the treatment methods against breast cancer. As all therapies, radiation is linked with side effects. Utmost goal during the treatment with radiation is to maximize the benefit for the patient (efficacy of the treatment) while sparing other vital organs from radiation that could lead to organ's toxicity. The assessment of the overall benefit of a radiation treatment can be modelled with the help of linear quadratic model. That model simulates the cell killing for a specific type of cell (each cell cancerous or healthy has different properties: radiosensitivity, proliferation) under a given radiation prescription and schema. With the help of modelling, oncologists and medical physicists can simulate and predict the outcome of a radiation treatment schema.

1. Introduction

Breast cancer is the most common malignant disease among Western women and represents a major public health problem, with more than 370.000 new cases and 130.000 deaths per year in women aged 35–64 years in Europe alone. It accounts for one third of the cancer-related deaths in women aged 35–55 years [1, 2].
For women with newly diagnosed, non-metastatic breast cancer, treatment consists of a multidisciplinary approach that involves input from surgery, radiation oncology, and medical oncology. The aim of adjuvant radiation therapy is to eradicate any tumour cells remaining following surgery for patients treated by either breast-conserving surgery or mastectomy.
However, as all therapies, radiation is also linked with side effects. Some studies have shown association with a greater toxicity profile while others do not [23,35]. The degree of the toxicity strongly depends on anatomical structures and the associated radiation treatment plan [3, 4].

Early toxicities could range from arm edema, breast skin dermatitis, decreased range of motion, and pneumonitis and pericarditis to fat necrosis and rib fracture.

2. RT Dose and scheduling

Most women receive conventionally whole breast radiation treatment, which is delivered to the entire breast in 1.8 to 2 Gy daily fractions over 4.5 to 5 weeks to a total dose of 45 to 50 Gy. Another option is a hypofractionated schedule that has been associated with fewer toxicities[5]. In general, a hypofractionated regimen delivers more radiation per dose, but the overall treatment duration is shorter (40 to 42.5 Gy in approximately three to five weeks with or without a boost).

3. Tumour control probability

Tumour control probability (TCP) for a given tumour is represented by a sigmoid curve in which an increase in dose results in greater tumour cell kill.

$$TCP = e^{-N_0 e^{-\alpha\, BED}} \qquad \text{(Eq. 1)}$$

Where: N_0 is the initial number of clonogenic cells, α [Gy^{-1}] is a constant for the radiosensitive and BED [Gy] is the biologically effective dose[6] aka EQD0, as defined in the linear quadratic model [7, 8].

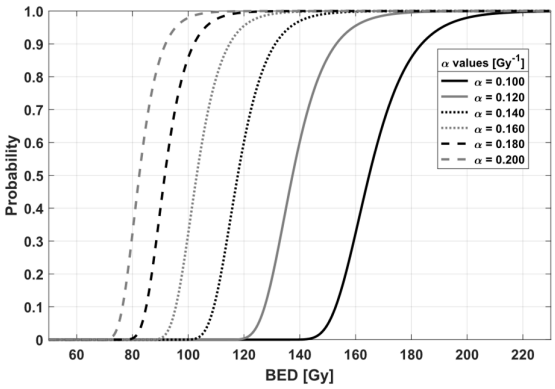

Figure 1: Tumour control probability against of α parameter values

4. Normal tissue control probability

The normal tissue complication probability (NTCP) is also represented by a sigmoid curve. Example of a model for normal tissue complications is the relative seriality model[9, 10]. The basic assumption of the model is the poison statistics for

describing the cell survival and the organization of the normal tissue in serial and parallel substructures.

The formula of the model is:

$$P(D_i) = 2^{-e^{e\gamma(1-\frac{D_i}{D_{50}})}} \quad \text{(Eq. 2)}$$

(Eq. 2) describes the response to a homogeneous dose distribution. Parameter D_{50} gives the 50% complication probability [11], while the slope of the dose-response curve is given by the parameter γ. ΔV_i is defined as v_i/V where v_i is the volume of a particular sub-volume in the DDVH (differential DVH) and V is the volume of the whole organ.

$$NTCP_{relative\ seriality} = [1 - \prod_{1}^{n}[1 - P(D_i)^s]^{\Delta V_i}]^{\frac{1}{s}} \quad \text{(Eq. 3)}$$

(Eq. 3) describes the tissue response in respect to arbitrary dose distribution. The parameter "s" is the seriality factor of the tissue/organ. The values of "s" parameter range between zero (parallel structure) to one (serial structure).

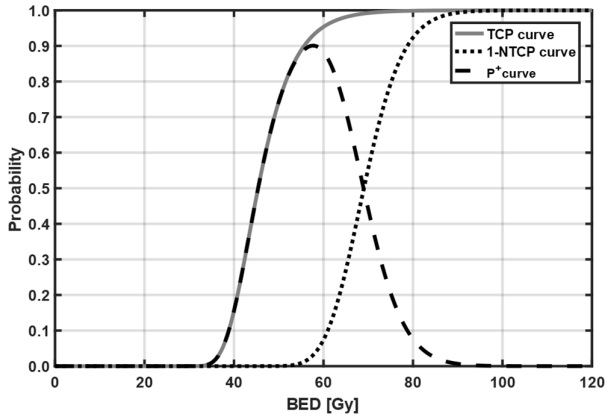

Figure 2: Presentation of NTCP and TCP and the principle of therapeutic ratio

The relationship between these two sigmoid curves (TCP and NTCP) is called the therapeutic ratio (see Figure 2). Ideally, the TCP and NTCP curves are separated so that a dose can be delivered to tumour without any concern for toxicity. In addition, in Figure 2, we show the complication free tumour control probability P^+. It evaluates the effectiveness of a given dose distribution by the comparison of its advantages in

terms of tumour control probability against its disadvantages considering normal tissues complications probability[10]. P+ is given by (Eq. *4*.

$$P^{+} = TCP * NTCP \qquad \text{(Eq. 4)}$$

5. NTCP calculation based on DVHs

In this section, we will give an example of calculating NTCP for the heart structure for a clinical case. In the literature [9] can be found that parameters of D_{50} and γ and s for the heart:

Parameters	Heart	
	Value	**Asymmetric error**
D_{50} (Gy)	52.3	(-3.3 to +4.7)
γ	1.28	(-0.24 to +0.36)
s	1.00	(-0.27)

Table 1: Relative seriality parameters for heart

Following, we plot the P_{injury} = 1 – NTCP, where NTCP is given by (Eq. 3).

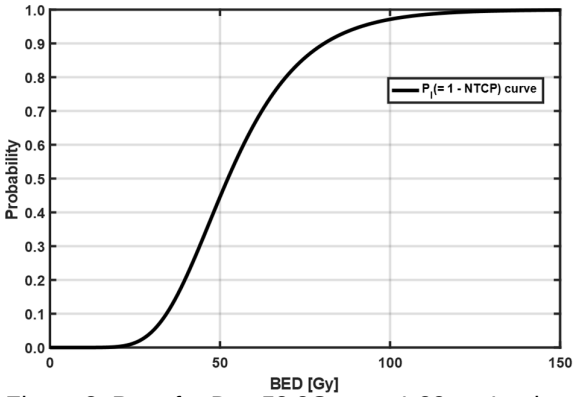

Figure 3: P_{injury} for D_{50}=52.3Gy, γ = 1.28, s=1 values

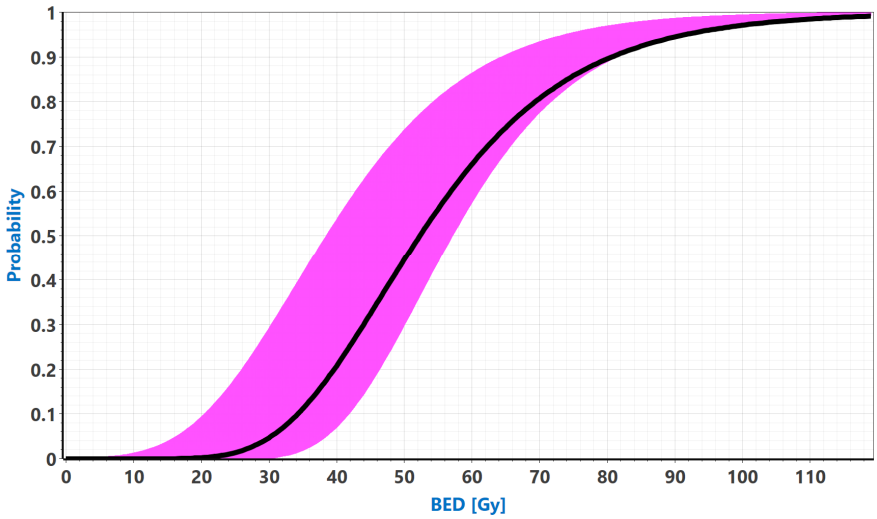

Figure 4: P_{injury} for D_{50}=52.3Gy, γ = 1.28, s=1 with asymmetric errors as shown in Table 1

As we can see in Figure 4, uncertainties in parameter D50, γ and s play a central role to the outcome of the normal tissue control probability. The above figures have been produced with the assumption of a homogeneity/uniform dose.

Now, we will calculate the NTCP on a simulated clinical plan, where the dose is not uniform distributed.

In Figure 5a, the targets and organs at risk have been delineated. In Figure 5b, we can see the dose distribution for the right breast eradiation of external treatment plan.

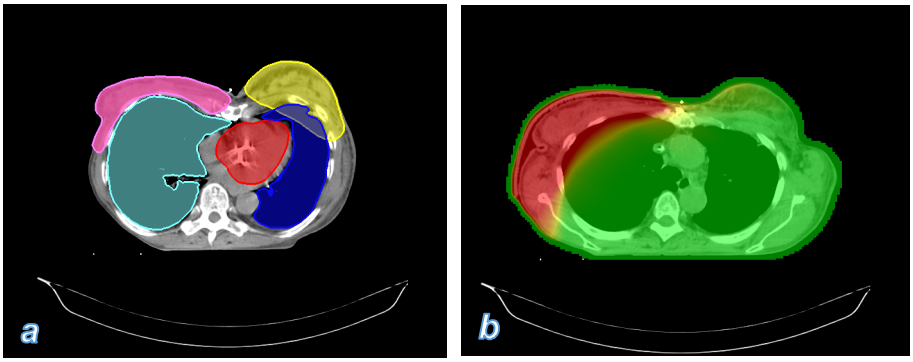

Figure 5: (a) Delineation of targets and organs at risks, (b) Dose distribution

Based on 3D dose distribution and the geometry of the contoured targets and organs at risk (OARs), we can calculate the dose-volume-histograms for each ROI (region of interest), as depicted in Figure 6.

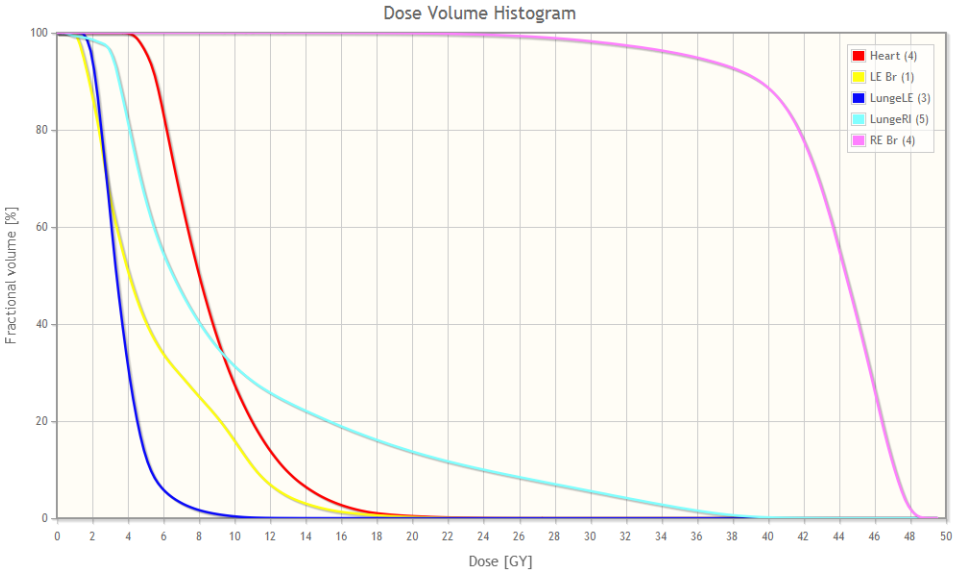

Figure 6: Cumulative dose-volume-histogram

Calculating the NTCP for D_{50}=52.3Gy, γ = 1.28, s=1 and the differential DVH as input, we have NTCP = 0.14%. (α/β = 3 Gy, #fractions = 17).
Taking into account the parameters uncertainties, as shown in Table 1, we calculated the NTCP value for 306E+06 iterations for the plan above.
The mean value of NTCP was 0.88% with standard deviation 1.94%. The minimum and maximum values of NTCP were [0%, 16.26%].

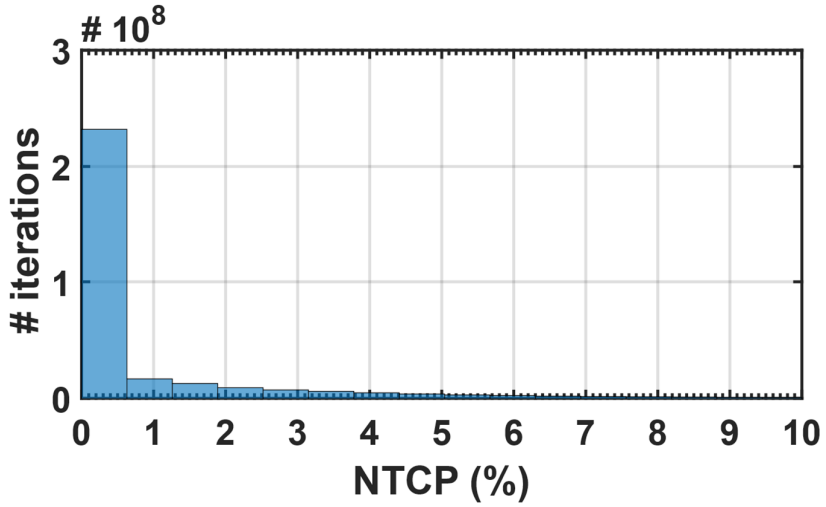

Figure 7: NTCP distribution over parameter uncertainties

6. Conclusions

Modelling of normal tissue complication is a very helpful tool for the evaluation and comparison of radiation treatment plans[12]. It can also be a quick check of the quality of the produced plans in the clinical routine. However, great attention should be paid to the parameters of the model(s) and their uncertainties. As we depicted in previous section model parameter uncertainties introduce deviations to the probability outcomes. Without any statistical uncertainties in place the NTCP is calculated to 0.14%. However, with uncertainties in parameters the mean values of NTCP is calculated to 0.88% with a standard deviation of 1.94%.

7. Acknowledgment

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