



A software tool for organ-specific second cancer risk assessment from exposure to therapeutic doses

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ABSTRACT

The aim of this study was the development of a software tool (SCRcalc) for the automatic estimation of the patient- and organ-specific cancer risk due to radiotherapy. SCRcalc was developed using the Python 3.8.7 programming language. It incorporates equations and parameters of mechanistic models for the calculation of the organ equivalent dose (OED), the excess absolute risk (EAR) and the lifetime attributable risk (LAR) of carcinogenesis for various organs due to radiotherapy. Data from differential dose-volume histograms, as defined by a treatment planning system, could be automatically inserted into the program. Eighteen different cancer risk estimates for various organs were performed of patients subjected to radiation therapy with conventional and modulated techniques. These software estimates were compared with manual calculations. SCRcalc was developed as a standalone executable program without any dependencies. It enables direct estimations of the OED and LAR for various organs at risk. An important aspect of the software is that it does not require pre-processing of the DVH data. No differences were found between the SCRcalc results and those derived from manual calculations. The newly developed software offers the possibility to medical physicists and radiation oncologists to directly estimate the probability of radiotherapy-induced secondary malignancies for various organs at risk.

Key words: radiotherapy; radiation risk assessment; secondary malignancies; Python, software development

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Introduction

The cancer death rate has been continuously reduced since 1991 leading to an overall decrease of 29% nowadays [1]. The advances in anticancer treatment have contributed to the above drop of the mortality rate [1]. Radiation therapy remains one of the main modalities for the management of several malignant diseases. However, the exposure of a cancer patient to high doses of ionizing radiation may lead to the development of a secondary malignant neoplasm [2]. The use of modern modulated irradiation techniques which involve extended treatment times and expose a larger volume of healthy

tissues compared to conventional radiotherapy may further increase the second cancer risk [2, 3].

The risk of developing radiotherapy-induced malignancies has been extensively determined on the basis of epidemiological data [4, 5]. The collection of these data requires the follow-up of irradiated patients for a very long time taking into account that the latency for the development of solid tumors is more than 10 years and reaches 60 years [6]. Leukemia appears in a period of 15 years following radiation exposure [6]. Linear and non-linear models may provide the required data for estimating the probability of cancer incidence following exposure to ionizing radiation. Linear

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models suggest the direct proportion of the cancer risk and radiation dose [7, 8]. This linearity is presented up to radiation doses of about 2.5 Gy [3]. The linear relationship between dose and risk is not evident for the high doses delivered during radiotherapy [9]. Several non-linear models have already been applied for the assessment of the second cancer risk to organs exposed to high therapeutic doses [10–13]. These mathematical models involve the use of equations and/or parameters making their application sometimes difficult and time-consuming in clinical practice. Moreover, some of these approaches ignore the impact either of the target dose fractionation during the entire treatment course or of the cell repopulation in the probability of subsequent carcinogenesis [10, 11, 14, 15].

The purpose of this study was to develop a software tool for the automatic estimation of the patient- and organ-specific cancer risk due to external-beam radiotherapy, on the basis of treatment planning data, a non-linear model [16], accounting for cell killing, tumor dose fractionation and tissue proliferation, and a bell-shaped model [17].

Materials and Methods

Model-based cancer risk estimates

Almost 50% of the radiotherapy-induced secondary malignancies are presented in organs located in the margin area of the treatment volume [18]. The radiation dose to these structures is inhomogeneously distributed and portions of the organs receive therapeutic doses of more than 2 Gy. The linearity between the radiation dose and the risk of carcinogenesis is in dispute for the above high doses [3]. The probability of carcinogenesis in these heavily exposed organs can be calculated with a non-linear mechanistic model proposed by Schneider et al. [16]. This model has been defined from the combined Japanese A-bomb and Hodgkin cohorts. The model is based on the calculation of the organ equivalent dose (OED) using differential dose volume histograms (DVH) obtained by the treatment planning system as follows:

$$OED = \frac{1}{V_T} \sum_i V_i \frac{\exp(-a'_i D_i)}{a'_i R} \left[\frac{1 - 2R + R^2 \exp(a'_i D_i)}{(1 - R)^2 \exp\left(-\frac{a'_i R}{1 - R} D_i\right)} \right] \quad (1)$$

where V_T is the total organ volume, V_i is the volume of the organ at risk (OAR) absorbing a ra-

diation dose of D_i , R is the organ-dependent repair parameter and a'_i is an organ-specific factor related to the cell killing. The a'_i is given by the equation:

$$a'_i = a + \frac{\beta D_i}{n} \quad (2)$$

where a and β are parameters from the linear-quadratic model and n is the number of fractions.

The mechanistic model proposed by Schneider et al. [16] allows calculation of the OED for the lungs, rectum, stomach, fem-breast, bladder, liver, esophagus, colon, brain-cns, salivary gland, mouth-pharynx and small intestine. The thyroid gland was excluded from the analysis of Schneider et al. [15]. The bell-shaped model as previously described [17] was used for calculating the OED of the thyroid as follows:

$$OED_{Thyroid} = \frac{1}{V_o} \sum_i V_{D_i} D_i \exp(-a'_i D_i) \quad (3)$$

The OED is required for estimating the organ-specific excess absolute risk (EAR) for second cancer induction after radiotherapy as follows:

$$EAR = \beta_{EAR} OED \exp \left[\gamma_e (A_e - 30) + \gamma_a \ln \left(\frac{A_a}{70} \right) \right] \quad (4)$$

where β_{EAR} is the slope of the dose-response curve at low doses, A_e is the patient's age during irradiation, A_a is the attained patient's age and γ_e and γ_a are the age modifying factors. The parameters in the equations (1), (2) and (3) were taken from the literature [16, 19]. The sum of the EARs up to the maximum attained age ($Age_{a,m}$) provides the site-specific lifetime attributable risk (LAR) of carcinogenesis:

$$LAR = \sum_{A_e+L}^{A_{a,m}} EAR(A_e, A_a) \frac{S_a}{S_e} \quad (5)$$

where L is a cancer risk free interval of 5 years and S_a/S_e is the probability of a healthy person to survive from A_e to A_a as obtained by the U.S. life tables [20].

Algorithm and graphical user interface (GUI) development

SCRcalc was developed using the Python 3.8.7 programming language. The Python script consists of three sections. The first section incorporates thirteen callable functions. Each function returns the

parameters β_0 , γ_e , γ_α , α , β and R for a specific OAR. Moreover, this section included two lists with the male and female surviving probabilities as obtained by the U.S. life tables [20]. The second section of the script is the computational part of the algorithm. The callable functions integrated in this section calculate the OED, a'_i , EAR as well as the LAR through equations 1, 2, 4 and 5, respectively. For thyroid, the algorithm calculates the OED through equation 3. The algorithm was developed to derive D_i and V_i values from the differential dose-volume histogram (DVH) text file which is exported from the treatment planning software. The third section of the script incorporates the code for the development of the graphical user interface (GUI). The mathematical calculations are assessed using the math module while for the development of the GUI the tkinter module was employed. The final script was compiled to a standalone executable program.

The SCRcalc's GUI consists of three windows as Figure 1 indicatively shows. In the first window the user selects the preferable OAR. Following the selection of the organ, the second window appears, and the user imports the age of the patient during the treatment period, the attained age, the number of fractions as well as the DVH text file. Pre-processing of the DVH text file is not required. Thus, the user can export the DVH text file from the treatment planning software and directly import it

into the SCRcalc software. Finally, by selecting the gender of the patient, the third window appears, presenting the calculated values of the OED and LAR. The software offers the option of saving the report as a text file by clicking the Print Report button (Fig. 2).

Patients

The newly developed software was employed to estimate the second cancer risks for nine patients subjected to radiotherapy for several malignancies. The patients' age and gender and the applied treatment parameters are presented in Table 1. The left breast and supraclavicular lymph nodes of patient no. 3 were treated. For patient no. 6, 50.4 Gy were given to the pelvic lymph nodes while the prostate received a simultaneous integrated boost to 67.2 Gy. The treatment plans were created with the Monaco system (Elekta AB, Stockholm, Sweden) for use in an Infinity linear accelerator (Elekta AB, Stockholm, Sweden) generating 6 MV photons. The two partial or full arcs rotated in opposite directions in all volumetric modulated arc therapy (VMAT) plans. Differential DVHs showing the dose distribution of the partially in-field organs were inserted into the software environment for estimating the organ-specific cancer risk. The software-based estimations were compared with the risks derived from manual calculations.



Figure 1. In the first window (left) the user selects the organ of interest. In the second window (middle) the user imports the age of the patient during radiotherapy, attained age, number of fractions and the dose volume histograms (DVH) data. By selecting the gender of the patient, the third window (right) appears presenting the calculated values of organ equivalent dose (OED) and lifetime attributable risk (LAR)

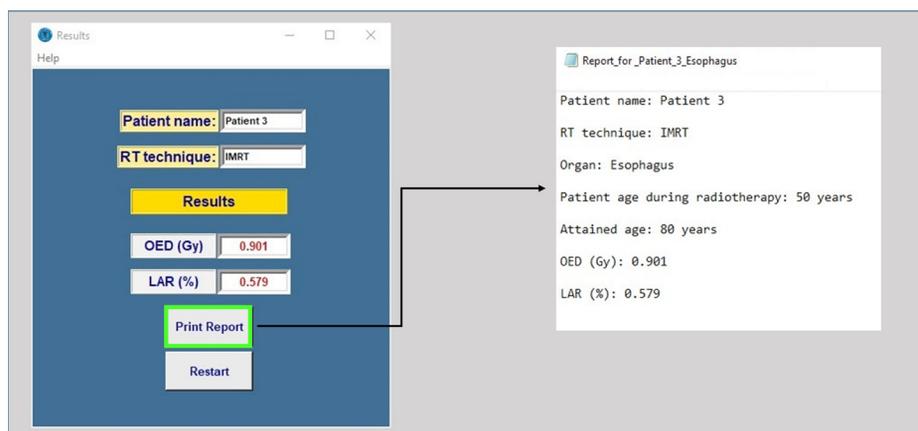


Figure 2. The user has the option to save the report as a text file with the Print Report button. Here, the results and report of patient 3 esophagus are presented

Table 1. Patients’ age and gender and the applied treatment parameters

Patient	Gender	Age* (years)	Primary disease	Target dose [Gy]	No. fractions	RT technique	Fields/Arcs
1	Male	57	Graves orbitopathy	20	10	3D-CRT	2 lateral fields
2	Male	59	Laryngeal cancer	70	35	VMAT	2 partial arcs
3	Female	50	Left breast cancer	50	25	IMRT	7 fields
4	Male	64	Stomach cancer	45	25	VMAT	2 full arcs
5	Female	61	Endometrial cancer	45	25	VMAT	2 full arcs
6	Male	67	Prostate cancer	67	28	VMAT	2 full arcs
7	Female	52	Rectal cancer	50	28	3D-CRT	4 field box
8	Male	44	Testicular cancer	20	10	3D-CRT	AP-PA
9	Female	49	Cervical cancer	50	28	IMRT	7 fields

*"Age" refers to the age of patient during radiotherapy; 3D-CRT — 3-dimensional conformal radiation therapy; VMAT — volumetric modulated arc therapy; IMRT — intensity modulated radiation therapy

Results and Discussion

In the current study, 18 different OED and LAR calculations were carried out using the SCRCalc for various critical organs of patients irradiated with 3-dimensional conformal radiation therapy (3D-CRT), intensity modulated radiation therapy (IMRT) or VMAT. Table 2 presents the calculated values. The OED values were found to be 0.2–10.7 Gy. The LAR varied from 0.03% to 8.39% by the OAR and the treatment site. These values were also calculated manually to confirm the accuracy of the software. No differences were found between the above OEDs and LARs with those derived from manual calculations.

The manual cancer risk assessment is a time-consuming task based on the processing of DVH data and the implementation of a set of complex equations.

Different formulas should be predefined for each OAR using the proper organ-dependent parameters. SCRCalc software enables direct estimations of the OED and LAR for various organs at risk. An important aspect of the software is that it does not require pre-processing of the DVH data. The user should import the DVH text file to the SCRCalc without any pre-processing, define patient’s age and gender to obtain OED and LAR values in seconds. Moreover, the software was developed as a standalone executable program without any dependencies. It can be installed to any workstation and its use does not require programming skills. This offers the possibility to medical physicists and radiation oncologists to directly estimate the probability of radiotherapy-induced secondary malignancies for various organs at risk.

Secondary malignant neoplasms usually occur either inside the primary radiation field or in the

Table 2. Calculated organ equivalent dose (OED) and lifetime attributable risk (LAR) values

Patient	Organ	OED [Gy]	LAR (%)
1	Brain	0.928	0.052
2	Thyroid	3.751	0.054
3	Esophagus	0.901	0.579
	Contralateral Breast	2.342	1.927
	Ipsilateral Lung	5.013	8.385
4	Esophagus	0.580	0.183
	Liver	0.740	0.102
5	Bladder	0.226	0.057
	Rectum	9.774	0.223
6	Bladder	0.204	0.027
	Rectum	10.720	0.123
7	Small intestine	0.245	0.145
	Bladder	0.765	0.337
8	Stomach	0.541	0.602
	Colon	4.011	2.534
	Liver	0.520	0.185
9	Bladder	0.636	0.323
	Rectum	0.494	0.026

beam-bordering region [21–23]. Diallo et al. [21] found that 78% of the secondary tumors in the examined irradiated cancer survivors appeared in the aforementioned regions. Welte et al. [22] reported that 69% of the second malignancies in their cohort were positioned within the primarily irradiated volume and at the field margins. Berrington de Gonzalez et al. [23] also found that 54% of the radiotherapy-induced tumors occurred at sites located at distances smaller than 3 cm from the field borders. These sites received high radiation doses exceeding 5 Gy.

The proposed tool can be applied in clinical practice whenever the second cancer risk needs to be estimated for critical organs which are entirely or partly encompassed by the radiotherapy fields. The use of the software is limited to the following organs with high predilection for radiation carcinogenesis: lungs, rectum, stomach, fem-breast, bladder, liver, esophagus, colon, brain-cns, salivary gland, mouth-pharynx, small intestine and thyroid. For each of the above organs, Schneider et al. [16] provided the required parameters for calculating the OED and LAR values. It should be mentioned that the LAR estimates contain a lot of uncertainty due to errors in the definition of the organ-specific

model parameters. Furthermore, the software cannot be used for cancer risk assessment to distant sites from the treatment volume exposed to low doses due to secondary radiation. Different computational or measurement methods should be used for estimating the out-of-field organ doses and radiogenic risks [24, 25].

Conclusion

SCRcalc is a newly developed software tool for the automatic estimation of the patient- and organ-specific cancer risk due to radiotherapy. The software's GUI is self-explanatory and no programming skills are required from the user. SCRcalc offers the possibility to radiation oncologists and medical physicists to compare the radiation-induced cancer risks for various organs at risk from different radiotherapy treatment techniques and choose the option with the minimum risk for each patient. As no pre-processing of the DVH data is required, and the calculations are performed in seconds, the evaluation of the radiotherapy treatment plans can be implemented in every-day clinical practice with minimum added workload.

Conflict of interest

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