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Integration of second cancer risk calculations in a radiotherapy treatment planning system

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Abstract. Second cancer risk in patients, in particular in children, who were treated with radiotherapy is an important side effect. It should be minimized by selecting an appropriate treatment plan for the patient. The objectives of this study were to integrate a risk model for radiation induced cancer into a treatment planning system which allows to judge different treatment plans with regard to second cancer induction and to quantify the potential reduction in predicted risk. A model for radiation induced cancer including fractionation effects which is valid for doses in the radiotherapy range was integrated into a treatment planning system. From the three-dimensional (3D) dose distribution the 3D-risk equivalent dose (RED) was calculated on an organ specific basis. In addition to RED further risk coefficients like OED (organ equivalent dose), EAR (excess absolute risk) and LAR (lifetime attributable risk) are computed. A risk model for radiation induced cancer was successfully integrated in a treatment planning system. Several risk coefficients can be viewed and used to obtain critical situations where a plan can be optimised. Risk-volume-histograms and organ specific risks were calculated for different treatment plans and were used in combination with NTCP estimates for plan evaluation. It is concluded that the integration of second cancer risk estimates in a commercial treatment planning system is feasible. It can be used in addition to NTCP modelling for optimising treatment plans which result in the lowest possible second cancer risk for a patient.

1. Introduction

In several major analyses of the atomic bomb survivor data a dose-response relationship for radiation carcinogenesis up to one or two Gy has been quantified. This low dose range is important for radiation protection purposes. For the estimate of radiation induced cancer risk it is also important to know the shape of the dose-response curve for higher dose ranges. A dose-response model for radiotherapy relevant dose ranges can be achieved by combining the linear-no-threshold model (LNT) derived from the atomic bomb survivors from Hiroshima and Nagasaki with cancer risk data available from about 30,000 patients with Hodgkin’s disease who were irradiated with localized doses of up to around 40Gy.

Especially for children and adolescent patients, who were treated with radiotherapy, second cancer risk is one of the important side effect, as other side effects are reduced by using of organ sparing treatment techniques, like IMRT, VMAT or IMPT, developed in the last decade. To minimize radiation induced cancer risk corresponding analyzing tools should be available in the treatment
planning process selecting an appropriate treatment plan for the patient. However in recent treatment planning systems this criterion is not subjected.

2. Methods
A dose-response model [1] for carcinoma induction, whose dose ranges are valid for radiotherapy treatment, was integrated into a commercial treatment planning system (Eclipse 11.0, Varian) using the Eclipse Scripting API 11.0 class library. Based on the three-dimensional dose distribution the risk equivalent dose distribution (RED(D)), including cell killing, fractionation and repopulation/repair effects, was calculated. RED is a parameter measured in Gy proportional to second cancer risk. Besides a dose-response model for carcinoma induction,

\[
RED(D) = \frac{e^{-\alpha'D}}{\alpha'R} \left( 1 - 2R + R^2 e^{\alpha'D} - (1-R)^2 e^{-\frac{\alpha'R_D}{R}} \right),
\]

an additional model for sarcoma induction was implemented [2]

\[
RED(D) = \frac{e^{-\alpha'D}}{\alpha'R} \left( 1 - 2R + R^2 e^{\alpha'D} - (1-R)^2 e^{-\frac{\alpha'R_D}{R}} - \alpha' RD \right),
\]

where it assumed that the tissue is irradiated with a fractionated treatment schedule of equal dose fractions \(d\) up to a dose \(D\). The number of cells is reduced by cell killing which is proportional to \(\alpha'\) and is defined using the linear quadratic model

\[
\alpha' = \alpha + \beta d = \alpha + \beta \frac{D}{D_T} d_T,
\]

where \(D_T\) and \(d_T\) is the prescribed dose to the target volume with the corresponding fractionation dose, respectively. The repopulation/repair parameter \(R\) characterizes the repopulation/repair-ability of the tissue between two dose fractions and is 0 if no and 1 if full repopulation/repair occurs. The \(R\) values for the different tissues were taken from [2]. It is assumed here an \(\alpha/\beta = 3\)Gy for all tissues.

Based on the RED-Volume histograms (REDVH) several organ specific risk coefficients are computed. The excess absolute risk (EAR) is factorized into the dose-response function RED(D) and a modifying function \(\varphi(\text{agea}, \text{agex})\) that depends on the variables age at exposure (agex) and age attained (agea), including a gender specific factor and the organ specific incidence value \(\mu\):

\[
\text{EAR} = \frac{1}{V_T} \sum_i V(D_i) \cdot \beta \cdot \text{RED}(D_i) \cdot \mu(\text{agex}, \text{agea})
\]

with the total organ volume \(V_T\), the bins of the dose-volume histogram \(V(D_i)\) and dose \(D_i\) of the voxel \(i\) of the organ.

The organ equivalent dose (OED) [2]:

\[
\text{OED} = \frac{1}{V_T} \sum_i V(D_i) \cdot \text{RED}(D_i)
\]
is a dose-response weighted dose variable averaged over the whole organ volume. OED values are independent of the initial slope $\beta$ and the modifying function $\mu$. Its corresponding uncertainties are at a minimum.

At last the lifetime attributable risk (LAR) [3] :

$$LAR = \int_{\text{age} x} \text{EAR}(D, \text{age} x, \text{age} a) \frac{S(\text{age} a)}{S(\text{age} x)} d(\text{age} a)$$ (6)

with the conditional probability $S(\text{age} a)/S(\text{age} x)$ of a patient alive at age $\text{age} x$ to reach at least age $\text{age} a$ are calculated for different organs.

In addition to the risk coefficients EAR, OED and LAR of different organs the organ specific RED-volume histograms were computed.

3. Results
The TPS-integrated risk model was tested with a typical Hodgkin treatment. Using the Alderson phantom three different Hodgkin plans were prepared. The first plan (MA) is a classical mantle field technique treatment displayed in figure 1, the second one includes involved fields (IF) and for the third an involved node (IN) technique was used. The calculated risk coefficients are showed in figure 2.
Figure 2. Risk coefficient evaluation (LAR, EAR, OED and RED-volume-histogram) of three different Hodgkin patient plans: 1) mantle field (MF), 2) involved field (IF) and 3) involved node (IN) technique.

For MA the computed LAR for breast and lung cancer was 12.4% and 18.6%, respectively. The calculated risks are in satisfying agreement with literature data of historical mantle field treatments [4, 5]. The expected potential risk improvement for the involved field respectively the involved node techniques are confirmed by LAR values of 4.4% for breast cancer and 13.8% for lung cancer and respectively 2.7% and 8.8% for the IN plan. On the right side of figure 2 the RED-Volume histograms for the breast are shown. EAR is calculated for age 30 and age 60 years.

The calculated risks allow to judge different treatment plans with regard to second cancer induction and to choose the best plan with regards to second cancer risk.

4. Discussion

The model described by Equation (1) and (2) include several assumptions to simplify the biological processes leading to cancer induction. This includes the design of tissues, the repopulation process and processes which result in the formation of a tumor cell. This was done to keep the number of model parameters at a minimum. However, this is associated with uncertainties.

One assumption of the presented model is that single dose fractions of a radiotherapy treatment are treated independently. Therefore the linear-no-threshold theory for cancer induction could be applied to each single dose fraction. Although this may be valid for a single exposure lower than 3Gy, it is not clear whether it can be applied for dose fractions which are separated by days when in fact not all cells are fully repaired.

It is also not clear whether the same cell kill parameter $\alpha'$ applies for normal cells and transformed cells as it is applied in Equation (1) and (2). It may be necessary to use a different $\alpha'$-values.

Another assumption made here is that all biological processes occur instantaneously. It is known that in contrast to the physical processes involved, the biological changes act on a longer time scale. To account for such time delays, in particular for repopulation, a feed-back term in the differential equations would be required.
Many problems and uncertainties are involved in modelling the underlying biology of radiation induced cancer. However, since the models are used for a relative comparison of different treatment plans regarding cancer induction the uncertainties are smaller than for if the models are used for absolute cancer risk estimates.

5. Conclusion
A risk model for radiation induced cancer was successfully integrated in a treatment planning system. Quantitative risk values like OED, EAR and LAR were calculated. It is concluded that the integration of second cancer risk estimates in a treatment planning system is feasible. The risk coefficients can be easily attained during the planning process by one additional click. The plan evaluation tool can be used in addition to NTCP modeling for optimizing treatment plans which result in the lowest possible second cancer risk for a patient.

References