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Radiobiological Aspects in Determination of Residual Normal Tissue Tolerance Doses for Various Re-irradiation Scenarios

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Abstract: *Introduction.* The current state of re-irradiation in radiation oncology is characterized by the high heterogeneity of re-irradiation practices between institutions. The implementation of imaging methods and new irradiation techniques has created scope for the development and application of more accurate re-irradiation procedures associated with the use of radiobiological modelling, that are allowing often the replacement of palliative intent by radical. Therefore, the preparation of a planning protocol for re-irradiation is a significantly more complex process than for primary treatment planning. It requires quantified dose-volume records from primary and second series, radiobiological knowledge of the regeneration capacity of organs at risk (OaR) and using an appropriate SW-tool for modelling tumour control probability (TCP) versus normal tissue complication probability (NTCP) from individual DVH and pause between series taking into account significant differences in OaR regeneration capacity. Significant restoration takes place within 3-6 months e.g. in the skin, spinal, cord, brain, brain stem and lungs. Other tissues, e.g. kidneys, heart, bladder, have only a small regenerative capacity. This knowledge should be included in the process of preparing a re-irradiation protocol for an individual patient. *Purpose:* In this contribution we present - an overview of residual tolerance doses for selected OaR in the measure% $EQD2_{cum}$ (biologically equivalent dose of 2 Gy in percents) for 15 - the most critical OaR extirped from retrospective studies (e.g.%$EQD2_{cum}$ for brain stem, spin cord and bladder are 170%, 140%, 125%, respectively). *Material and methods:* A description of simultaneous determination of residual doses in re-irradiation with an original OaR regeneration model (REG_{pause}) by the authors of paper included into the calculation of the normal tissue complication probability (NTCP) for individual irradiation scenarios of re-irradiation using the "BioGray" program developed in the workplace of authors. *Results:* A demonstration of the benefits of the tumour control probability (TCP) versus NTCP prediction depending on the location and volume of the clinical tumour volume (CTV) in the primary and second series. *Conclusion:* The use of the methodology of radiobiological modelling brings a shift from paradigm of verbalism and estimations in the management of re-irradiation to quantitative evaluation of these processes and utilization of translation research knowledge linked to the current technological possibilities of application IMRT, VMAT, SRS/SBRT and proton therapy.

Keywords: Re-irradiation, Cumulative EQD2, REG_{pause}, NTCP, SW BioGray

1. Introduction

The issue of re-irradiationing cases of relapse of cancer or infield of secondary malignancies is a significantly more demanding decision-making process in assessing its benefit versus risk to the patient compared to the process of initial radiotherapy. While retrospective studies provide an estimate of the tolerable cumulative doses per OaR [1, 2, 4-6, 11, 12, 15, 18] they do not provide algorithms and methods for determination ofthe residual tolerance doses in complex individual clinical scenarios of re-irradiation.

The expert panels in the works [7, 12] after targeted multi-institutional surveys of the management of re-irradiation procedures in both H&N and extra-cranial tumors concluded

that the status quo is characterized by:

1. high heterogeneity of re-irradiation practices between institutions!
2. Insufficient data from retrospective studies.
3. Critical selection of patients for re-irradiation.

Expert groups from the above reviews recommended compliance with the following conditions for the indication of re-irradiation:

1. Contra-indications to surgery.
2. Vorable localization of relapse or secondary tumors.
3. Re-irradiation with a curative intent requires EQD2 >= 60Gy should be.
4. Associated with chemotherapy (including biological therapy).
5. Realistic options for minimizing the dose in OaR.
6. Sufficient interval from initial RT >=6 months.
7. A well-defined volume of relapse or secondary tumor (CTV).
8. Use of more advanced therapeutic technologies and hypo-fraction modes (IMRT, VMAT, SRS, FSRT, proton therapy).

In the context with these recommendations, setting an acceptable plan for the second series with a palliative or curative intent is actually the solution of the multi-parameter NTCP function with parameters:

$$NTCP = F(BED_1, DVH_1, REG_{pause}, BED_2, DVH_2) \quad (1)$$

where

DVH_1 and DVH_2- available from treatment planning systems (TPS);

BED_1 and BED_2 – biological effective doses in series 1 and 2;

REG_{pause} is the OaR regeneration model described below.

Addressing this complex task requires a quantifiable inclusion and simultaneous assessment of these parameters not only from TPS, but also the use of appropriate software for radiobiological modeling BED / EQD2 and biostatistic measures TCP/NTCP. For calculation of mentioned measures in our program BioGray we use the models described at the work [9]. Unfortunately, such a tool is not standard equipment for radiotherapeutic centres at present.

2. Purpose

The purpose of the contribution is to provide:

1. A tabular overview of residual tolerance doses in EQD_2 for selected OaR determined from retrospective re-irradiation studies.
2. A description of analytical model REG_{pause} for calculation of residual tolerance dose to OaR.
3. A demonstration of the benefits of TCP/NTCP simulation depending on the location and volume of CTV in the primary and second series.

3. Material and Methods

From retrospective studies [1, 2, 4-6, 11, 12, 15] it was found that late-response tissue and organ regeneration (OaR) allows the application of the second series up to 50-80% of BED in relation to initial series. This means that if the organ tolerance level in the first series has already reached the accepted tolerance threshold, in the second series OaR may tolerate a cumulative dose of BED at 150-180% initial. In a situation where the organ in the first series was irradiated only at the level of e.g. 50% of its tolerance the dose in the second series may be applied substantially higher (by the calculated difference in the level of tolerance not achieved). The volume dependence of OaR tolerance in re-irradiation, the interval between initial radiotherapy and re-irradiation also play a very important role. OaR regeneration is predominantly saturated within 2 years. [2, 9]

In order to estimate or determine the residual tolerance of OaR, author at the work [18] proposed the concept of so-called "cumulative percentage dose" (hereinafter$\%BED_{cum}$), which can be expressed by:

$$\%BED_{cum} = \%BED_{1.series} + \%BED_{retr.} \quad (2)$$

Relationship $\%BED_{retr.}$ versus $\%BED_{1.series}$ for four selected tissues (skin, lung, spinal cord, kidney) is demonstrated in the figure 1.

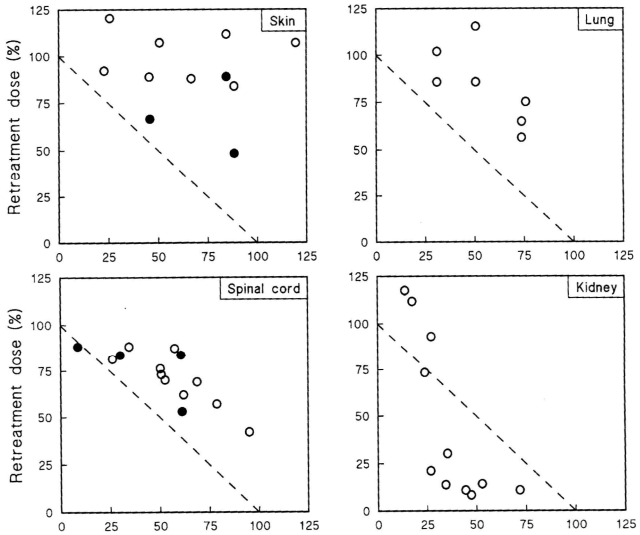

Figure 1. *Demonstration of the% BED_{retr} vs.% $BED_{1.series}$ for some tissues.*

Interpretation: Coordinate X determines the initial dose size as a percentage of the tolerance dose for *the monitored OaR*, the Y-coordinate determines the applied dose as a percentage of initial series, the intermittent line represents the level of tolerance in hypothetical - zero tissue regeneration. The points above the dashed line represent the successful results of the re-irradiation, the points below the dashed line represent the results of insufficient regeneration capacity of the organ (e.g. kidney - source: Stewart 2006) (18).

The radiobiological quantity of BED is more often expressed at the value of the NTD (a normalized total dose) or EQD2 (a biologically equivalent dose of 2 Gy per fraction) defined by the relationship:

$$NTD = EQD_2 = \frac{BED}{RE} = N_{new} \cdot d_{new} \cdot \frac{(d_{new} + \alpha / \beta)}{(2 + \alpha / \beta)} \quad (3)$$

where RE expresses the relative efficiency of the new fractionation in the form:

$$RE = (1 + d_{new}/(\alpha/\beta))$$

N_{new} = selected new number of fractions d_{new} = selected new dose/fraction α/β = coefficient of radiosensitivity.

For late reacting tissues is a generally accepted value α/β = 3Gy except for the spinal cord where α/β = 2 Gy.

From a retrospective study [11] on brain re-irradiation in 3 therapeutic modalities - conformal external therapy (CRT), stereotactic surgery (SRS) and fractionated stereo radiotherapy (FSRT), data were obtained on the amount of the tolerated cumulative dose expressed in EQD_2 that did not lead to brain radio-necrosis. The results are summarized in the table 1.

Table 1. *Results of retrospective analysis – tolerance of brain during re-irradiation.*

Type of modality	Accepted EQD2 (brain)	Cumulative EQD2 (brain)	Cumulative EQD2 in% initial dose
CRT	60 Gy	< 80 - 100 Gy	< 133 – 170%
SRS	60 Gy	< 90 - 140 Gy	< 150 – 233%
FSRT	60 Gy	< 112 -137 Gy	< 186 – 228%

The above retrospective analysis provided two other significant conclusions:

1. There is no correlation in the occurrence of radionecrosis and the length of the interval between initial radiotherapy and the second series.
2. There is a statistically significant correlation between the occurrence of radionecrosis and irradiated brain volume (p=0.016).

The following conclusions were drawn at the work [17] devoted to retrospective analysis of re-irradiation of spinal cord*:*

1. Permissible $EQD_{2(cum)}$ <=60 Gy (% $EQD_{2(cum)}$ <= 140%).
2. No significant correlation of radiation myelitis has been established at an interval greater than 1 year.

At the work [4] the acceptable cumulative doses for additional OaR were described. Those database been converted (for consistency with data in the table 1.) to the EQD2. The table 2 contains data for OaR in H&N region, the table 3 for OaR in extra-cranial area.

Table 2. *Cumulative and residual tolerance doses in EQD2 for H&N region.*

Organ at Risk	InitialEQD2 (Gy)	Cumulative EQD2 (Gy)	Cumulative EQD (in%)	Acceptable residual EQD2 (for pause = 1 year)
Brain **	60	100	170	<=40
Brain stem**	54	80	150	<=36
Spinal cord ***	44	60	140	<=17
Opt. nerve / chiasma***	50	66	150	<=8
Retina***	45	63	140	<=18
Eye lens ***	9	12	130	<= 3
H&N soft tissues **	60	96	160	<=36
Parotid***	32	45	150	<=13
Mandible (TMJ)**	60	84	160	<=24

Legend: *= partial volume 1/3, **=partial volume 2/3, *** whole volume.

Table 3. *Cummulative and residual tolerance doses in EQD2 for OaR in extracranial area.*

Organ at Risk	Initial EQD2 (Gy)	Cumulative EQD2 (Gy)	Cumulative EQD2 (in%)	Accepted residual EQD2 (Gy) (pause >= 1 year)
Heart *	60	80	133	<=20
Great vessels **	60	100	160	<=40
Lung **	35	56	160	<=21
Esophagus	55	74	135	<= 9
Rectum***	60	96	160	<=36
Bladder ***	65	72	110	<= 7
Femoral Head***	52	71	140	<=18

Legend: * partial volume 1/3, **partial volume 2/3, *** whole volume.

It should be noted and stressed that the estimation of tolerance residual doses in the last column of the tables 2 and 3 represent only the first gross approximation related to the following conditions:

1. The initial RT series were administered at the limits of the OaR tolerance dose (column 2).
2. It is set to pause between series >=1 year.
3. It does not include variability of OaR tolerance depending on irradiated OaR volume.
4. The limits of residual tolerance doses of OaR are considered to be identical with partial volume quoted in the first column of the table.

From the above it follows that residual tolerance doses may be significantly higher at the lower dose-volume load of

OaR in the initial series, but also in the re-irradiation series. These dependencies can be comprehensively addressed only using a suitable software involving real data from DVH, EQD2 calculations and a real pause between series.

Using extirped data from retrospective studies summarized in the tables 2 and 3 on acceptable cumulative%EQD2, we attempted to develop an analytical model that could allow the calculation of the residual tolerance dose and simulate NTCP prediction in the clinical scenarios.

Regeneration Model REG$_{pause}$

Recovery at OaR with a late response begins after 7-8 weeks from the start of radiotherapy and ends mostly after 2 years. However, this process of tissue regeneration is not linear. Therefore, the authors of the paper proposed an analytical model that replaces the linear regeneration aproximation with a sigmoidal curve expressed by the Poisson function in the form of:

$$F(x) = \sum_{i=?1}^{x} \frac{\exp(d_{\inf}) / d_{\inf}^{x}}{i!} \quad (4)$$

where

x = number of days on pause between initial and second series d_{inf} = dose in inflexion point on sigmoidal curve (in Gy)

The application of the model REGpause is presented in the Figure 2 for spinal cord.

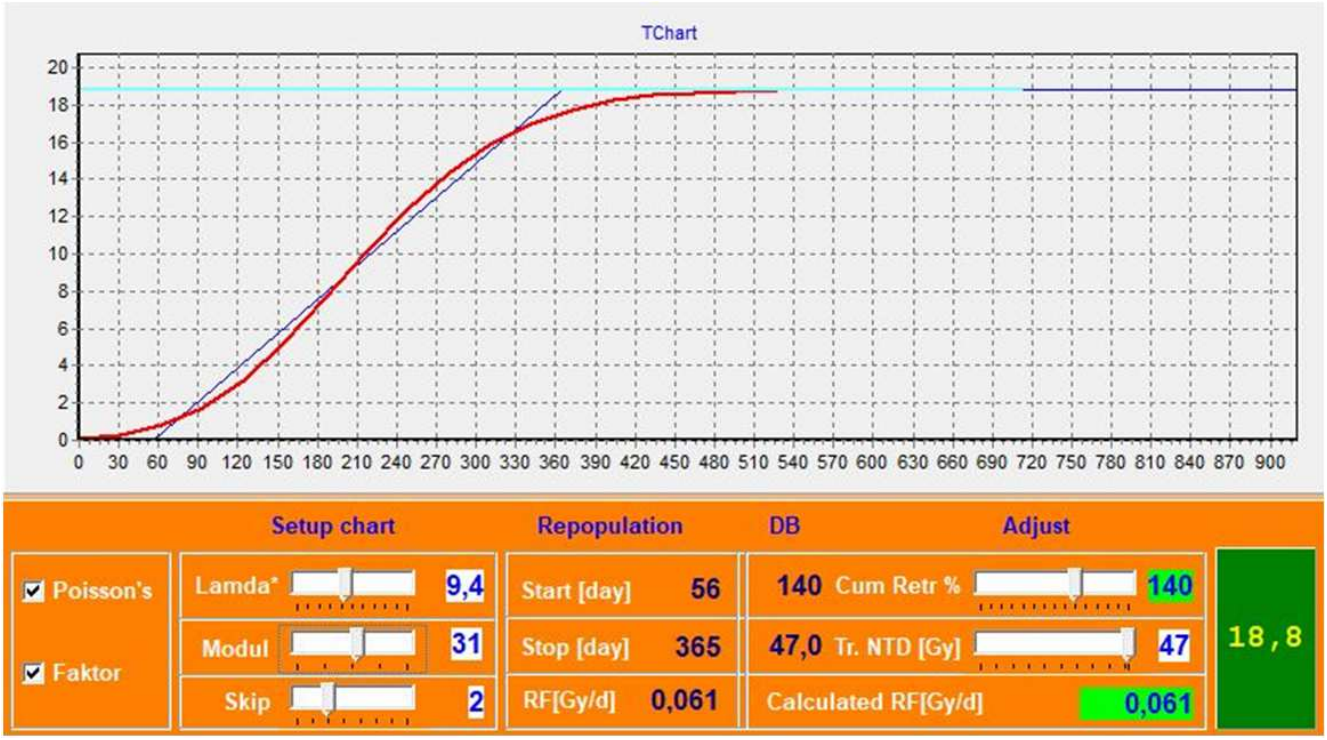

Figure 2. *Graphical presentation of the model REG$_{pause}$ for determination of residual tolerance dose in re-irradiation of the spinal cord.*

By fitting the model constant at the inflection point (d_{inf} = λ= 9,4 Gy) from experimental data [17]. The residual tolerance dose can be determined for any time interval between the first series and the re-irradiation.

Example: When we are applying full spinal cord tolerance EQD2= 47 Gy in the initial seriesforre-irradiation after 6, 12, 18 months the residual tolerance dose reaches: 7,8Gy, 17,5Gy and 18,8Gy, respectively. The residual tolerance dose at greater pause is no longer increased.

The parameters of Poisson's function F(x) for residual tolerance doses of other OaR listed in table 2 and 3 have been obtained using the same procedure as shown for the spinal cord in the figure 2. These data will be gradually refined from new clinical data from retrospective studies. The REG$_{pause}$calculation algorithm is implemented in the SW BioGray and in an interactive dialogue (by changing the number of fractions or dose pre fraction) the different scenarios can be simulated for an optimal re-irradiation plan.

4. Results

The use of the proposed REG$_{pause}$ model for determination of residual tolerance dose in re-irradiation is demonstrated in the example of re-irradiation of a patient with Ca laryngis. The patient received primary treatment with TD = 70 Gy in 35fr./2Gy. (25fr./2Gy +boost 10fr./2Gy). After 23 months, there was an indication of secondary malignancies with CTV localisation displaced cranially by 3.5cm. The re-irradiation plan consisted of the radiotherapy with the curative intent of TD =70 Gy in 35fr. /2 Gy. The Figure 3. shows isodose plans with CTV applied in the first series in 2015 and the second series in 2017.

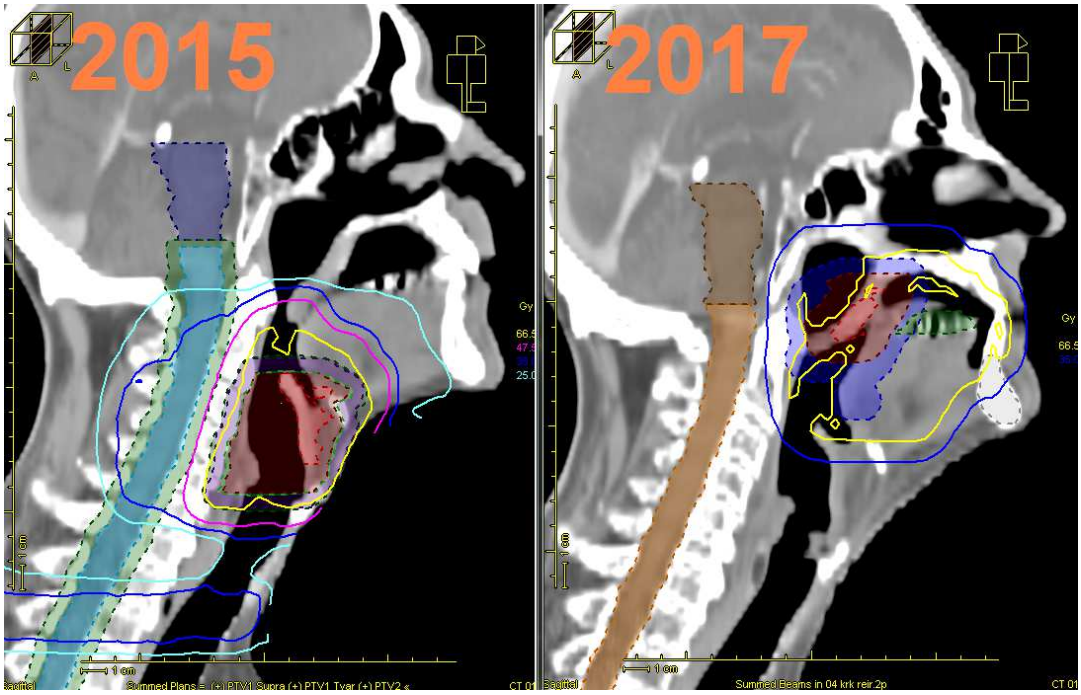

Figure 3. *Lateral isodose plans from the initial series in 2015 and re-irradiation in 2017.*

It is clear from the pictures that the CTV of secondary malignancies is shifted cranially by 3,5 cm, in which the treatmentplan already causesa minimal load on the spinal cord during re-irradiation. From DVH_1 statisticsof the initial series we received $D_{max(spin.cord)}$= 47 Gy. From DVH_2 statistics of the treatment plan in second series – 35fr./ 2Gy we receive $D_{max(spin.cord)}$ = 9 Gy.

The output of TCP/NTCP from SW BioGray for real scenario – different CTV is shown in the figure 4. Applications of the SW Biogray are described at the works [8-10].

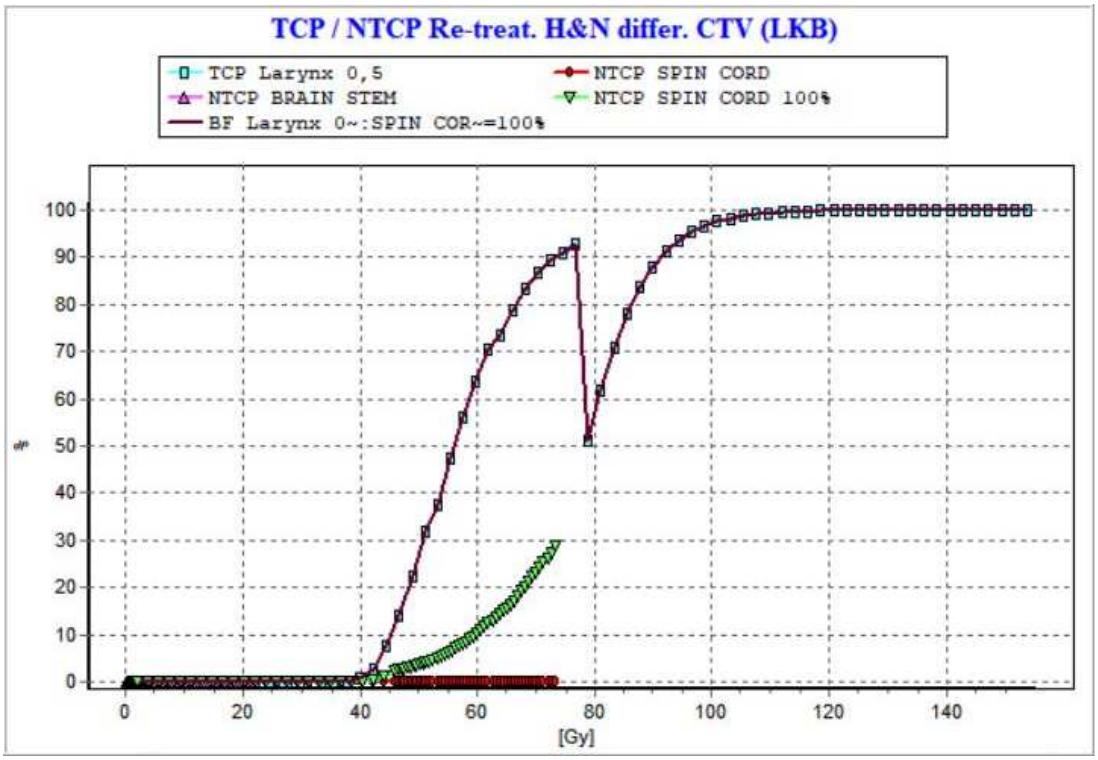

Figure 4. *Outputs of TCP/NTCP for real scenario – different CTV in initial and second series (SW BioGray). $NTCP_{spin.cord}$= 0%(red curve).*

Note 1: In the figure 4. is also displayed an NTCP curve that responds to a hypothetical situation - if the spinal cord would have no regenerative capacity ! In this case, the NTCP prediction would be =30%. (green curve).

In the figure 5 is shown the output of the TCP/NTCP for a hypothetical scenario – when CTV matches in series 1. and 2. which would result in a high dose load on the spinal cord and thus exceed its tolerance (EQD2 = 66Gy; NTCP= 33.2%)!

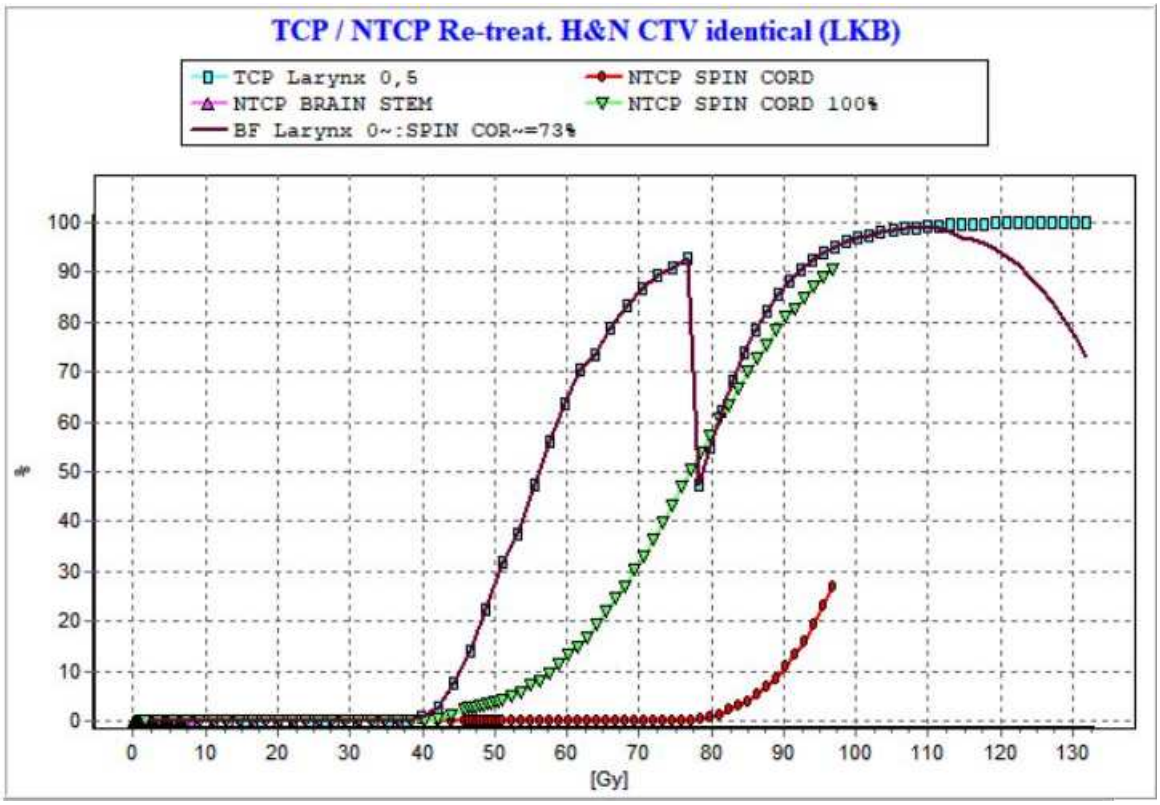

Figure 5. *Output of TCP /NTCP for a hypothetical scenario - (CTV are the same in both series), NTCP $_{spin.cord}$ = 28%(red curve).*

Note 2: In the figure 5 is also displayed a hypothetical situation - when the spinal cord would be without regeneration capacity. Then NTCP would be = 93% ! (green curve).

Comment and summary: The outputs TCP/NTCP allocate on crucial significance of CTV locations in initial and second series. When the position of the new CTV is markedly different the residual tolerance dose of OaR can be sufficiently higher for the second series which made it possible to apply re-irradiation with the curative intent. In not the case there exists a risk of overrun of tolerance.

5. Discussion

Current data from the knowledge base on re-irradiation is still insufficient. There is a lack of works with a more detail description of re-irradiation management including available radiobiological knowledge. International recommendations do not include base knowledge data from observed outputs of accepted cumulative EQD2. The first quatitative outputs in the measures EQD2 offer the works [5, 6, 10, 11, 17, 19]. Our contribution is an attempt quantitatively to assess the complex relationships in the re-irradiation process-using dose - volume statistics and the use of mathematical models to describe the OaR regeneration processes and their implementation in the NTCP calculation.

The use of the methodology of radiobiological modeling could bring a shift from paradigm of verbalism in the management of re-irradiation to quantitative evaluation of these processes and utilization of knowledge from translational research linked to the current technological possibilities of application of re-irradiation by techniques IMRT, VMAT, SRS/SFRT and proton therapy.

6. Conclusion

The quantification of residual tolerance doses to OaR from retrospective studies and the implementation of the proposed REG_{pause} model describing the time dependence of OaR regeneration after initial radiotherapy and the use of dose-volume histograms (DVH) from TPS opens up possibilities for more detailed radiological analysis in the measure EQD2 and biostatisical measures TCP/NTCP with the simulation of various scenarios in the decision-making process in re-irradiation.

The model REG_{pause} and computing procedure is currently embedded in the SW BioGray developed by authors and that option has become available to its users. The need for further targeted research in the management of re-irradiation using the tools currently provided by the "queen of sciences" - mathematics in various fields of medicine, including radiation oncology.

Competing Interest

The authors declare that they have no competing interests.

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