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THE INFLUENCE OF RADIOBIOLOGICAL MODELS IN EVALUATION OF A TREATMENT PLAN REGARDING THE RISK OF TOXICITY OF NEURAL STRUCTURES IN A PATIENT WITH GLIOBLASTOMA TREATED WITH RADIOTHERAPY

BY

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Abstract. For a patient with fronto-parietal glioblastoma treated with radiotherapy, four different treatment plans, two with IMRT and two with 3D-CRT, have been analyzed.

All treatment plans were compared based on dose-volume histograms, coverage of the target volume and dose received by the OARs in order to establish which one had the best results.

We observed that one of the 3D-CRT plans was approved based on the already mentioned standards, as the best option available. Once the normal tissue complication probability was calculated, we found that for some organs, the risk of toxicity, although the evaluation of dose volume histograms did not suggest an increased risk, was higher in the approved plan.

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It is important to take into consideration the NTCP for a better review of the risks that are most likely to appear after a shorter or a longer period of time, which will affect the patients' quality of life.

Keywords: fronto-parietal glioblastoma; IMRT; 3D-CRT; risk of toxicity; NTCP.

1. Introduction

For oncologists, high-grade gliomas (HGGs) is a very frustrating topic, as no significant progress has been made since the addition of Temozolomide (TMZ) concomitant and adjuvant to radiotherapy (Dhermain, 2014).

Glioblastoma is the most aggressive and frequent brain glial tumor. Standard treatment consists of surgery followed by radiotherapy concomitant with Temozolomide. Using high doses (60Gy) and irradiating large volumes (with 2-2.5 cm margins) around porencephal cavity makes it even more difficult to protect the OARs, such as brainstem, optic chiasm and optic nerves.

Afterwards, the risk of neuropathy was calculated with the help of radiobiological models such as Lyman-Kutcher Burman and EUD.

2. Materials and Methods

For a 57-year-old patient diagnosed with left parieto-occipital glioblastoma, with oligodendroglial component, concomitant postoperative radiotherapy has been proposed. Four treatment plans were proposed, 2 obtained using a 3D conformational and 2 with IMRT technique.

The patient was planned for radiotherapy up to 60Gy along with concurrent Temozolomide (75 mg/m^2). The patient was positioned with a thermoplastic immobilization mask system and 3 mm CT scans of the head were obtained.

The European Organization of Research and Treatment of Cancer (EORTC) recommended a single-phase of 30 fractions with 2Gy/fraction technique. The GTV was defined on preoperative CT/MRI as the region of enhancement (without edema) or the surgical tumor BED plus any residual enhancing tumor that is seen on the planning scan for surgical treated patients using image fusion and rigid registration algorithm between of pre- and postoperative MRI/CT (Fig. 1).

The Clinical Target Volume (CTV) was defined from the Gross Target Volume (GTV) adding an isotropic margin of 2 - 3 cm, but this margin can be reduced in anatomical regions where tumor dissemination is unlikely. The planning target volume (PTV) was created adding a 0.5 to 0.7 cm, depending on systematic and random errors in dose delivery (Dhermain, 2014).

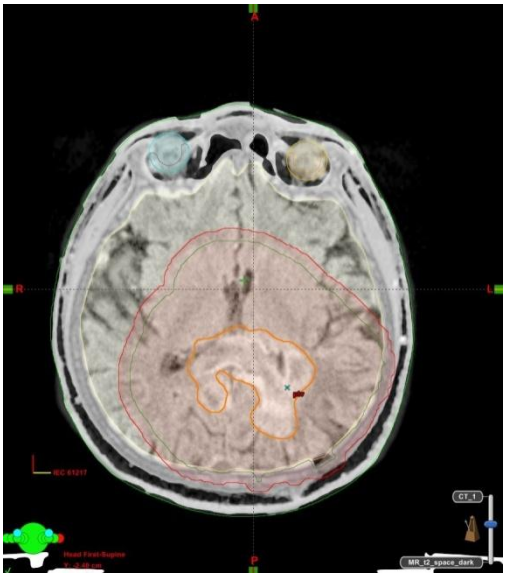

Fig. 1 – Image fusion and rigid registration between diagnostic MRI and CT simulation- target volume delineation.

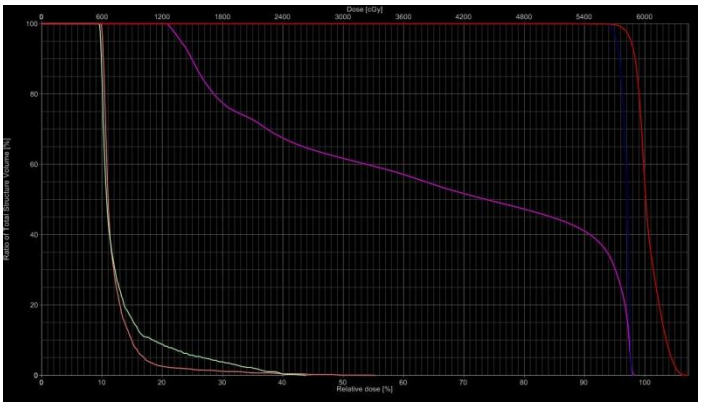

Fig. 2 – DVH curves for OARs (3D approved plan; light orange- left optic nerve, white- right optic nerve, purple- brainstem, blue- chiasm, red- PTV).

Following the treatment plan evaluation (coverage of the target volume, PTV, doses for OARs and dose-volume histograms) the treatment plan based on the 3D technique with a 6 MV beam was chosen (Fig. 2).

One of the plans prepared using the 3D-CRT technique, which was also among the approved ones, had the following characteristics: it was built on the 10 MV accelerator, the energy used was 6 MV, the total dose prescription was

60Gy delivered in 30 fractions with 2Gy/fraction. Five fields were used, the monitor units (MU) varied from 18 to 137, and 95% of PTV was covered by 97.68% of dose. The other 3D-CRT plan was completed on the 15 MV accelerator, the energy used was 6 MV and had the same fractionation. Five fields were used here also, MU varied from 18 to 136 and 95% of PTV was covered by 97.43% of dose. One of the plans made with the IMRT technique was delivered on the 10 MV accelerator, with a beam of 6 MV energy, same fractionation as the other two mentioned above. Here 7 fields were used, MU varied from 73 to 122 and 95% of the PTV was covered by 93.5% of dose. The other plan made by IMRT technique was made on the 10 MV accelerator, with a beam of energy of 6 MV, 9 fields were used this time, and 95% of the PTV was covered by 96% of dose (Fig. 3).

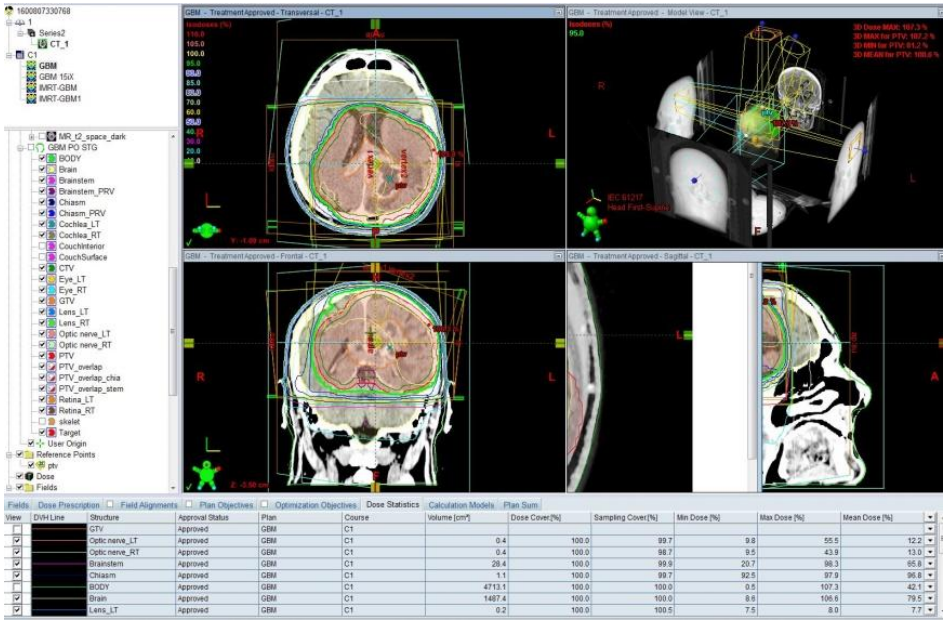

Fig. 3 – Glioblastoma 3D treatment plan (images from TPS eclipse).

Subsequently, the risk of neuropathy was calculated with the help of radiobiological models such as Lyman-Kutcher Burman (LKB) and EUD. One can use them to compute normal tissue complication probability (NTCP) and tumor control probability (TCP). The results are displayed in percents.

Parameters used for the LKB model are *TD*50, number of fractions, *n*, *m*, α/β and dose per fraction. The formula that describes the Lyman-Kutcher Burman model is

$$NTCP=\frac{1}{\sqrt{2\pi}}\int_{-\infty}^{t} e^{\frac{x^2}{2}}\,dx \qquad (1)$$

where

$$t = \frac{D_{ef} - TD_{50}}{mTD_{50}} \tag{2}$$

and

$$D_{ef} = (\sum_i v_i D_i^{1/n})^n \tag{3}$$

Parameter *n* determines the dose-volume dependence of a tissue and thus accounts for differences in tissue architecture; *m* controls the slope of the dose-response curve; *TD*50 represents the dose at which there is a 50% chance of complication, and thus dictates the position of the dose-response curve (Warkentin *et al*., 2004). D_{ef} is the dose that, if distributed uniformly to the entire volume, will lead to the same NTCP as the real dose that unevenly distributed, and D_i is the dose given to a subvolume v_i.

The EUD model is described by the following formula:

$$NTCP = \frac{1}{1 + (\frac{TD\,50}{EUD})^{4\gamma 50}} \tag{4}$$

where the equivalent uniform dose is

$$EUD = (\sum_i v_i D_i^a)^{\frac{1}{a}}. \tag{5}$$

EUD is defined as the equivalent biological dose that, when distributed uniformly, will lead to the same biological effect as the real one given by the unevenly distribution of the dose. Also, *a* and γ_{50} are dimensionless parameters, *a* having specific values for each tissue.

For the normal tissue complication probability (NTCP) evaluation RADBIOMOD was used, an application using Visual Basic for Applications (VBA) for Microsoft Excel. It includes multiple mathematical models for biological radiotherapy plan evaluation, a free, user-friendly program that offers similar results to other radiobiological modeling programs (Chang *et al*., 2016).

For the evaluation, the DVHs for organs at risk are exported from the treatment planning program Eclipse, into ASCII format.

3. Results

The volumes in cmc of target volumes of the primary tumor (GTV, CTV and PTV) and D_{max} and D_{mean} for all treatments were compared (Figs. 4 and 5).

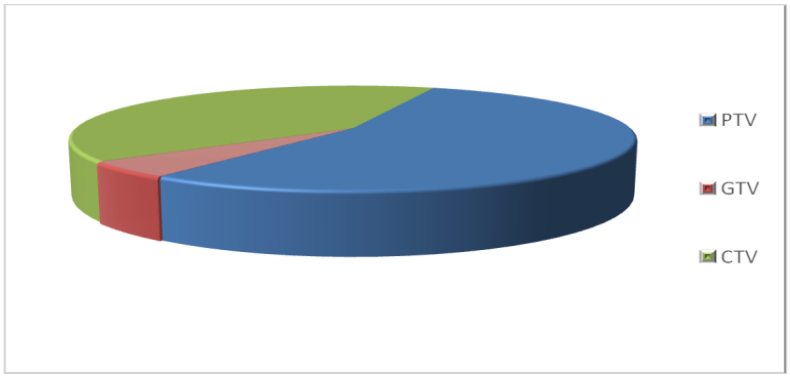

Fig. 4 – Graphic representation of Planning Target Volume (PTV), Gross Target Volume (GTV) and Clinical Target Volume (CTV).

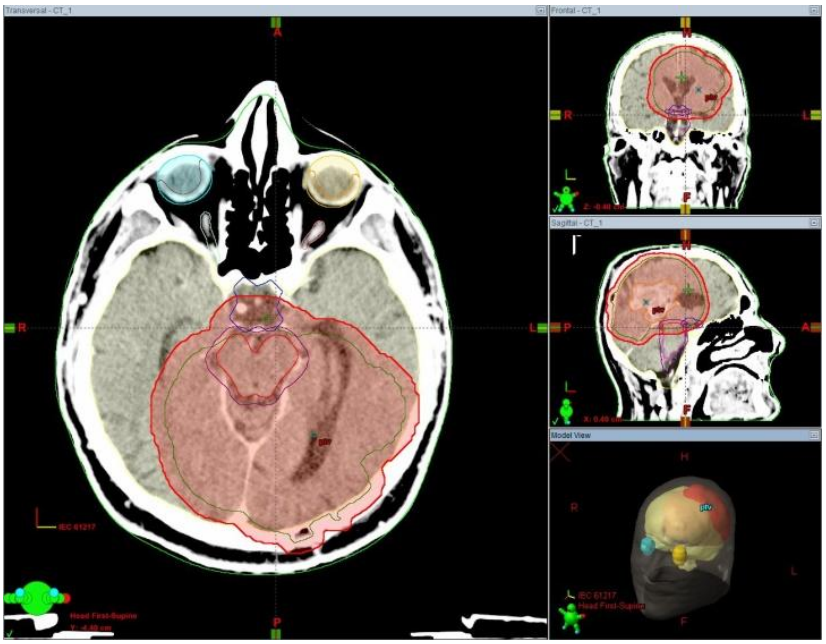

Fig. 5 – Target volumes and OARs for a glioblastoma radiotherapy plan.

For the brainstem, the maximum value of D_{max} was obtained for the 3D approved plan, (59Gy) and the maximum dose of D_{mean} for brainstem was 39.49Gy for the 3D approved plan. For chiasm, the maximum value of D_{max} was obtained for the 3D unapproved plan, 64.23Gy, and the maximum dose for D_{mean} was 58.1Gy, for the 3D approved plan (Figs. 6 and 7).

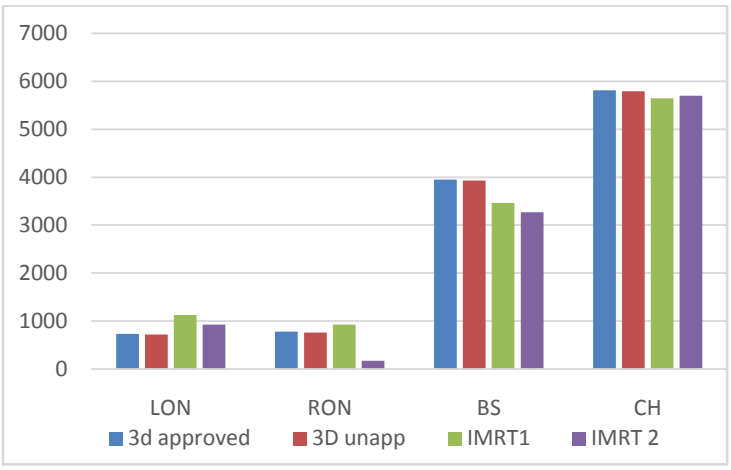

Fig. 6 – Graphic representation of Dmean for all 4 proposed plans
(blue- 3D approved plan; red- 3D unapproved plan; green- IMRT1; purple- IMRT2).

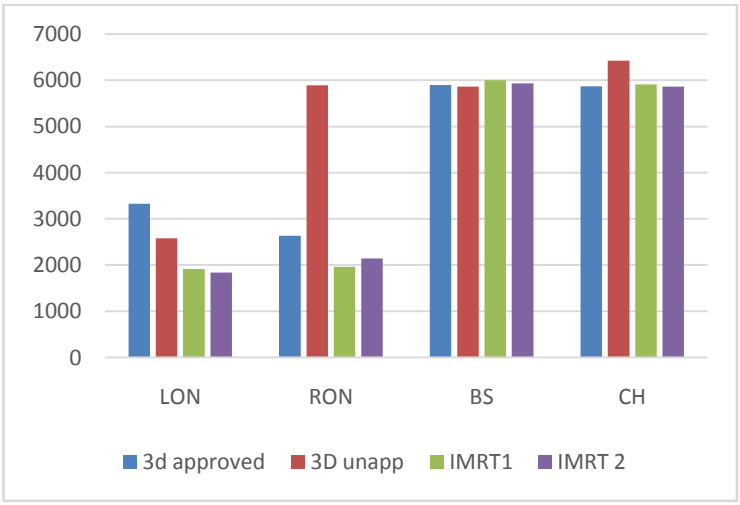

Fig. 7 – Graphic representation of Dmax for all 4 proposed plans
(blue- 3D approved plan; red- 3D unapproved plan; green- IMRT1; purple- IMRT2).

NTCP values evaluated by the LKB model for left optic nerve were 0% for all 4 plans, and also the same for the right optic nerve. For brainstem NTCP was 0.49% for the approved 3D plan, 28.92% for the unapproved 3D plan, 0.82% for one IMRT plan (IMRT 1), and 0.37% for the other IMRT plan (IMRT 2). For the chiasm, values were: 2.92% for the 3D approved plan, 2.59% for the 3D unapproved plan, 1.84% for IMRT 1, and 2.1% for IMRT 2 (Fig. 8).

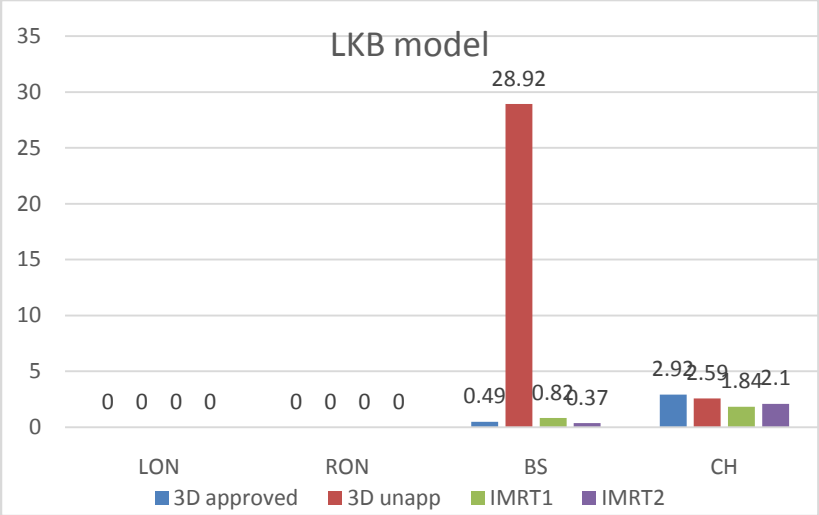

Fig. 8 – Graphic representation of LKB model values obtained for radiotherapy plans.

Different values were obtained when using EUD model. For the left and right optic nerve the values were equal to 0%. For brainstem, values were: 1.3% for the 3D approved plan, 22.49% for the 3D unapproved plan, 0.99% for IMRT 1 and 0.48% for IMRT 2. For chiasm we got 12.67% for the 3D approved plan, 11.93% for the unapproved 3D plan, 9.72% for IMRT 1 and 10.02% for IMRT 2 (Fig. 9).

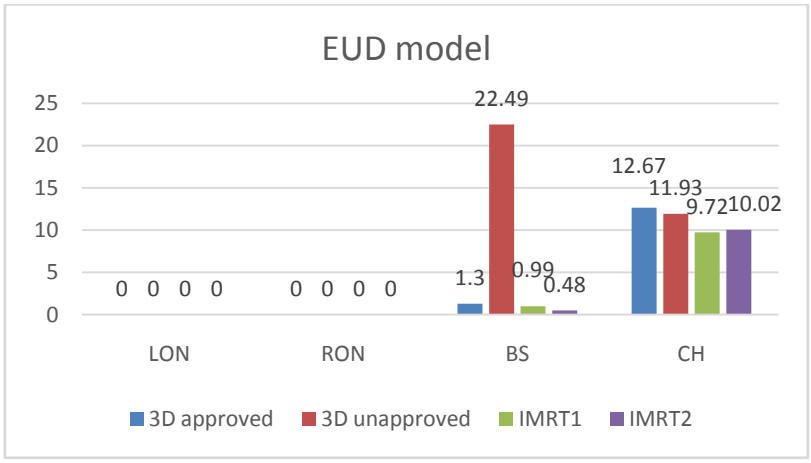

Fig. 9 – Graphic representation of EUD model values obtained for radiotherapy plans.

4. Discussions

In a cohort of 20 patients, Hermanto and coworkers demonstrated that IMRT maintained equivalent target coverage, and enabled dose reductions of neural structures: brainstem D_{mean} by 19.8% and D_{max} by 10.7%, optic chiasm D_{mean} by 25.3% and D_{max} by 22.6%, right optic nerve D_{mean} by 37.3% and D_{max} by 28.5%, and left optic nerve D_{mean} by 40.6% and D_{max} by 36.7% (Hermanto *et al.*, 2007).

Most of the studies have proved equivalence comparing 3D-CRT and IMRT for radiotherapy of glioblastoma in terms of target coverage, dose conformity an dose homogeneity (Wagner *et al*., 2009).

The damage to optical structures can lead to optic neuropathy with potential of blindness, but toxicity to the brainstem can have fatal consequences. The entire brainstem may receive up to 54Gy using conventional fractionation with limited risk of severe or permanent neurological effects. Smaller volumes of the brainstem (1-10 mL) may tolerate a D_{max} of 59Gy for standard fractionation (Scoccianti *et al*., 2015).

A number of studies have been published which investigated the use of IMRT technique in glioblastoma treatment, but the results are hard to analyze because the heterogeneity of the cases included. Some patients were treated for recurrent diseases and only in some cases chemotherapy was administrated. Aherne *et al*. observed a study including 31 patients treated with IMRT and 23 of there received chemo-irradiation with Temozolomide. The combination of IMRT at standard radiation doses with Temozolomide can lead to an increase in median overall survival. It may be possible that IMRT radiotherapy improves the quality of life of long-term surviving patients by reducing the dose to critical normal structures and normal brain tissue (Aherne *et al*., 2014).

Few studies were reported on the comparison of clinical outcomes between IMRT and 3D-CRT in the treatment of high grade gliomas. A study including 54 patients try to determine whether IMRT improves clinical outcomes related to 3D-CRT for glioblastoma radiotreated patients. With no significant difference for toxicities between this techniques results suggested that IMRT is unlikely to improve local control and overall survival compared with 3D-CRT (Chen *et al*., 2013).

5. Conclusions

A higher risk of brainstem toxicity corresponded to the approved plan, and a lower risk corresponded to an unapproved plan using the IMRT technique.

For minor differences between the values of D_{mean} and D_{max}, DVH and slide by slide evaluation of the dose curves, NTCP is a helpful tool for plan approval by the clinician.

In conclusion, even if the radiobiological models are not standard in the evaluation process of the treatment plan, under the circumstances of a complex dose distribution obtained through an IMRT technique, they can have a guiding role in therapeutic decision.

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INFLUENȚA MODELELOR RADIOBIOLOGICE ÎN EVALUAREA UNUI PLAN DE TRATAMENT PRIVIND RISCUL DE TOXICITATE A STRUCTURILOR NEURALE LA UN PACIENT CU GLIOBLASTOM TRATAT CU RADIOTERAPIE

(Rezumat)

Pentru un pacient cu glioblastom fronto-parietal radio-tratat, s-au analizat patru planuri diferite de tratament, două cu IMRT și două cu 3D-CRT.

Toate planurile de tratament au fost comparate pe baza histogramei doză-volum, acoperirea volumului țintă și a dozei primite de OAR pentru a stabili care dintre ele a avut cele mai bune rezultate.

Am observat că unul dintre planurile 3D-CRT a fost aprobat pe baza standardelor deja menționate, ca fiind cea mai bună opțiune disponibilă. Odată ce probabilitatea de complicații a țesutului normal a fost calculată, am constatat că, pentru unele organe, riscul de toxicitate, deși evaluarea histogramei volumului dozei nu a sugerat un risc crescut, a fost mai mare în cazul planului aprobat.

Este important să se țină seama de NTCP pentru o mai bună revizuire a riscurilor, care sunt cel mai probabil să apară după o perioadă mai scurtă sau mai lungă, ceea ce ar afecta calitatea vieții pacienților.