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Evaluation of doses in re-irradiation of the spinal cord: impact of the use of two different calculation algorithms - Acuros External Beam (AXB) vs Anisotropic Analytical Algorithm (AAA)

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INSTITUTO DE CIÊNCIAS BIOMÉDICAS ABEL SALAZAR

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“What you do makes a difference,
and you have to decide what kind of
difference you want to make.”

Jane Goodall

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RESUMO

Introdução: A re-irradiação de regiões comuns em diferentes tratamentos é um problema importante devido à dose cumulativa administrada nos órgãos em risco, podendo causar efeitos graves.

Objetivo: Este estudo foi desenvolvido em duas fases. O objetivo da primeira fase consistiu na avaliação e comparação de parâmetros de tratamento e doses administradas em casos de tratamento prévio de Radioterapia (RT) e re-irradiação envolvendo a medula espinal e o tronco cerebral, em pacientes tratados no Serviço de Radioterapia do Instituto Português de Oncologia do Porto, (IPO – Porto). Na segunda fase, foram recalculados os planos de tratamento previamente realizados com o Algoritmo Analítico Anisotrópico (AAA), mas desta vez com o algoritmo Acuros External Beam (AXB) para os casos analisados na primeira fase.

Métodos: Na primeira fase, foram incluídos 91 pacientes nos quais foram administrados dois ou mais tratamentos de RT com sobreposição da região na medula espinal ou tronco cerebral. Estes pacientes foram tratados na instituição entre setembro de 2008 e junho de 2019. Na segunda fase, foram incluídos 71 pacientes, totalizando 149 planos recalculados. Para o recálculo, foi utilizado o sistema de planeamento de tratamento Eclipse™ (Varian Medical Systems, Palo Alto) versão 13.5.

Resultados: Foram considerados três grupos, o grupo I e o II correspondem à irradiação da medula espinal e tronco cerebral, respetivamente, quando o volume-alvo está próximo destes órgãos. O grupo III corresponde à irradiação da medula espinal quando o volume alvo são metástases nas vertebras. Doze casos foram submetidos a três ou mais tratamentos de RT. O tempo médio entre os tratamentos foi de 20,5 (1 -129) meses para o grupo I, 18 (5 - 80) meses para o grupo II e 10 (3 - 78) meses para o grupo III. A Dose Biologicamente Efetiva (BED) cumulativa dos tratamentos realizados foi de 76,49 (0,77 – 179,66) Gy_2, 92,79 (3,77 – 132,73) Gy_3 e 123,85 (83,18 – 245,59) Gy_2 para os grupos I, II e III, respetivamente. Nenhum efeito colateral na medula espinal ou tronco cerebral foi relatado. Na segunda fase, o grupo III obteve mais parâmetros dosimétricos com diferenças estatisticamente significativas na comparação do cálculo da dose do algoritmo AXB com o AAA. A dose máxima na medula espinal calculada com AAA e AXB para o primeiro tratamento no grupo III foi de 20,84 (8,16 – 47,74) Gy e 21,79 (8,22 – 49,21) Gy, respetivamente.

Conclusões: Para a BED cumulativa calculada neste estudo, a re–irradiação da medula espinal e do tronco cerebral mostrou–se uma opção terapêutica segura. O algoritmo AXB calcula valores de dose aparentemente superiores do que o AAA em regiões com densidades heterogêneas.

ABSTRACT

Background: Re–irradiation of common regions in the different treatment courses is an important problem due to the cumulative dose delivered in the organs at risk, which can cause serious effects.

Aim: This study was developed in two phases. The objective of first phase consists in the evaluation and comparison of the parameters of treatment and delivery doses in cases with previous Radiotherapy (RT) treatment and re–irradiation involving the spinal cord and brainstem, in patients treated in the Department of Radiotherapy at the Portuguese Oncology Institute of Porto, (IPO–Porto). In the second phase, re–calculated of treatment plans previously performed with the Anisotropic Analytical Algorithm (AAA), but this time with the Acuros External Beam (AXB) algorithm for the cases analysed in the first phase.

Methods: In the first phase, 91 patients were included in which two or more RT treatments were administered and there was an overlap of the spinal cord region or brainstem. These patients were treated at our institution between September 2008 and June 2019. In the second phase, 71 patients were included, in total 149 plans were recalculated. For recalculation, the Eclipse^{TM} treatment planning system (Varian Medical Systems, Palo Alto) version 13.5 was used.

Results: Three groups were considered, group I and II correspond to the irradiation of the spinal cord and brainstem, respectively, when the target volume is close to these organs. Group III corresponds to the spinal cord irradiation when the target volume is spinal metastases. Twelve cases underwent three or more RT treatments. The median time between treatments was 20.5 (1 – 129) months for group I, 18 (5 – 80) months for group II and 10 (3 – 78) months for group III. The cumulative Biologically Effective Dose (BED) of the treatments performed was 76.49 (0.77 – 179.66) Gy_2, 92.79 (3.77 – 132.73) Gy_3 and 123.85 (83.18 – 245.59) Gy_2 for group I, II and III, respectively. No side effects on the spinal cord or brainstem have been reported. In the second phase, group III obtained more dosimetric parameters with statistically significant differences when comparing the AXB dose calculation with the AAA algorithm. The maximum spinal dose calculated with AAA and AXB for the first treatment course in group III was 20.84 (8.16 – 47.74) Gy and 21.79 (8.22 – 49.21) Gy, respectively.

Conclusions: For the cumulative BED calculated in this study, spinal cord and brainstem re–irradiation proved to be a safe therapeutic option. The AXB algorithm calculates dose values apparently higher than AAA in regions with heterogeneous densities.

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LIST OF ABBREVIATIONS

3DCRT	Three-Dimensional Conformal Radiotherapy
AAA	Anisotropic Analytic Algorithm
AAPM	American Association of Physicists in Medicine
AXB	Acuros XB Dose calculation algorithm
BED	Biologically Effective Dose
BEV	Beam's-Eye-View
C/S	Convolution/Superposition
cBED	Cumulative Biologically Effective Dose
$cEQD_2$	Cumulative Dose Equivalent in Fractions of 2 Gy
CNS	Central Nervous System
CT	Computed Tomography
$D_{2\%}$	Two percent of the Dose
D_{2cm3}	Dose in 2 cm^3 of the volume
$D_{m,\,m}$	Dose-to-medium in medium
D_{max}	Maximum Dose
D_{mean}	Mean Dose
D_{min}	Minimum Dose
DNA	Deoxyribonucleic Acid
DVH	Dose-Volume Histogram
$D_{w,\,m}$	Dose-to-water in medium
$D_{w,\,w}$	Dose-to-water
EQD_2	Dose Equivalent in Fractions of 2 Gy
FSU	Functional Subunits
HU	Hounsfield Unit
IAEA	International Atomic Energy Agency
ICRU	International Commission for Radiation Units
IGRT	Image-Guided Radiotherapy
IMRT	Intensity Modulated Radiotherapy
IORT	Intraoperative Radiotherapy
LQ	Linear-Quadratic Model

LTBE	Boltzmann's Linear Transport Equation
MC	Monte Carlo
MV	MegaVolts
NTCP	Normal Tissue Complication Probability
OARs	Organs at Risk
PTV	Planning Target Volume
QUANTEC	Quantitative Analyses of Normal Tissue Effects in the Clinic
RT	Radiotherapy
RTOG	Radiation Therapy Oncology Group
SBRT	Stereotactic Body Radiotherapy
SPB	Single Pencil Beam
SRS	Stereotactic Radiosurgery
TCP	Tumor Control Probability
TPS	Treatment Planning Systems
VMAT	Volumetric-Modulated Arc Therapy

I. INTRODUCTION

1. THE ROLE OF RADIATION THERAPY

The use of radiation is an established practice in medicine, both for the diagnosis and treatment of different pathologies (1). Radiotherapy (RT) is a treatment based on the administration of high doses of ionizing radiation in limited target volumes. This treatment has been used in clinical practice for several decades as one of the therapeutic options for most cancer cases (2).

RT treatment is based on the interaction of the ionizing radiation administered with the medium. It deposits energy along the way, which will be absorbed by the cells and cause various interactions. These interactions damage the Deoxyribonucleic Acid (DNA) of the irradiated cells, altering their structure by breaking the molecular bonds (2).

The major objective of RT is based on the damage caused to cells by ionizing radiation, so the prescribed dose and the optimization of the treatment plan consists of maximizing the damage in the target volume and minimizing it in the adjacent normal tissues (3).

Since the effects of radiation cause damage to the tumor and adjacent normal tissues, also denominated Organs at Risk (OARs), it is important to establish an acceptable therapeutic ratio – defined as the probability of tumor control vs the probability of unacceptable toxicity – requiring that the doses administered are within defined tolerances for each irradiated organ (2).

Approximately 5.5 million patients are treated with RT annually worldwide. RT treatments can be prescribed for different purposes depending on various factors such as tumor histology, stage, general condition of the patient and other therapies administered. Therefore, the purposes of the RT prescription are (2):

- **Curative Radiotherapy:** achieve cure through high doses of radiation with minimal damage to normal tissues.
- **Palliative Radiotherapy:** relieve the symptoms caused by cancer at lower doses.
- **Prophylactic Radiotherapy:** prevention of possible metastases or recurrences through the application of appropriate doses.

Radiation therapy can be administered singly or in synergy with other oncological treatments such as surgery, chemotherapy, immunotherapy, or hormone therapy. Thus, RT can be considered neoadjuvant (when administered prior to another treatment), adjuvant (when administered after another treatment) and concomitant (when administered in the same timeline) (2, 3).

In the last decades, RT delivery techniques have undergone a substantial evolution, contributing to the higher precision and effectiveness of these treatments. As noted in Table 1, treatments can be administered in different ways: internal radiotherapy when radiation sources are inserted in the patient (brachytherapy, Intraoperative Radiotherapy (IORT)) and external radiotherapy when the dose is administered outside the patient, using a linear accelerator or another radiation emitting equipment (cobalt units, proton units, etc.) Three–Dimensional Conformal Radiotherapy (3DCRT), Intensity Modulated Radiotherapy (IMRT), Stereotactic Radiosurgery (SRS), and Stereotactic Body Radiotherapy (SBRT) are some of the available techniques for radiation delivery (1).

Table 1 – Different techniques of internal and external radiotherapy (1).

	Treatment Technique	Description
Internal Radiotherapy	Brachytherapy	Use of radioactive sources (temporary or permanent) placed close to the target volume. They can be inserted directly into the tumor or placed through applicators in a body cavity.
	Intraoperative Radiotherapy (IORT)	Delivered in intraoperative conditions, usually by electron beams or low energy x–rays. It is used after resection of the primary tumor and, in many cases, additional external RT is required.
External Radiotherapy	Three–Dimensional Conformal Radiotherapy (3DCRT)	3D anatomical data provided by different imaging techniques are used to identify tumor volume and the relationship with adjacent critical organs. The plans of this technique generally use a high number of radiation fields modulated using Beam's–Eye–View (BEV) to conform to the target volume.
	Intensity Modulated Radiotherapy (IMRT)	Highly conformal dose distribution around the target using non–uniform beam intensities, which is possible using static or dynamic segments. The isodose distribution can then be closely monitored by the target, modulating the intensity. Volumetric–Modulated Arc Therapy (VMAT) is an evolution of IMRT since it combines the conformation of the dose provided by this technique with the speed of arc treatment to obtain complex dose distributions.
	Stereotactic Radiosurgery (SRS) and Stereotactic Body Radiotherapy (SBRT)	Both stereotactic radiosurgery and stereotactic radiotherapy can administer radiation through multiple small beams focused on the three–dimensional target, enabling single precise delivery or a few large dose fractions with high conformation.

In parallel with the treatment techniques, imaging modalities have also shown a considerable evolution in recent times. Image–Guided Radiotherapy (IGRT) allowed to increase the accuracy of RT due to the improvements verified: in the acquisition of planning Computed Tomography (CT), in reduction of the internal margins of the outlined volumes, daily image with quality to assess deviations, and the possibility of tumor–tracking (1).

2. PRINCIPLES OF RADIOBIOLOGY

Radiobiology is the science that investigates the interactions of ionizing radiation with living systems and their consequences (3).

The area of radiobiology contributes to the development of RT in different aspects: creation of conceptual bases for radiation therapy (through the identification of mechanisms and processes in the response of tumors and normal tissues to irradiation), establishment of treatment strategies that allow the development of new approaches in RT (as in the case of hyper and hypofractionated treatments and cellular hypoxia sensitizers), and also to implement protocols for clinical practice (4).

In the last twenty–five years, important contributions of radiobiology have been observed in the clinical practice of RT, such as (5):

- Quantitative analysis of the cell dose–survival curves.
- Randomness of cell killing by radiation.
- Probabilistic basis of the response to irradiation of tumors and normal tissues.
- Understanding the biological mechanisms underlying radiation response.
- Rationale for dose–time and fractionation in RT.
- Introduction of the concepts of Tumor Control Probability (TCP), Normal Tissue Complication Probability (NTCP), and Biologically Effective Dose (BED).
- Relationship TCP–dose, BED –α/β, BED –fraction size and BED –treatment time.
- Problems associated with the accelerated regeneration of surviving tumor clonogens during fractionated RT.
- New demands of knowledge on oncology and radiation therapy derived from heterogeneous dose distributions.
- Biological basis of normal tissues tolerance to re–irradiation.

2.1 Radiobiological parameters of normal irradiated tissue

The DNA of irradiated cells undergoes several biological changes, namely cell death, loss of clonogenic capacity, genetic mutations and chromosomal aberrations, consequently causing somatic, hereditary, teratogenic, and carcinogenic effects (4).

Cell death induced by radiation consists of the inability to correct lesions in the double strand of DNA and manifests itself in the subsequent attempt at cell division. Therefore,

most proliferative cells show damage or die much earlier than cells with longer proliferation times. For this reason, the radioinduced biological changes in cells and tissues occurs after a latency period, which can vary from minutes to weeks or even years, depending for example on the dose rate, cell kinetics and control of regular genes of the cell cycle (6).

Contrary to what happens in tumor tissue, cell proliferation in normal tissues is well organized due to homeostatic control, with a balance between cell production and loss of more differentiated cells. The action of radiation on cells can remain inactive for a few hours to months, because in most normal and tumor tissues, cell death occurs when the cell attempts new division, depending on the proliferative characteristics of the tissue (7).

Another important factor is the sensitivity of the tissue since it varies according to the type of cell that makes up the tissue, influencing the response to radiation. Cells most sensitive to radiation are the most metabolically active, dividing more quickly and undifferentiated. The most resistant cells are those with greater differentiation and lower cell proliferation (8).

The response of tissues to radiation is also influenced by the cellular organization in proliferative and functional compartments, divided into two categories: hierarchical cellular organization and flexible cellular organization, whose characteristics are mentioned in Table 2 (6, 8).

Table 2 – Characteristics of different organization: hierarchical cellular and flexible cellular (6, 8).

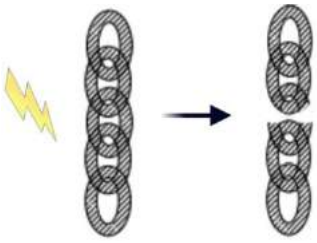
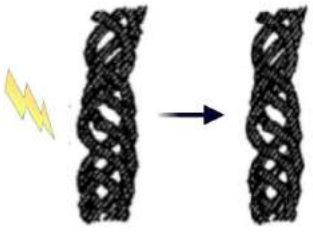
Organization	Description
Hierarchical cell	Tissues with a clear separation between the proliferative compartment and the differentiated cell compartment, responsible for organ functions. Example: more proliferative tissues such as the hematopoietic system, cells of the basal layer of the epidermis and the lining of the gastrointestinal system and spinal cord. The development of acute reactions in these tissues after irradiation is correlated with the lifetime of differentiated functional cells. The intensity of these reactions depends on the rate of destruction of stem cells and the rate of regeneration of surviving clonogenic cells.
Flexible Cell	Tissues there is no clear separation between the two compartments, though some cells exhibit a capacity for self–renewal. Low proliferation rate observed in this type of tissues, such as the kidney and lung, there is no such evident relationship between cell death and tissue response. However, the delayed effects are not restricted only to slow cell renewal tissues.

The different types of lesions can occur sequentially in an organ or tissue due to different mechanisms and cellular interactions. The major difference between acute and late effects can be explained by the progression: while acute effects are quickly repaired by the high proliferation of stem cells and can even be completely reversible. On the other hand, late effects can be mitigated, but never completely repaired since they result from the association of vascular lesions with loss of parenchymal cells (3, 8).

The difference between these effects has relevant biological consequences since during the conventional RT treatment that occurs in approximately four to six weeks, acute reactions to the treatment can be observed, being thus possible to act to allow the survival of the stem cells that will repopulate and ensure cell proliferation. In contrast, late effects occur months or years after RT treatment is completed and are much more sensitive to changes in fractionation than acute effects (8).

Radiation damage caused to an organ also depends on the structural architecture: serial or parallel as can be seen in Table 3 (3).

Table 3 – Response to radiation in serial and parallel organs [Adapted to (3)].

Structural Architecture	Response to Radiation	Illustration of Functional Subunits Damage
Serial Organs	If irradiation damage occurs in any functional subunit, complications can be observed in the whole organ. Examples: spinal cord, brainstem, optic structures, esophagus, rectum, and coronary arteries.	
Parallel Organs	If irradiation damage occurs in any functional subunit, only complications are observed in this subunit, with organ function being preserved. Examples: lungs, kidneys, liver, and myocardium.	

Tolerance of normal tissues takes on an important role and must be assessed individually for each irradiated OARs. Several factors influence normal tissues tolerance, which may be associated with treatment factors (total dose and fraction size, dose rate, total treatment time, energy and irradiated volume, use of other concomitant treatments), patient (age and comorbidities) or specifically the irradiated organ in question (development of toxicity, variation in the organs intrinsic radiosensitivity) (5, 8).

The most important factor that limits dose is the tolerance of the adjacent tissues to the irradiated field. Several analyses on the quantitative dose–response and dose–volume relationships for the different side effects in normal tissues have been performed. The "Tolerance of normal tissue to therapeutic irradiation" and Quantitative Analyses of Normal Tissue Effects in the Clinic (QUANTEC), has developed practical guidelines that allow the clinician to classify the toxicity risk for different OARs (9, 10).

There is a risk–benefit ratio of RT as, on one hand, it is necessary to use sufficient radiation dose to damage tumor cells causing cell death or less of clonogenic capacity, however, protection of the adjacent normal tissues is essential in order to avoid serious complications (3).

Whenever a change in treatment strategy is considered, it is imperative to assess both the effects on the tumor response and the damage to normal tissues. Radiobiology takes an important role in the evaluation of the quantifiable biological aspects inherent to the treatment of RT and possible changes (3).

Since it is verified that as the radiation dose increases, the effects of radiation may increase in degree and / or incidence, models of dose–response evaluation have been developed (3):

- **Tumor Control Probability (TCP)** is directly proportional to the dose and inversely proportional to the number of cells in the tumor target volume. There are several factors that affect TCP, such as: associated with the tumor (intrinsic radiosensitivity, tumor location and size, tumor cell type, and oxygen effect) and those associated with treatment (dose and fractionation, radiation quality, dose rate, use of radiosensitizers, combination of radiotherapy with surgery and / or chemotherapy, technique and treatment modality) (3).

- **Normal Tissue Complication Probability (NTCP)** is the function of total dose, dose fractionation, number of fractions and the volume of tissue exposed to radiation. There are several factors that affect NTCP, such as: these associated with the irradiated organ (tissue radiosensitivity, organ volume, type of organ in series or parallel) or associated with treatment (dose and fractionation, radiation quality, dose rate, use radioprotectors, combination with surgery and / or chemotherapy, technique and treatment modality) (3).

The therapeutic index is defined by the relationship between the TCP and NTCP for the different doses used. Normal tissues can be damaged by the dose needed to control the tumor if the damage caused does not exceed the defined doses and causes severe

damage that is not tolerated. Thus, the ideal balance between TCP and NTCP is an important objective of RT (3).

The effectiveness of the RT treatment is evaluated by the locoregional TCP and the NTCP. They are used to estimate the success and effects of treatments. The dose–volume histograms created by treatment planning systems, the mathematical model of TCP and NTCP are useful for graphically demonstrating damage rates in normal tissue within the irradiated volume, assisting dosimetrists and clinicians in the execution and evaluation of plans of treatment (3).

To decrease the lateral effects of providing high doses of RT, several fractions are administered at low doses per fraction. The principles of fractional radiotherapy are based on five resources called “R’s of Radiobiology” whose characteristics are illustrated in Table 4 (3).

Table 4 – Description of the 5 R's of Radiobiology (3).

R's of Radiobiology	Description
Repair of DNA damage	RT causes sub–lethal damage to tumor cells and normal tissues. The application of dose fractions allows normal tissues to have time to repair these damages. The ideal time interval between treatment fractions is 6 to 12 hours. (In the case of the spinal cord, the repair is slower than other tissues, so the time interval must be at least 8 hours).
Redistribution of cells in cell cycle	Different phases of the cell cycle have different sensitivities to radiation. The most sensitive phases are M and G2, while the most resistant is the S phase. In radioresistant phases of the cycle, they can progress to a more sensitive phase during the next RT fraction, thus the probability of tumor cells being exposed to radiation in a sensitive phase increases throughout the treatment.
Reoxygenation	As the tumor volume increases, the vascularization of this tissue becomes insufficient, with hypoxic and necrotic regions. Hypoxic cells are 2–3 times more resistant to radiation. On the other hand, well–oxygenated cells are radiosensitive and die during RT treatment. With the death of more peripheral tumor cells, there is a greater oxygen supply to hypoxic regions, making them more radioresistant.
Repopulation	Tumor cells and normal tissues continue to proliferate even during RT treatment. Proliferation is a physiological response of cells to a decrease in the number of cells. Repopulation allows tumor cells to partially resist the lethal effects of RT. This effect is slow at the beginning of RT but accelerates after the first fractions, being considered a phenomenon of "accelerated repopulation", which may increase if treatment interruptions occur. In normal tissues, repopulation is also observed, it is important for the repair of acute side effects. Therefore, RT treatments must be defined to allow this phenomenon in normal tissues.
Radiosensitivity	It is the result of what happens in the remaining R’s since they influence individual sensitivity to radiation. The more tumor tissue dies, the greater the radiosensitivity.

The fractionation scheme used will directly influence the 5 R's of Radiobiology previously presented. There are different types of fractionation such as conventional fractionation, hyperfractionation, accelerated fractionation, moderate and extreme hypofractionation (described in Table 5) (3, 4).

Table 5 – Characteristics of different fractionations dose (3, 4).

Fractionations / Characteristics	Conventional Fractionation	Hyperfractionation	Accelerated fractionation	Moderate Hypofractionation	Extreme Hypofractionation
Fraction dose	1.8 – 2 Gy	1.2 – 1.5 Gy	1.8 – 2 Gy	> 2 Gy and <4 Gy	≥ 4 Gy
Number of fractions per day	1	2	1 or 2	1	1
Number of fractions per week	5	10	Usually 6	≤ 5	1 – 5
Number of fractions per treatment	25 – 35	50 – 70	25 – 35	≤ 25 – 35	1 – 10
Total dose	45 – 70 Gy	55 –77 Gy	45 –70 Gy	< 45 – 75 Gy	8 – 50 Gy

Abbreviations: Gy – Gray

Conventional fractionation delivers doses per fraction of 1.8 – 2 Gy, single daily fractions totalling five weekly fractions. Hyperfractionation consists of doses per fraction of 1.2 and 1.5 Gy, in two daily fractions spaced in time, making a total of ten weekly fractions. Accelerated fractionation is administered in dose fractions of 1.8 – 2 Gy, in two daily or single fractions, usually 6 weekly fractions. Hypofractionation can be considered moderate when single daily fractions of a dose is ≥2 Gy and <4 Gy in a maximum of five fractions per week are administered; or extreme when administered single daily fractions of dose ≥ 4Gy in a maximum of five fractions per week (3, 4).

2.2 Linear–Quadratic Model – LQ

The Linear–Quadratic (LQ) model is advantageous for the calculation of iso–effect doses in the treatments of multi–fractionated RT. This model assumes that the breaking of the double strand of DNA is responsible for the clonogenic cell death induced by radiation and that hypoxic cells are fully reoxygenated during the irradiation interval (11).

The LQ model is clinically useful in predicting the sparing effect of fractionated radiotherapy on tissues and in comparing the equivalent total dose of different fractionation schemes. Over the past few years, changes have been made to the LQ model that take repair and repopulation into account (12).

Mathematically, the LQ model describes the survival fraction (*SF*) of clonogenic or stem cells as a function of the radiation dose (*D)*, illustrated in Equation 1 (12).

$$SF\ (D) = e^{-\alpha.D-\beta.D^2} \qquad \textit{(Equation 1)}$$

The estimate of the therapeutic result depends strongly on the reliable estimate of the α and β parameters of the LQ model. The α and β values represent the intrinsic radiosensitivity of irradiated cells. Cells with a higher α and β value are more sensitive to radiation (12).

The $^{\alpha}/_{\beta}$ ratio is a measure of cell fractionation sensitivity. Cells with higher $^{\alpha}/_{\beta}$ ratio are less sensitive to the sparing effect of fractionation, therefore, more sensitive to radiation (12).

The α and β radiation sensitivity parameters can be measured in vitro on tumor cell lines, however, cell cultures may not be representative for clinical radiobiological calculations. According to some assumptions present in the LQ model, these parameters can be derived from clinical data to RT treatments, namely from TCP (12).

2.3 Biologically Effective Dose – BED

Biologically Effective Dose (BED) is an inherent part of the LQ model with respect to cell survival, indicating the radiosensitivity of normal or tumor cells to the effect of radiation (13).

Mathematically, BED represents the physical dose necessary to achieve a certain effect. Since the radiobiological effect depends not only on the total dose provided but also on the dose per fraction used, the expression is given by Equation 2 (13, 14).

$$BED = D\left[1 + \frac{d}{^{\alpha}/_{\beta}}\right] \qquad \textit{(Equation 2)}$$

Where *D* corresponds to the total dose, *d* to the dose per fraction and $^{\alpha}/_{\beta}$ ratio of the tumor or normal tissue to which the dose is evaluated for a given effect (14).

BED allows, in a simple way, to compare different fractionation schemes that are used in clinical practice and who, therefore, have different radiological effects. For each treatment of RT there are two BED values: that of the tumor and that of the irradiated OARs, so it is important to take both into account for a correct evaluation of the treatment. BED values allow for comparison as reference values and assist in the decision of dose compensation in cases where treatment interruptions occur (13, 14).

Since the BED equation includes the $^{\alpha}/_{\beta}$ ratio, the BED value will be influenced, in other words: for cases of late response tissues in which the $^{\alpha}/_{\beta}$ ratio assumes lower values (0.5 to 6 Gy), therefore, the BED value is higher. In the case of acute response tissues in which the $^{\alpha}/_{\beta}$ ratio is higher (7 to 20 Gy), the BED value is lower (3, 15).

The $^{\alpha}/_{\beta}$ ratio values for tumor tissues also differ. For example, in cases of head and neck and lung carcinomas, the values are identical to those presented in the acute response tissues. Whereas cases such as melanomas, sarcomas, prostate and breast tumors may have low values such as late–response tissues (4, 13).

2.4 Dose Equivalent in Fractions of 2 Gy – EQD_2

Like BED, the Equivalent Dose in Fractions of 2 Gy (EQD_2) originates from the LQ model and allows the calculation of the iso–effect of different RT treatment schemes (4).

EQD_2 consists of converting each fractionation scheme into fractions of 2 Gy for the same biological effect. It is a simpler method of comparison because 2 Gy dose fractions are more used in clinical practice, so the values obtained in this calculation are more familiar to radiotherapists (4).

Mathematically, the calculation of EQD_2 is performed using Equation 3 (4):

$$EQD_2 = D\frac{d+{}^{\alpha}/_{\beta}}{2+{}^{\alpha}/_{\beta}} \qquad \textit{(Equation 3)}$$

Where *D* is the total treatment dose, *d* is the dose per fraction and the $^{\alpha}/_{\beta}$ ratio value for each evaluated tissue.

3. RE–IRRADIATION

Over the past decades, cancer treatments have evolved and, consequently, improvements in accuracy and efficiency have been observed, resulting in higher survival rates. The increased survival of cancer patients confronted radiation oncologists with the need of the denominated "re–treatment" or "re–irradiation", in cases of local recurrence, metastases or second tumors located inside or near previously irradiated sites (16).

Re–irradiation is a therapeutic option with an important role. In existing studies related to re–treatment with RT, few cases have been reported that are intended to be curative. The palliation of symptoms after initial cancer treatments also contributes to the more frequent use of re–irradiation in clinical practice (17, 18).

Re–irradiation with curative intent is important to evaluate the BED and the delayed effects of the initial treatment. On the other hand, in palliative re–irradiation, late toxicity to some high–risk organs may not manifest during the patient's limited life (16).

Nieder *et al.* (2018) through the illustration of several clinical cases concluded that the second irradiation has the potential to provide valuable palliative effects without causing evident late toxicity during the remaining lifetime (17).

The great paradigm consists of many cases of recurrences, metastases and second tumors occur in previously irradiated regions. For this reason, the decision of re–irradiation by the multidisciplinary team must consider some factors illustrated in Figure 1 (16).

The re–irradiation decision should take into account the location of the target volume to be treated, if is in the previously irradiated region and the relationship with the surrounding organs at risk that may receive a significant dose again with this treatment. It is also important to consider information about the first treatment, such as the dose and fractionation scheme used, irradiated risk organs and doses administered, reported side effects and time between RT courses. Other treatments administered initially, and their kinetics are also relevant factors for the decision of re–irradiation. Other possible therapeutic options for the cases in question must also be considered (16, 17).

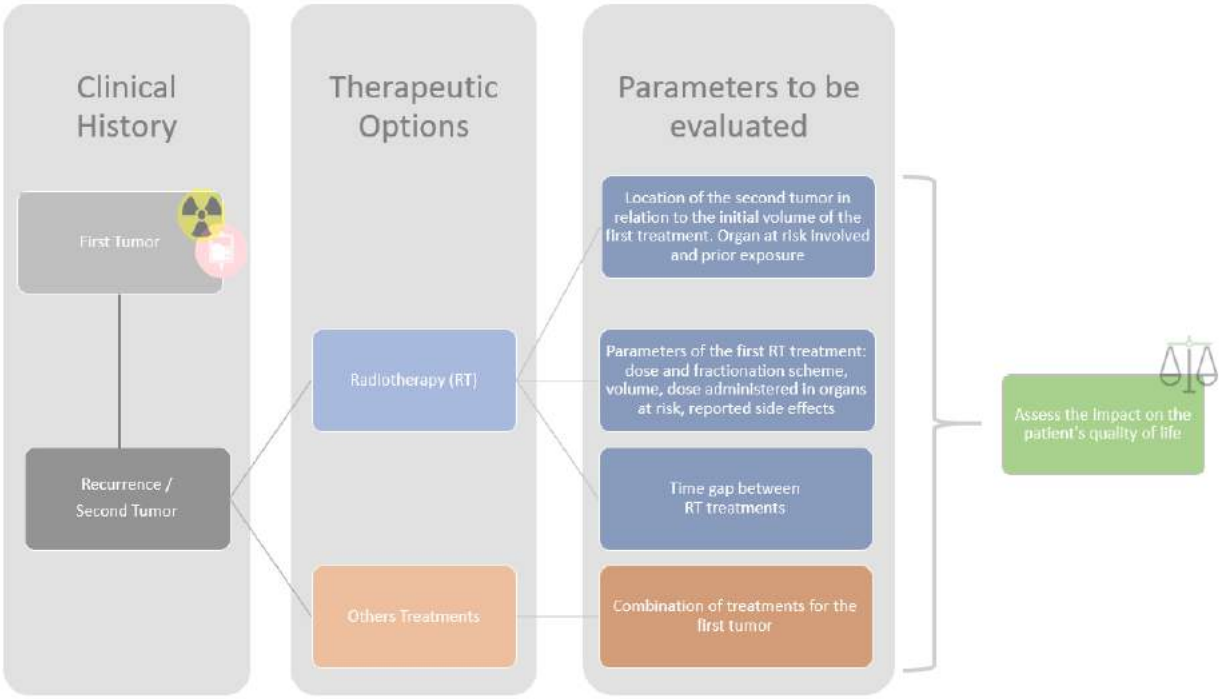


Figure 1 – Factors evaluated in the decision of a second RT treatment. [Diagram developed based on information from (16)]

Re–irradiation assessment is more complex compared to the first treatment. One of the major concerns is the tolerance doses of adjacent organs, which in the case of the second treatment is significantly reduced in re–irradiation when compared to the first treatment. Thus, it is important to consider whether the tolerance dose of an organ has already been reached in the first treatment period, the possible damage caused and the time between treatments, for a realistic assessment of the possible toxicities that may occur (16).

The initial dose conditions, the recovery of the damage caused by the radiation during the first treatment, as well as the realization of a possible second treatment. Re–irradiation with higher doses is possible if lower doses were used in the first treatment and for longer intervals occur between treatments (16, 17).

The benefit of re–irradiation has been demonstrated for cases of new tumors, recurrences or metastases. However, it is necessary to clearly establish the cumulative dose restrictions of the risk organs involved in the irradiations. Of these organs, the spinal cord and the brainstem stand out (17, 19).

3.1 Spinal Cord

The spinal cord is one of the most dose–limiting OAR in RT treatments, due to strong serial character and high sensitivity to radiation even when a small segment of the entire length is irradiated (20).

High doses of curative treatments are associated with an increased likelihood of damage to normal tissues. In certain irradiation techniques, part of spinal cord may be located within the irradiated volume in most cases of irradiation in the head and neck, thoracic and lumbar region, it can receive considerable doses to be evaluated (20, 21).

There are two types of damage that can be caused to normal tissues, acute and late damage, with the risk of being developed increasing with dose. The acute effects of irradiation of spinal metastases are associated with increased edema, causing or exacerbating possible spinal compressions (20, 22).

There are subacute effects of Central Nervous System (CNS) irradiation associated with transient demyelination mediated by radio–induced damage to oligodendrocytes or changes in capillary permeability. Clinical manifestations are transient radiation myelopathy or L'hermitte's syndrome after spinal cord irradiation. The development of L'hermitte's syndrome is associated with the spinal cord length irradiated (22).

Non–transient myelopathy, also called progressive or chronic, usually manifests between six and fifteen months, but in some cases, it can take up to three years after irradiation. It is, therefore, considered a late effect of spinal cord irradiation (22, 23).

The manifestation of progressive myelopathy is associated with paraesthesia, sensory disorders and in some cases with the late development of intestinal and bladder dysfunction (23).

These serious pathological changes are associated with vascular and oligodendrocyte damage by radiation, resulting in white matter necrosis and demyelination. Such changes may even result in irreversible damage (23).

Radiation myelopathy is assessed in the presence of clinical symptoms, diagnosis is made by exams such as myelography, computed tomography and magnetic resonance imaging (24). The severity of the injury is estimated by scoring protocols, as an example the Radiation Therapy Oncology Group (RTOG) criteria (25).

The risk of chronic progressive myelopathy is associated with different factors such as: total dose, dose per fraction, irradiated volume of spinal cord, segment of the spinal cord, and re–radiation of the cord to control malignancy (23). Other factors such as the

patient's individual sensitivity to radiation and the impact of the synergy of various oncological treatments are also described as factors influencing the development of this effect (20).

3.1.1 Dose and fractionation

Although in the treatment planning one of the main objectives is dose minimization in the spinal cord, this organ receives, throughout its extension, important doses to be taken into account. There is an established relationship between the total dose and the likelihood of developing myelopathy (9, 23).

In the study developed by Schultheiss *et al.* (2008) the incidence of cervical myelopathy for prescribed doses of 45 Gy and 50 Gy was 0.03% and 0.2%, respectively (26). These data are consistent with the previous reports, verifying that the risk of spinal cord injury increases to higher total dose values (22, 27).

Therefore, considering a treatment that provides a maximum dose of 50 Gy with conventional fractionation of 1.8 – 2 Gy per fraction, the data obtained experimentally indicate that the dose reduction per fraction below 2 Gy does not significantly alter the absolute dose–response (23).

However, due to the fact that in the last decades different fractionation schemes have started to be used, more cases of myelopathy associated with doses by higher fractions have been observed (23). Spinal cord tolerance estimates for single–dose fractions can be extrapolated through clinical data (22).

For the same dose and fractionation, it is estimated that the spinal cord tolerance for pediatric cases is less than 10% compared to that of adults, although more evidence is needed to clarify this value (22).

3.1.2 Irradiated Volume

The existence of an irradiated spinal cord volume/length effect and the incidence of radiation myelopathy is questioned (23). Emami *et al.* (2013) set the tolerance dose for the spinal cord to 50 Gy for a length of 10 cm, with a 5% probability of developing complications in five years (9, 28).

The volume effects may be related to vascular supply, collateral circulation and / or the ability to restore the damaged vasculature by revascularization of the affected volume. The release of cytokines and inflammation mediators can be affected by volume. In cases of irradiation of large volumes of spinal cord, the release of larger quantities of substances with a damaging potential occurs. Thus, the response to damage caused by radiation in the spinal cord is associated with vascular damage caused in the irradiated volume (23).

According to the study by Adamus–Gorka *et al.* (2008), the cervical spinal cord is characterized as a high–volume dependent, as it happens in parallel organs. They also observed in the studied cases that developed myelopathy in the cervical spinal cord occurred in the high dose region and with a large number of irradiated vertebrae, suggesting a relationship between the manifestation of radiation myelitis with dose threshold and volume effect (20).

Factors such as decreasing the dose administered and reducing the length of the irradiated medulla can reduce the risk of radiation myelitis (20).

3.1.3 Irradiated Segment

Experimental study irradiating the spinal cord of rats with proton beams have shown differences in the sensitivity of this organ. The biggest differences were found in the cervical medulla, concluding that the lateral white substance is more sensitive to radiation than the central one. They also found that the gray substance is highly radioresistant since no lesion was observed even after a single fraction with 80 Gy (29).

Another experimental study developed by Philippens *et al.* (2007) with non–uniform distribution dose in rats concluded that lumbar nerve roots are more radiosensitive compared to the thoracic ones (30).

Due to the difficulty of collecting uniform data on radiation–induced complications in the human spinal cord, few studies have been conducted with large patient populations (20).

The possibility of the existence of variations in sensitivity along the length of the spinal cord may be related to the structural organization of its Functional Subunits (FSU), since there are structural differences between the different parts of the spinal cord, especially with regard to proportions of white and gray matter (20).

The composition of matters in a human spinal cord varies, the gray matter contains mostly entire cells, while white matter contains mostly axons with myelin sheaths. The myelin sheaths work as insulators, radiation damages this function making the white matter a more sensitive structure to radiation. It is known that the amount of white matter decreases with increasing distance from the brain along the spinal cord since there are fewer axons in these regions. Thus, the greater sensitivity of the white matter would be related to the presence of more Schwann cells that constitute myelin. Therefore, the more radiosensitive region contains more white matter (20).

Based on Figure 2, it is possible to observe that the tendency of white matter to decrease with increasing distance from the brain. This difference may influence the radiosensitivity of different parts of the spinal cord (20).

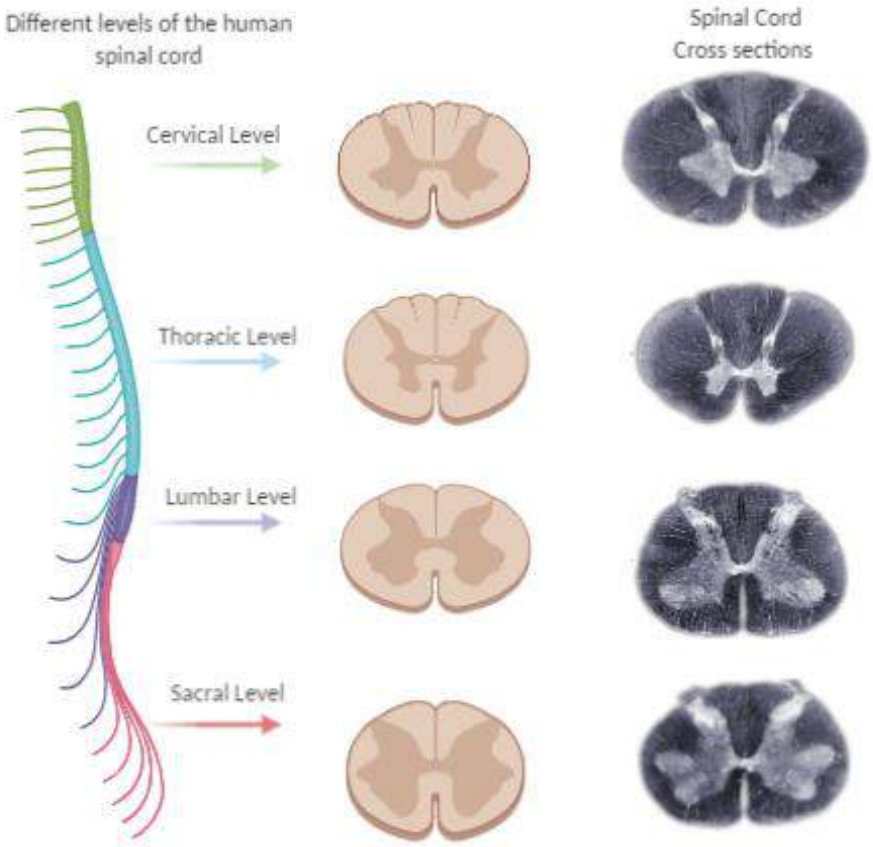


Figure 2 – Cross sections through the human spinal cord at cervical, thoracic, lumbar, and sacral level. Sections were prepared to emulate myelin staining [Cross sections images taken from (31)].

Another possible reason for the differences in radiosensitivity in the different regions of the spinal cord is the supply and vascular density. The thoracic spinal cord is considered more sensitive than the cervical spinal cord due to insufficient arterial vascular supply since it is intrinsically less oxygenated (23). Extrinsic conditions such as smoking history or effects of previous treatments can result in less oxygenated nerve tissues (26).

The importance of an accurate $^{\alpha}/_{\beta}$ ratio is due to the possibility of optimizing fractionation and the use of second radiation treatment in some patients. There is evidence of recovery of spinal cord tissue after radiation therapy. The repair capacity seems to depend on the $^{\alpha}/_{\beta}$ ratio of the LQ model (20).

Due to the differences in radiosensitivity observed in the spinal cord, there are authors who attribute different $^{\alpha}/_{\beta}$ ratio to the region of the spinal cord involved in the

treatment. Therefore, $^{\alpha}/_{\beta}$ ratio of 2 Gy is assigned to the cervical spinal cord and 4 Gy to the thoracic and lumbar spinal cord. Thus, for a dose administered of 50 Gy in daily fractions of 2 Gy, the equivalent BED is 100 Gy_2 and 75 Gy_4, respectively (11).

On the other hand, other authors such as Sahgal et al. (2013) define only an $^{\alpha}/_{\beta}$ ratio for the 2 Gy spinal cord regardless of the irradiated region (32).

3.1.4 Re–irradiation of Spinal Cord

Due to the more effective first–line treatment and better treatment options for metastatic tumors, it is expected that the number of patients with indication for retreatment will increase (33). The reluctance to perform re–irradiation is due to the possibility of causing irreversible damage to the spinal cord. Spinal cord complications can result in changes in the patient's quality of life. In addition, treatment options for radiation myelopathy are still limited (34).

The re–irradiation decision must be considered based on the assessment of the potential risks and benefits. Retreatment with a radical or palliative approach to cases of recurrent, metastatic tumor or primary seconds near the previously irradiated region is increasingly used in clinical practice (19).

In spinal cord retreatment for disease control, cumulative doses of 80 – 90 Gy in fractions of 1.8 – 2.0 Gy do not necessarily result in myelopathy, however, the risk should not be overlooked. Retreatments in less than 2 years may carry an increased risk since spinal cord damage occurs late and the accumulation of dose may encourage it (23).

The initial dose provided in the first treatment influences the time intervals necessary for recovery until possible re–irradiation. If lower doses are used in the first treatment, the organ tolerance dose is not exceeded and the time between treatments is longer, it is possible to use higher doses in later RT courses (17, 19).

According to Brenner *et al.* (2008) for a total dose of 34 Gy in the spinal cord, one year after irradiation it is estimated that there is a 76% damage recovery. In the case of a total dose of 38 Gy, it is estimated that two years after irradiation the recovery is 85% (11).

The spinal cord tolerance to re–irradiation is influenced by the level of initial damage and the latency time until the damage develops (21). When the time interval between RT treatments is less than six months, it is important to take into account the biologically effective dose since there is a greater likelihood of injury development when the time between treatments is shorter depending on the dose used (34).

The time between treatments is an important factor since recovery occurs after initial exposure and is dependent on time and dose if it is subclinical damage, as is the case of endothelial cell depletion whose loss is probably responsible for myelopathy related to the white substance (35).

Ang *et al.* (1993) in a study with Rhesus monkeys indicated that approximately 75% recovery from radiation injury occurred 2 years after the administration of 44 Gy in 20 fractions (36). The extrapolation of recovery observed in experimental animal studies should be performed with caution since the histological pattern of myelopathy in animals differs from that observed in humans and the repair kinetics is different, resulting in similarly different recovery times (22).

Jones and Hopewell (2019) developed a time–dependent model that incorporates data from all published radiobiological experiments concerned with the in vivo re–irradiation of the spinal cord using photons. This model allows estimating the increasing recovery of spinal cord tissue tolerance with the time elapsed after the initial course of treatment and preventing the development of myelopathy. According to the experimental evidence, the recovery rate depends on the BED of the initial treatment. Using this model, the clinician can determine the BED and then calculate the dose fractionation scheme for re–irradiation. Through this model, it is possible to predict that the recovery of irradiated spinal cord tissue occurs more quickly after a time interval above 70 days after exposure (19).

Nieder *et al.* (2005) concluded that the risk of cumulative BED myelopathy of ≤135.5Gy_2 is low when the interval between treatments was not less than six months and the treatment dose of the first treatment ≤98 Gy_2, close to the tolerance dose recognized for the spinal cord of 50 Gy in fractions of 2 Gy, using 5 daily fractions per week corresponding to 100 Gy_2 (34).

Nieder *et al.* (2018) suggest that the elapsed time interval was greater than or equal to 12 months after the last irradiation, to recover from the hidden damage. Despite the various limitations of different studies, the published data suggest the feasibility and safety of re–irradiations (17).

3.1.5 Irradiation of metastases in the Spinal Cord

Bone metastases are an increasingly observed complication of the clinic. In most cases, bone metastases develop after the treatment of the primary tumor, however, about 20% of cases at the time of diagnosis already show bone metastases (33).

The development of metastases is associated with the primary and its location, about 85% are originating from breast, prostate and lung cancer develop metastases. Due

to the different histologies of the primary and the different treatments used in the treatment initially, cases of metastases represent a heterogeneous group of patients (33).

For most cases of metastases, retreatment is necessary due to several factors such as pain, difficulty in walking, pathological fractures, spinal cord compression and neurological deficits (33).

Bone metastases occur in about 40% of cases in vertebral bodies. They are associated with complications such as uncontrolled pain and neurological dysfunction, often caused by spinal cord compression (37).

Spinal metastases are the most common spinal tumor. Most extradural spinal metastases are derived from primary tumors of the breast, lung, prostate, hematopoietic and kidney. This phenomenon occurs mainly due to the prevalence of certain neoplasms and their predilection for invading bone tissue. Most metastatic tumors of the spine are bone metastases, on the other hand, metastatic deposits in the dura mater or in the marrow itself are rare (22).

RT has assumed a fundamental role in the treatment of cases of bone metastases in the spinal cord over the last decades, mainly in the palliation of pain (22). However, the rate of pain control after RT to large metastases is only seen in 20% of patients (37).

Since the purpose of treatment in these cases is palliative, low doses are normally used in order to balance the palliation effect with the possibly induced toxicity. Different fractionation schemes can be used, for example, 20 to 40 Gy in fractions of 2 to 4 Gy, or even single dose fractions (22, 37). One of the fractionations most commonly used in clinical practice is 30 Gy in 10 fractions, 20 Gy in 5 fractions and 8.5 Gy in a single fraction (38).

SBRT to the spine has been studied and implemented in clinical practice over the last few years mainly as a therapeutic option in cases of bone metastases in the spine (39).

Due to advances in image orientation, targeting and radiation delivery methods, they have enabled treatment with SBRT to deliver high ablative doses to small tumor volumes with minimal doses to surrounding normal tissues. It is used for extracranial tumors and is administered in 1 to 5 fractions (40).

Initially, this technique was used to palliate spinal metastases even for tumors with radioresistant histologies. The observed results served as the basis for the generalized extrapolation of SBRT for the treatment of primary tumors of the spine and benign tumors of the spinal cord (39).

The use of the SBRT technique in the treatment of metastases in the spine has been studied. Tseng *et al.* (2017) in the re–irradiation of metastases in the spine with SBRT they verified rates of local control that varied from 66% to 92% in one year (39).

Radiation myelopathy is a late toxicity effect rare in the modern era of conventionally fractionated three–dimensional shaped RT. This devastating late effect has resurfaced as a direct result of the practice of SBRT, in which high–dose radiation is distributed adjacent to the spinal cord to be spared (32). Taking this paradigm into account, the dose tolerance limits for OAR and the dose–volume response of the tumors strongly depend on the number of fractions used and the dose per fraction (39).

Sahgal *et al.* (2019) found that for spinal cord metastases treatments with SBRT, the maximum dose points (D_{max}) in this OAR associated with a risk of 1% to 5% of radiation myelopathy were: 14.0 Gy in a single fraction, 17.0 Gy in two fractions, 20.3 Gy in 3 fractions, 23.0 Gy in 4 fractions and 25.3 Gy in 5 fractions (41).

Complication rates after single–fraction SBRT to the spine are clearly associated with the dose administered to the spinal cord and peripheral nerve roots. The justification for using fractional RT is based on radiobiological principles. On the other hand, the justification for the use of single fractions with SBRT lies in the rigorous administration of high doses in the tumor and relatively low doses in the surrounding tissues (22).

Single fraction SBRT may be beneficial for some patients with metastatic spinal disease. Indications may include patients with a previous history of spinal cord irradiation or considerably small metastases volume (22, 39).

The general prognosis of the patient, the cost associated with each type of treatment and the expected benefit for each patient are factors to be taken into account when considering the treatment technique to be used (22).

3.2 Brainstem

As described in the spinal cord, the brainstem is an organ with an important dose–limiting risk. This organ is located at the base of the skull and connects with the cervical spinal cord. It is mainly responsible for regulating cardiac and respiratory function, supply of cranial nerves and regulation of the central nervous system (42).

RT is administered in the treatment of brain and head and neck tumors, so for these cases, the brainstem can be included in the treatment fields, receiving a significant dose, thus limiting the total treatment dose (42). Limit doses for the brainstem depend on the RT technique, for 3DCRT the maximum dose tolerance limit on this organ is 60 Gy administered in 30 fractions in a volume greater than 0.03 cm^3 (43). For the same technique, QUANTEC

assumes that the risk of complications in the brainstem increases for maximum doses above 64 Gy. For low–fractionated SRS and SBRT, it assumes a risk of less than 5% probability of serious complications with maximum point doses below 12.5 Gy (44).

The ICRU classifies the brainstem as a serial risk organ, serious injuries can compromise the functional prognosis since the damage to a subunit of the organ can compromise its entire function. The ICRU also reports dose prescriptions used with SBRT treatments for these cases (45). Generally, severe toxicity caused by RT treatments occurs after a long latency period that can vary from six months to several years after irradiation (46).

It is estimated that after RT, 70% of the effects of radiation–induced toxicity occurs in the first two years and 90% of cases up to five years. These effects are mainly cognitive disorders without dementia, cranial nerve damage, disorders of motor and sensory function, necrosis and neurological toxicities (46).

Many cases of brainstem radionecrosis have been underestimated over the years due to several factors, such as: few studies focusing on the effects caused by RT in the CNS, lower incidence of this effect, difficulties to diagnose, the survival of most cases is low to develop the lesion, the classification of the effects on the brainstem it is subjective and it is difficult to distinguish between side effect and disease progression (42, 46).

The toxicity induced by RT treatments remains difficult to evaluate, as well as cases of necrosis, since they are rarely authenticated by magnetic resonance and anatomopathologist. The low number of cases reported in the studies, the short follow–up times make it even more difficult to verify the side effects (46).

Neurological examinations must be performed prior to treatment and during follow–up so that there is a comparison of results and thus a possible diagnosis of the effects of RT (46).

It is crucial to have dose criteria defined in order to have a correct risk–benefit assessment between tumor control and minimal toxicity in normal tissue (47). According to the QUANTEC review, it is recommended that the maximum dose in the brainstem is less than 64 Gy for an irradiated volume less than $1cm^3$ (48). However, the tolerance doses for the brainstem are discussed and more studies need to be developed (47).

According to Mayo *et. al* (2010), the entire brainstem can be treated up to 54 Gy using conventional fractionation for a low risk of severe or permanent neurological effects. The same study states that smaller brainstem volume can be irradiated to maximum doses

of 59 Gy in dose fractions ≤ 2 Gy, however, the risk seems to increase markedly for doses above 64 Gy (44).

According to Li *et al.* (2017), two patients from a 1544 cohort developed brainstem necrosis after 12.3 months and 18.5 months of irradiation in the head and neck region using the IMRT technique for average total doses of 60 Gy (47).

For doses above 60 Gy with dose per fraction of 2 Gy and for other fractionations, the evidence of a dose–effect relationship for the brainstem is still limited (44).

There are no consistent data to prove a dose and volume ratio of the irradiated brainstem. However, there is the idea of determining a dose restriction according to the central or peripheral irradiated region, recommending maximum doses of 53–54 Gy for the central region of the brainstem and 63–64 Gy for the peripheral region (46).

In the treatment of brain tumors, radiosurgery is used, so the admissible point doses according to Timmerman *et al.* (2008) for one, three and five fractions must be lower than 15 Gy, 23 Gy and 31 Gy, respectively. The risk of radiation–induced toxicity is associated with volumes greater than 1 cm^3. Concomitance with chemotherapy should be avoided due to the risk of increased radiation–induced toxicity (49).

Brainstem metastases are in many cases non operable, so the use of RT treatments has an important role in the treatment of these cases. The re–irradiation of the brainstem occurs in clinical practice, and as in the spinal cord, it is important to consider the decision taking into account the dose parameters of the first treatment and the time between treatments (42).

When the dose administered in the first treatment varied from 60 to 70 Gy, the residual dose in order to reach the dose tolerance for the brainstem is 10 – 15 Gy. Head and neck re–irradiation cases with prescription doses of 60 to 70 Gy, the residual dose of 10 –15 Gy corresponds to approximately 20%, thus limiting the prescribed for re–irradiation (42).

The calculation of BED for the different treatment and cumulative courses is important for the assessment and correct comparison. For CNS structures such as the brainstem, authors assume an α/β ratio of approximately 3 Gy (50).

Dose–response prediction models are essential for biological optimization of radiation in treatment planning. Well–informed clinical judgment should always supersede model predictions, considering the maxim: the spinal cord and brainstem should not be irradiated at doses greater than necessary. However, these results can serve to guide the clinical in cases where the dose of the OAR must be increased to achieve a satisfactory tumor response (26).

Further studies that assess cases of re–irradiation involving the spinal cord and brainstem are needed in order to clarify cumulative doses and possible damage caused by RT treatments (16, 17).

4. DOSE CALCULATION ALGORITHMS

With the evolution of RT treatment techniques over the last few decades, the precision and accuracy of Treatment Planning Systems (TPS) are imperative. To obtain an optimal treatment plan, it is important that the dose distribution is calculated for each irradiated volume, the accuracy of this calculation is essential for the correct evaluation of the plan and the forecast of possible complications (51).

According to the *International Commission for Radiation Units* (ICRU), the general uncertainty of the dose administered to the patient should not exceed 5%. This means that the accuracy of the dose calculation algorithm should be 2 – 3% (52).

Most recent TRS–430 recommendations from the *International Atomic Energy Agency* (IAEA) are in line with the values stipulated by the ICRU (53). While the *American Association of Physicists in Medicine* (AAPM) Task Group 65 set the target of 1 – 2% for heterogeneous dose calculations (54).

One of the main components that plays an important role in dose distribution and in the extent of tumor dose heterogeneity is the dose calculation algorithm. For advanced techniques, it has been found that the incidence of modulated radiation beams from different directions results in dose heterogeneity within the tumor and small volumes of normal tissues receive high doses. Therefore, the accuracy of the dose calculation becomes relevant for the therapeutic decision and the consideration of possible treatment complications (55, 56).

Calculation algorithms for Megavolts (MV) photon beams can be divided into two groups (51):

- **Analytical algorithms** model the transport of radiation in tissues like water and consider heterogeneities such as water of different electron densities. In this way, dose distribution is reported in terms of absorbed dose–to–water ($D_{w,w}$). It includes current standard algorithms such as convolution or convolution–superposition and achieves the necessary precision in water–like media. However, dose distributions may be unreliable and may not meet the precision criteria when tissue heterogeneity exists. Examples of analytical algorithms: pencil beam, Anisotropic Analytic Algorithm (AAA) and Convolution/Superposition (C/S) (51).
- **Model–based or advanced algorithms** model the physics of radiation transport in any medium. They include algorithms based on Monte Carlo and Boltzmann's Linear Transport Equation (LTBE). Monte Carlo algorithms simulate the random trajectories of individual particles using knowledge of the probability distributions that

govern individual interactions in media to keep track of physical quantities for many events. On the other hand, LBTE models describe the transport of radiation in media macroscopically. In advanced algorithms, voxel doses can be reported depending on whether they are considered as water or medium, choosing between water voxels surrounded by medium ($D_{w,\ m}$) or voxels in the medium surrounded by medium ($D_{m,\ m}$). Advanced algorithms solve most problems of analytical algorithms and represent an evolution in dose calculations in radiotherapy. Its use is recommended in situations where its performance is significantly superior, as in the case of stereotaxic treatments involving small fields and / or non–homogeneities, pacemakers, or metallic implants. Examples of model–based algorithms: Acuros XB (AXB) dose calculation algorithm and Monte Carlo (MC) (51).

4.1 Anisotropic Analytical Algorithm – AAA

The AAA algorithm is one of the most used in clinical practice and is convolution / superposition–based, that is, it is an improved pencil beam algorithm, which uses multiple pencil beam dose kernels to determine the dose contribution from different radiation sources of a clinical beam (57).

AAA is incorporated into the TPS Eclipse Varian Medical Systems. The AAA implementation was divided into two parts: configuration and dose calculation. In the configuration part, an optimization method was developed to determine the parameters of for a multiple source model by means of the basic beam data measurements and the dose calculation algorithm. Regarding the dose calculation part, it is based on exponential functions to better model the dispersion near the boundaries of lateral heterogeneities. The final dose distribution is calculated as a superposition of the dose deposited by the primary and secondary photons and the contamination electrons. In addition, some simplifications have been developed in modelling the dose in the accumulation region in order to significantly reduce the time needed for the calculation of the dose (56).

The AAA was developed to replace the Single Pencil Beam (SPB) model in order to improve aspects such as: modelling of the penumbra and the low dose regions, field profiles for symmetric and asymmetric open and wedged fields. Improvements in the dose calculation were observed for heterogeneous media, especially for high–energy photons, however, suboptimal modelling of the dose at the interface is still observed. Accurate modelling of the electron contamination parameters should contribute to an improved dose calculation in the build–up region of the beam (56).

Semi–analytical algorithms (pencil beam convolution algorithms, Anisotropic Analytical Algorithm (AAA) or superposition/convolution algorithms) used to calculate the

dose of photon beams are known for their limited accuracy in regions of great heterogeneity (58).

4.2 Acuros XB Dose calculation algorithm – AXB

The advanced dose calculation with AXB has been implemented in the treatment planning system Eclipse (Varian Medical Systems, Palo Alto, USA). These algorithm models the physical interaction of radiation with matter and for this feature the dose deposition in regions of large inhomogeneities is well estimated (58).

AXB explicitly solves the LBTE by numerical methods. It is an advanced algorithm that discretizes in space, angle and energy and solves the equation in a particular range of energy, space and angle. The major disadvantage of discretization is that it can produce systematic errors. MC indirectly obtains the solution of LBTE by following many particle transports through successive random sampling in media and the simulation of a finite number of particles can produce stochastic errors. In contrast to AAA where density scaling of the kernels occurs, AXB uses the chemical composition of the medium in each dose calculation voxel. From the CT calibration curve, the Hounsfield Unit (HU) is converted in the mass density values for each voxel (58).

In the presence of heterogeneities, it is necessary that the dose calculation algorithms are able to consider the heterogeneities present in the irradiated tissue and provide an accurate dose calculation of the electron transport near the tissue–air interface (57).

Several validation studies of the AXB algorithm have shown results of the dose calculations obtained achieve precision comparable to the MC methods in both homogeneous and heterogeneous water media (58).

The standard way of reporting dose with AXB is dose–to–medium in medium ($D_{m,m}$). However, AXB can also report dose–to–water ($D_{w,m}$) is the traditional measure through a dose conversion. These two ways of reporting the dose differ only in the post–processing stage, in which the energy–dependent fluency calculated by the AXB transport is multiplied by different dose–response functions (59).

However, one of the impediments to using this method in the clinical routine is associated with the time–consuming calculations verified. In this way, all the improvements that can be investigated and introduced in this model to decrease computing time are an asset (56).

In order to implement the AXB algorithm in clinical practice, the dose calculation obtained with this algorithm must be compared with the current algorithms based on the convolution method in order to evaluate the existing differences (59).

4.3 AAA vs AXB: clinical practice

Currently, most of the TPSs used in oncologic centres convolution–based methods such as Anisotropic Analytical Algorithm (AAA) in treatment planning (59).

Clinical practice is generally based on dosing in water, mainly for historical reasons: first the reference dosimeters are calibrated in water and second the clinical trials were carried out using dose calculation algorithms linked to these reference dosimeters and which score the dose in water (60).

The clinical experience based on advanced algorithms has been growing since they are available in commercial planning systems. For several decades, dose comparison means calculated for different media have been the subject of scientific debate and research (61). It is important to note that the literature does not provide consistent information and it is not clear how best to report the dose regarding the biological effect of radiation (62-64).

Three different dose quantities currently coexist ($D_{w,w}$; $D_{m,m}$ and $D_{w,m}$) and may differ in accuracy criteria. There are arguments for and against the different methods of reporting the dose, which is summarized in Table 6 (62-64).

Few clinical trials, protocols and guidelines address the dose amount. According to NRG Oncology and RTOG tests, $D_{m,m}$ is recommended (65). However, this amount is chosen for consistency rather than arguments in favour of its superior ability to predict clinical outcomes. However, some subsequent RTOG trials use $D_{w,m}$ (66). The ICRU–91 for stereotaxic treatments recommends $D_{w,m}$ for radiobiological reasons in contrast to the AAPM Task Group 329 which recommends $D_{m,m}$ (45, 67).

However, advanced algorithms introduce a new uncertainty: which way to report the dose should be used. The calculated dose distributions are very accurate in terms of the dose to water or the dose to medium separately. The differences between the modes are not relevant for tissue cases that are like water as they are within the precision of the calculation. On the other hand, for tissues such as bone, discrepancies may exceed the precision constraint. The case of the cortical bone is the extreme case where higher differences are observed (14% between $D_{w,m}$ and $D_{m,m}$ and 10–11% between $D_{w,m}$ and $D_{w,w}$) (62, 64).

Table 6 – Arguments favour and against to different methods of reporting dose (62-65).

Report Dose	Arguments in favour	Arguments against
Dose–to–water ($D_{w, w}$)	The current clinical experience is based mainly on treatment planning using analytical algorithms. Current clinical data are for dose–to–water. Quick dose calculation.	Limited accuracy in highly heterogeneous regions.
Water voxels surrounded by medium ($D_{w, m}$)	Voxel media includes connective and support tissues, which are responsible for their non–aqueous equivalence, however, the actual target cells are made mostly of water. Traceability compared to previous clinical experience, dose measurements and dosimetry protocols are dose based on water.	Current clinical data are for water–based dose, it is not equivalent to the doses obtained with this algorithm giving significantly different results in some cases. Slow dose calculation.
Voxels in the medium surrounded by medium ($D_{m, m}$)	Representativeness of the "true" dose because there are medium inside dose voxels. Slight differences for $D_{w, w}$ since most tissues are like water for MV photon beams. Calculated by most MC algorithms.	The standard method used in MC to convert it to $D_{w, m}$ introduces additional uncertainty. Media characterization from CT numbers is uncertain, making the medium potentially unknown. Slow dose calculation

Advanced calculation algorithms used in radiation photons according to the radiation transport model in any medium are one of the great evolutions of planning systems, however, they introduce new uncertainties and issues. Reporting doses for water voxels ($D_{w, m}$) or medium ($D_{m, m}$) and the impact of fluence changes introduced by the surrounding environment are some of these uncertainties. In this way, consistency between two reporting modes and the previous algorithms that are used in clinical practice can be compromised (62-64).

Since the clinical data are for dose–to–water, the hypothesis of conversion from dose of medium to dose to water arose. AXB has the functionality to convert from $D_{m, m}$ to $D_{w, m}$. However, this conversion must be avoided, since during processing it inserts errors that can be reflected in the dose obtained. (61).

Study developed by Reynaert *et al.* (2018) found that in regions of air and bone there were relatively large energy absorption ratios between the dose to medium and dose to water, about 5% for a 6MV beam (61).

According to Bassi *et al.* (2020), AXB could replace the AAA algorithm in VMAT treatments in regions where there are non–homogeneous regions and air. The main reason is the advanced modelling of the lateral electron transport of the AXB which allows more accurate dose calculation in heterogeneous regions which results in improved accuracy between different density interfaces (as in the cases of head and neck), compared to AAA. With the replacement of AAA for AXB, the coverage in areas adjacent to air gaps will differ since AAA shows smoothly changing isodoses in heterogeneous areas while AXB shows a deep gradient of dose after the air gap (58).

Sterpin *et al.* (2016) state that dose homogeneity in the Planning Target Volume (PTV) can also be influenced by its location and electronic density. Thus, it is important to carry out comparative studies of dose calculation algorithms that report the dose through different methods as it may influence the doses in PTV and OARs (60).

II. AIMS

The improvement of cancer treatments over the past few years has allowed an increase in patient survival and, consequently, the delay of development of local recurrence, metastases and second tumors. Re–irradiation of common regions in the different treatment courses is an important problem due to the cumulative dose delivered in the OARs, which can cause serious effects.

The accuracy of dose calculation is crucial for the correct evaluation of doses of target volumes and OARs, therefore the comparison of different calculation algorithms is extremely important.

Taking into account the paradigms presented, this dissertation project is divided into two phases:

i. The first phase consists of a retrospective cohort study where the main aim is the evaluation and comparison of the different parameters of treatment and delivery doses in cases with previous RT treatment and re–irradiation involving the spinal cord and brainstem, in patients treated in the Department of Radiotherapy at the Portuguese Oncology Institute of Porto, Portugal (IPO–Porto).

ii. The second phase of this dissertation consists in the recalculation of treatment plans performed with the AAA algorithm, but this time with the AXB algorithm for of the patients analyzed in the first phase of this project. The principal aim of this phase consists in determining whether a clinically relevant difference exists between the two calculation algorithms in this context.

III. MATERIAL AND METHODS

This dissertation project was developed at the Medical Physics, Radiobiology and Radiation Protection Group of the Research Center from IPO–Porto (approved by the Ethics Committee of IPO–Porto (CES–IPO: 382/019)).

1. FIRST PHASE

i. Patient population

The first phase consists of a retrospective cohort study. The institution's radiotherapy service database was used for the retrospective analysis and case selection. Cases defined by radiation oncologists in the internal network as “re–irradiation” were selected.

This study included cases that met the following inclusion criteria: patients initially treated with external RT subsequencial re–irradiation, whose treatment involved overlapping of the irradiated region of the spinal cord or brainstem, treated at the Department of Radiotherapy of IPO–Porto. Cases were excluded according to the following criteria: lack of information on all RT treatments performed in the current internal network of the service, did not finish the second course of treatment, anatomically distant irradiated regions in the several treatments, non–overlapping common irradiated regions of the spinal cord or brainstem.

Thus, according to the flowchart illustrated in Figure 3, 202 cases were identified as "re–irradiation" in the statistics database. Initially, 30 cases were excluded due to the lack of information from all treatment courses, 172 cases were assessed in more detail. Of these, 78 cases were excluded because they did not meet the inclusion criteria. Three benign cases observed were not included in the study, however, as they met the inclusion criteria, they were analysed separately as a curiosity about the re–irradiation of benign cases.

Therefore, 91 cases were included in the first phase of this study. Three analysis groups were created considering the irradiated region. Group I and II correspond to the irradiation of the spinal cord and brainstem, respectively, when they are involved in the treatment of RT of anatomically close tumors. Group III included cases where the target volume of treatment was in the spine itself, involving the spinal cord. The number of cases included in groups I, II and III was 32, 41 and 18, respectively.

The selection of patients according to the overlapping of irradiated regions of the spinal cord and brainstem was performed considering the isodose distribution of each treatment plan performed and the sum of the distributions. The cases included underwent RT treatments between September 2008 and June 2019.

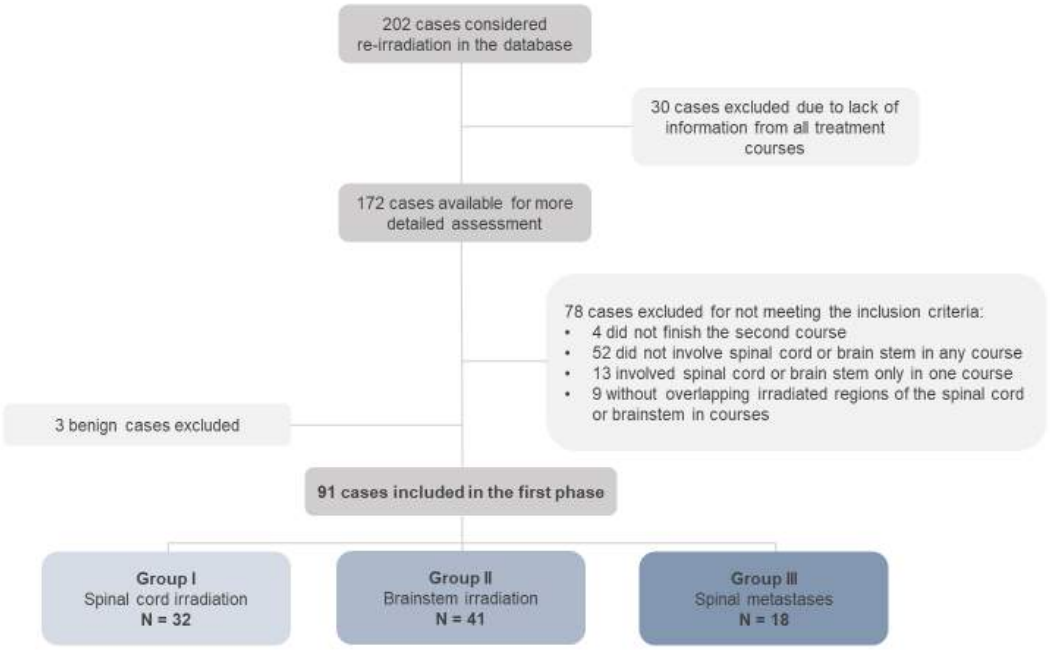


Figure 3 – Illustrative flowchart of patient selection and exclusion criteria for phase I.

All patients were followed up in consultations with radiation oncologists during the treatment period and subsequently in follow–up consultations. Treatment toxicities were assessed using physical, biochemical and imaging tests (such as radiography, CT, MRI or PET) and classified according to Common Terminology Criteria for Adverse Events version 4.0. Local recurrence was defined as tumor progression in the previously irradiated volume, determined by the clinician. All treatment plans for the cases were developed by dosimetrists and approved by radiation oncologists according to standard guidelines.

ii. Data collection

For the development of this study, it was necessary to collect data for all of the cases included in this study. The data consists in patient, pathology, RT treatments, dosimetric and after treatment data.

For data collection, multidisciplinary group consultations, radiation oncology and other relevant specialties, clinical history and follow–up medical records were reviewed for all patients, using the institution's internal network.

The Varian Radiotherapy Information System ARIA® and the Eclipse™ treatment planning system (Varian Medical Systems, Palo Alto) version 13.5 was used to collect data on the performed treatments and the respective treatment plans.

Table 7 shows the different variables that were collected for the study. It is important to note that the variables related to pathology, treatment and dosimetry were collected for all RT treatment courses for each patient. In summary, for the 91 cases included in this

study, a total of 194 treatment plans as well as all associated variables were reviewed. Since these are cases with multiple treatment courses, the sum of dose distributions and the cumulative doses were calculated.

Table 7 – Variables collected for the study.

Patient data	Pathology data	Treatment data	Dosimetric data	Data after treatment
• Date of birth • Gender • Previous treatments • Relevant comorbidities	• Tumor type • Location • Primary, recurrence or metastases • Date of diagnosis	• Dose prescription • Fractionation • Date of first and others RT treatments • Technique and energy used • Additional treatments • Volume of OAR irradiated • Spinal cord segment irradiated	• For OAR: D_{min}, D_{mean}, D_{max}, $D_{2\%}$ and D_{2cm}^3 • For target volume: D_{min}, D_{mean} and D_{max} • Overlapping regions of isodoses	• Side effects and toxicities observed • Date of last visit or date of death

Abbreviations: D_{min} – minimum dose, D_{mean} – mean dose, D_{max} – maximum dose, $D_{2\%}$ – two percent of the dose, D_{2cm3} – dose in $2cm^3$ of the volume.

iii. Dosimetric analysis

As shown in Table 7, dosimetric details were collected retrospectively. To compare the various fractionation schemes, BED and EQD_2 were calculated according to equations 2 and 3, respectively, clarified in the introduction of this project (4, 14).

Since the main objective is to evaluate and compare the doses that reach the OARs under study, calculations were made only for these. Thus, $^{\alpha}/_{\beta}$ ratio considered for the spinal cord and brainstem was 2 Gy and 3 Gy, respectively (32, 50).

The total dose value used in the calculation equations corresponds to the D_{max} value that reached the OAR in each treatment plan evaluated. The dose per fraction was obtained by dividing the D_{max} value by the number of fractions performed.

The cumulative BED (cBED) and the cumulative EQD_2 ($cEQD_2$) of the treatments performed for each case were calculated by adding the value of the BED or EQD_2 of the first treatment course with value of the BED or EQD_2 of the second treatment. In cases where more than two treatment courses have been taken, it will correspond to the sum of all values obtained in each course. No correction was made for variable times between the courses of RT treatment.

2. SECOND PHASE

i. Patient population

For the second phase, the 91 cases initially included were considered for inclusion. However, 20 cases were excluded due to the impossibility of recalculating the plan with AXB algorithm (4 MV beam is not commissioned; recalculation of plans of patients with high density artifacts or plans with dynamic conformal arcs would imply full re–plan, leading to large differences to the original plans).

As seen in the flowchart illustrated in Figure 4, 71 cases were eligible for this phase. The number of cases included in groups I, II and III was 25, 29 and 17, respectively.

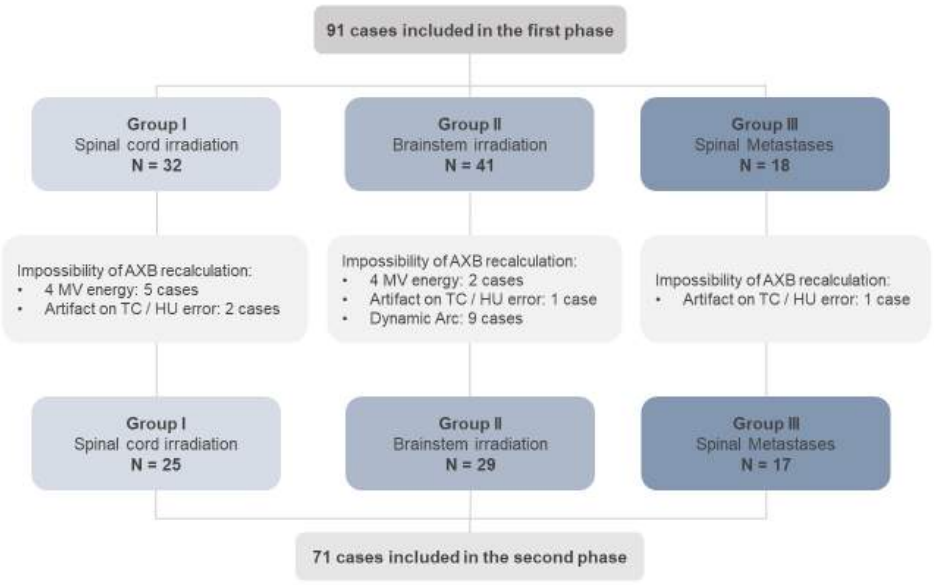


Figure 4 – Illustrative flowchart of patient selection and exclusion criteria for phase II.

ii. Recalculation with AXB

The calculation algorithm used in clinical practice at the institution is AAA. Therefore, the dosimetric values obtained in phase I were generated using this algorithm.

As the objective of phase II is to evaluate and compare AAA with the AXB algorithm, all case plans included in this phase have been recalculated with the new algorithm, maintaining all of the geometric characteristics of the original plans and considering the same normalization method. Of the 71 cases included, 149 plans were recalculated for all treatment courses under evaluation. The treatment techniques for these plans were 3DCRT, IMRT, VMAT and SBRT, and the energies beams were 6, 10 and 15 MV.

For the recalculation, it was necessary to copy the CTs corresponding to each treatment course. The outlined structures and the initial treatment plan were also copied and recorded on the corresponding CT. The calculation algorithm was defined from "AcurosXB_13.5" by recalculating the plans. After the recalculation of the plans of each case, the sum of them was carried out as it happened in phase I. This procedure was performed in the Eclipse® version 13.5 planning system and the dose reported by AXB was dose–to–medium in medium ($D_{m,m}$).

The dosimetric data collected in this phase with the AXB algorithm were the same as in phase I, which are: D_{min}, D_{mean}, D_{max}, $D_{2\%}$ and D_{2cm3} for OAR, D_{min}, D_{mean} and D_{max} for the target volume. These data were collected through the dose statistics and Dose–Volume Histogram (DVH) for each plan included as well as for the sum of the plans for each case.

iii. Statistical analysis

Continuous variables are presented as median and sample range (min–max) and categorical variables as frequencies and percentages.

Age at diagnosis was calculated as the difference between date of diagnosis and date of birth. Temporal interval between treatments was calculated as the difference between the subsequent treatment start date and the previous treatment end date.

Each patient was under observation from the end of second RT treatment until the date of their last visit in the institution or date of death.

In cases where an adverse treatment effect is observed, the time from the last RT treatment to the date of the medical record reporting the effect was calculated.

Overall survival was calculated from the beginning of the first RT treatment until the date of the last visit in the institution or date of death. Survival curves were estimated using the Kaplan–Meier method. Differences between survival curves of the different groups were analysed using the log–rank test.

To compare if there were any differences between the median values calculated with the AAA algorithm and the AXB algorithm, the statistical test applied was the Wilcoxon signed–rank test.

All tests of statistical significance were two–sided, and a p–value <0.05 was considered significant. Statistical analysis was performed using the SPSS Statistics version 26 (IBM Corporation, Armonk, N.Y., USA).

IV. RESULTS

1. FIRST PHASE

i. Patient, tumor and treatment characteristics

In this study, 91 cases (51 males and 40 females) met the inclusion criteria. These cases were divided into three groups: group I (n = 32) irradiation of the spinal cord as OAR in the treatment of adjacent target volumes, group II (n = 41) irradiation of the brainstem as OAR in the treatment of target volumes adjacent, and group III (n = 18) spinal cord irradiation in the treatment of spinal metastases. In all patients, the sequence of RT courses results in dose overlap in common regions of the spinal cord or brainstem.

Median age at the diagnosis of the primary tumor for group I, II and III was 61 (33 – 88) years, 52 (31 – 73) years and 59 (43 – 82) years, respectively.

Table 8 summarizes patients and tumors characteristics. The region of the primary tumor was categorized according to the cases included. Thus, for group I, 15 cases corresponded to head and neck tumors, 14 cases to lung tumors and 3 cases to others, such as esophageal, gastric and colon tumors. For group II, 40 cases corresponded to brain tumors or metastases in this region, on the other hand, all cases in group III corresponded to metastases in the spine.

Table 8 – Patient and tumor characteristics.

	Group I n = 32	**Group II n = 41**	**Group III n = 18**
Age at first diagnostic (years)	61 (33 – 88)	52 (31 – 73)	59 (43 – 82)
Sex			
Male	23 (71.88%)	16 (39.02%)	12 (66.67%)
Female	9 (28.12%)	25 (60.98%)	6 (33.33%)
Tumor region			
Head and neck	15 (46.88%)	1 (2.44%)	0 (0.00%)
Lung	14 (43.75%)	0 (0.00%)	0 (0.00%)
Brain	0 (0.00%)	40 (97.56%)	0 (0.00%)
Spinal	0 (0.00%)	0 (0.00%)	18 (100.00%)
Other	3 (9.37%)	0 (0.00%)	0 (0.00%)

All patients underwent at least two RT courses, with the second course corresponding to re–irradiation. However, 11 patients (six from group I, three from group II, and two from group III) underwent a third RT course. Only one case, included in group III, received four RT courses with the irradiated region overlapping the spinal cord or brainstem.

As described in Table 9, the first RT treatment was to the primary tumor in 28 and 21 cases in group I and II, respectively. The remaining cases correspond to treatment of recurrences or metastases of tumors previously treated with systemic therapy and / or

surgery. Information on other complementary treatments is described in Supplementary Table 1 in Appendix I.

In group II, two patients were initially treated prophylactically to the brain region due to the high probability of metastases of lung tumors, corresponding to the parameter "others" mentioned in Table 9.

Table 9 – RT treatments characteristics.

	Group I n = 32	Group II n = 41	Group III n = 18
1st RT treatment			
Primary tumor	28 (87.50%)	21 (51.22%)	0 (0.00%)
Local recurrence	2 (6.25%)	1 (2.44%)	0 (0.00%)
Metastases	2 (6.25%)	17 (41.46%)	18 (100%)
Others	0 (0.00%)	2 (4.88%)	0 (0.00%)
2nd RT treatment			
Second tumor	3 (9.38%)	0 (0.00%)	0 (0.00%)
Local recurrence	24 (75.00%)	40 (97.56%)	14 (77.78%)
Metastases	5 (15.62%)	1 (2.44%)	4 (22.22%)
Number of RT treatments			
Two	32 (100%)	41 (100%)	18 (100%)
Three	6 (18.75%)	3 (7.32%)	2 (11.11%)
Four	0 (0.00%)	0 (0.00%)	1 (5.56%)
Time between the 1st and the 2nd treatment			
Median (months)	20.5	18	10
Range	1 –129	5 –80	3 –78
Time between the 2nd and the 3 treatment			
Median (months)	8.5	13	9.5
Range	3 –13	11 –15	6 –13
Total Dose (Gy)			
1st course			
<20	1 (3.12%)	1 (2.44%)	2 (11.11%)
20 –29	4 (12.50%)	6 (14.63%)	9 (50.00%)
30 –49	7 (21.88%)	14 (34.15%)	5 (27.77%)
50– 59	2 (6.25%)	4 (9.76%)	1 (5.56%)
≥ 60	18 (56.25%)	16 (39.02%)	1 (5.56%)
2nd course			
<20	5 (15.62%)	1 (2.44%)	9 (50.00%)
20 –29	5 (15.62%)	12 (29.27%)	9 (50.00%)
30 –49	9 (28.14%)	27 (65.85%)	0 (0.00%)
50– 59	5 (15.62%)	0 (0.00%)	0 (0.00%)
≥ 60	8 (25.00%)	1 (2.44%)	0 (0.00%)
3rd course			
8	3 (50.00%)	0 (0.00%)	1 (50.00%)
20	1 (16.67%)	0 (0.00%)	1 (50.00%)
≥ 30	2 (33.33%)	3 (100%)	0 (0.00%)
4th course			
20	0 (0.00%)	0 (0.00%)	1 (100%)

Abbreviations: RT – Radiotherapy, Gy – Gray.

In the first course, 28 cases were treated with curative intent in group I and 21 in group II, and palliative treatment in the remaining cases of the three groups.

In the second course, three cases of secondary tumors were observed in regions anatomically close to the previously irradiated site. Also, in group I, 24 cases of local recurrences were treated, the remaining cases were considered progression of metastatic disease close to the irradiated region in the first treatment. In groups II and III, 40 and 14 re–treated cases were, respectively, local recurrences. For all the patients that underwent third and fourth treatments, it was considered that the purpose of treatment was palliative. It is important to note that most palliative RT treatments administered were aimed at controlling pain and symptoms caused by disease progression.

The median time interval between the first and the second courses was 20.5 (1 – 129) months, 18 (5 – 80) months, and 10 (3 – 78) months for groups I, II and III, respectively. For patients who received third treatment, the median time interval between the second and third course was 8.5 (3 – 13) months, 13 (11 – 15) months, and 9.5 (6 – 13) months for the group I, II and III, respectively. The fourth treatment was only verified for one case in group III, and the time since the third course was 10 months.

RT treatment prescription varied between the three groups as they refer to different cases treated for equally different purposes. The total doses were grouped into ranges in Table 9, in the first RT course 56.25% and 39.02% of the cases in group I and II, respectively, received a total dose equal to or greater than 60 Gy, while in group III, 50.00% of cases received total doses between 20 and 29 Gy. In the second RT course, 28.14% and 65.85% of the cases in group I and II, respectively, received total doses between 30 and 49 Gy. In group III, lower total doses were observed for all cases. Fractionation schemes were quite different and can be observed individually for each case and treatment course in Tables 10, 11, 12 and 13. Treatment modalities, just like the fractionation schemes, also differ within the group itself and between the three groups (this information is available in the Supplementary Table 1 in Appendix I).

ii. Re–irradiation characteristics

Of the 91 cases included in this phase, 194 treatment courses were evaluated. All patients completed the prescribed doses of their RT treatments. The following tables summarize for each case of this cohort: prescription doses, BED and EQD_2 calculated for OAR in each treatment course, time between treatments, overlap region and cumulative values of BED and EQD_2. Tables 10, 11 and 12 correspond to the data for groups I, II and III, respectively.

In these tables, the overlapping region corresponds to the common region irradiated in all treatments of each patient, including cases in which three or four treatments were administered. BED and EQD_2 were calculated for each course of treatment according to the maximum dose administered to the spinal cord or brainstem, the dose per fraction used was obtained by dividing the maximum dose of the OAR obtained in the planning system by the number of fractions of the corresponding treatment. The cumulative BED and EQD_2 correspond to the sum of the BED and EQD_2 of all treatments for each patient, including the cases that received three or four treatments.

Figure 5 shows three examples of overlapping irradiated regions in the spinal cord and brainstem resulting from re–irradiation with various treatment courses.

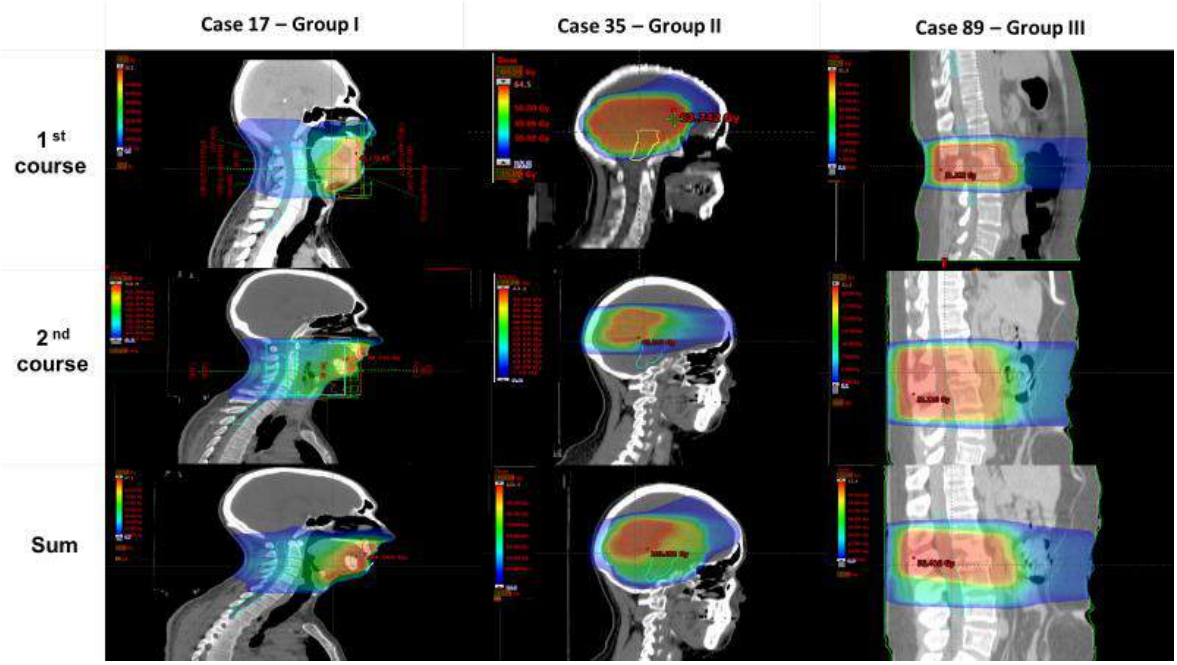


Figure 5 – Three examples of re–irradiations from the study groups. Dose distribution for two courses of radiotherapy and the respective sum, in sagittal view.
Case 17 belongs to group I, corresponds to a sarcoma of the jaw initially treated in 2013 with 45 Gy x 25 fractions, the BED in the spinal cord in this course was 19.21 Gy_2. The second treatment was in 2018 the local recurrence with 46 Gy x 25 fractions, the BED in the spinal cord was 37.21 Gy_2. The dose overlapping region was C1 – C6 and the cumulative BED of the two treatments was 56.42 Gy_2 in the spinal cord. **Case 35** belongs to group II, corresponds to an astrocytoma initially treated in 2008 with 60 Gy x 30 fractions, the BED in the brainstem in this course was 102.81 Gy_3. The second treatment was in 2014 the local recurrence with 40 Gy x 20 fractions, the BED in the brainstem was 19.96 Gy_3. The cumulative BED of the two treatments was 122.77 Gy_3 in this organ.
Case 89 belongs to group III, corresponds to a bone metastases in the spine, initially treated in 2018 with 30 Gy x 10 fractions, the BED in the spinal cord in this course was 76.87 Gy_2. The second treatment was in 2019 disease progression with 20 Gy x 5 fractions, the BED in the brainstem was 63.79 Gy_2. The dose overlap region was L1 – L3. The cumulative BED of the two treatments was 140.66 Gy_2 in the spinal cord.

Table 10 – Group I cases: characteristics of the first and second treatment courses.

Patient	Tumor region	1st RT treatment			Time between 1st and 2nd RT (months)	2nd RT treatment			Overlap region	cBED	$cEQD_2$
		Prescription Gy / fx	BED Spinal Cord Gy_2	EQD_2 Spinal Cord Gy_2		Prescription Gy / fx	BED Spinal Cord Gy_2	EQD_2 Spinal Cord Gy_2			
1	Head and neck	50 / 24 + 24 /12	84.74	42.37	71	46 / 23	4.05	2.02	C1 –C2	88.79	44.39
2	Head and neck	60 / 30 + 10 / 5	48.48	24.24	24	61 / 30	53.38	26.69	C1 –C2	101.86	50.93
3	Lung	30 / 10	58.59	29.29	5	20 / 5	64.37	32.19	T1 –T12	122.96	61.48
4	Lung	66 / 33	74.42	37.21	34	60 / 30	15.74	7.87	T2 –T8	90.16	45.08
5	Lung	60 / 30	36.84	18.42	19	20 / 5	59.03	29.52	T3 –T5	95.87	47.94
6	Head and neck	60 / 30	64.82	32.41	80	68 / 34	8.07	4.04	C1 –C4	72.90	36.45
7	Lung	26 / 4	47.11	23.56	35	50 / 20	20.29	10.14	T11 –T12	67.40	33.70
8	Head and neck	60 / 28 + 6 / 3	29.58	14.79	34	60 / 30	6.73	3.37	C1–C2	36.31	18.16
9	Lung	67 / 33	63.54	31.77	22	40 / 16	11.49	5.74	T8 –T11	75.03	37.52
10	Head and neck	60 / 30	64.76	32.38	7	61 / 30	11.63	5.82	C1 –T2	90.42	45.21
11	Lung	60 / 30	52.38	26.19	32	50 / 5	23.57	11.78	T9 –T11	75.95	37.97
12	Head and neck	60 / 28 + 10 / 5	77.69	38.84	27	60 / 30	5.70	2.85	C1 –C3	83.39	41.70
13	Head and neck	30 / 10	0.29	0.15	5	30 / 5	0.48	0.24	C1 –C3	0.77	0.39
14	Head and neck	33 / 15	37.41	18.70	5	50 / 20	8.30	4.15	C1 –C4	45.70	22.85
15	Lung	50 / 4	50.17	25.09	23	50 / 5	43.21	21.61	T5 –T7	93.38	46.69
16	Lung	50 / 4	11.53	5.76	15	40 / 5	14.68	7.34	T7 –T9	26.21	13.10
17	Head and neck	45 / 25	19.21	9.61	58	46 / 25	37.21	18.60	C1 –C6	56.42	28.21
18	Lung	60 / 30	62.42	31.21	48	50 / 5	14.62	7.31	T7 –T10	77.03	38.52
19	Esophagus	42 / 23	45.49	22.75	12	20 / 5	31.33	15.67	C7 –T6	82.79	41.39
20	Lung	60 / 30	72.10	36.05	22	20 / 5	11.41	5.71	T3 –T8	83.52	41.76

Abbreviations: RT - Radiotherapy, Gy - Gray, Gy_2 - Gray unit for α/β of 2 Gy, fx - fractions, BED - Biologically Effective Dose, EQD_2 - Dose Equivalent in Fractions of 2 Gy, cBED - Cumulative Biologically Effective Dose, $cEQD_2$ - Cumulative Dose Equivalent in Fractions of 2 Gy, C - Cervical Region, T - Thoracic Region, L - Lumbar Region.

Continuation of Table 10 – Group I cases: characteristics of the first and second treatment courses.

Patient	Tumor region	1st RT treatment			Time between 1st and 2nd RT (months)	2nd RT treatment			Overlap region	cBED	$cEQD_2$
		Prescription Gy / fx	BED Spinal Cord Gy_2	EQD_2 Spinal Cord Gy_2		Prescription Gy / fx	BED Spinal Cord Gy_2	EQD_2 Spinal Cord Gy_2			
21	Stomach	8 / 1	12.57	6.29	1	8 / 1	3.50	1.75	T9 – L2	19.12	9.56
22	Lung	70 / 35	21.18	10.59	33	30 / 10	15.14	7.57	T2 – T7	36.32	18.16
23	Lung	30 / 10	73.17	36.59	22	30 / 10	10.09	5.04	T1 – T7	83.26	41.63
24	Head and neck	50 / 25 + 24 / 12	74.59	37.30	129	9 / 3	1.82	0.91	C1 – C6	104.77	52.38
25	Head and neck	60 / 28 + 6 / 3	67.25	33.63	5	61 / 30	20.15	10.08	C6 – T3	87.41	43.70
26	Head and neck	40 / 16	39.35	19.67	16	30 / 10	21.35	10.68	C6 – T5	91.07	45.54
27	Lung	70 / 35	34.72	17.36	10	61 / 30	10.60	5.30	T6 – T8	45.31	22.66
28	Colon	20 / 5	10.16	5.08	9	8 / 1	4.71	2.35	L3 – L5	14.87	7.43
29	Head and neck	60 / 30	48.71	24.36	12	20 / 5	11.16	5.58	C1 – C7	59.87	29.94
30	Head and neck	20 / 5	8.45	4.23	10	8 / 1	6.46	3.23	C1 – C2	14.91	7.45
31	Head and neck	60 / 28 + 10 / 5	57.90	28.95	19	30 / 10	66.99	33.49	C1 – C2	179.66	89.83
32	Lung	20 / 5	41.50	20.75	5	8 / 1	7.23	3.61	T5 – T7	48.73	24.36

Abbreviations: RT - Radiotherapy, Gy - Gray, Gy_2 - Gray unit for α/β of 2 Gy, fx - fractions, BED - Biologically Effective Dose, EQD_2 - Dose Equivalent in Fractions of 2 Gy, cBED - Cumulative Biologically Effective Dose, $cEQD_2$ - Cumulative Dose Equivalent in Fractions of 2 Gy, C - Cervical Region, T - Thoracic Region, L - Lumbar Region.

Table 11 – Group II cases: characteristics of the first and second treatment courses.

Patient	Tumor region	1st RT treatment			Time between 1st and 2nd RT (months)	2nd RT treatment			Overlap region	cBED	$cEQD_2$
		Prescription Gy / fx	BED Brainstem Gy_3	EQD_2 Brainstem Gy_3		Prescription Gy / fx	BED Brainstem Gy_3	EQD_2 Brainstem Gy_3			
33	Brain	60 / 30	83.54	50.12	10	35 / 10	13.60	8.16	Brainstem	97.14	58.28
34	Brain	60 / 30	26.60	15.96	28	35 / 10	1.31	0.79	Brainstem	27.91	16.74
35	Brain	60 / 30	102.81	61.69	80	40 / 20	19.96	11.98	Brainstem	122.77	73.66
36	Brain	60 / 30	12.58	7.55	17	34 / 10	0.38	0.23	Brainstem	12.96	7.77
37	Brain	60 / 30	84.33	50.60	9	32 / 10	5.53	3.32	Brainstem	89.86	53.92
38	Brain	50 / 25 + 10 / 5	85.86	51.51	6	34 / 10	26.78	16.07	Brainstem	112.64	67.58
39	Brain	50 / 25 + 10 / 5	85.84	51.50	44	35 / 10	4.57	2.74	Brainstem	90.40	54.24
40	Brain	60 / 28 + 10 / 5	52.86	31.72	5	21 / 1	3.44	2.06	Brainstem	101.91	61.14
41	Brain	50 / 25 + 10 / 5	51.64	30.99	19	35 / 10	5.01	3.00	Brainstem	56.65	33.99
42	Brain	54 / 27	3.07	1.84	39	30 / 5	0.70	0.42	Brainstem	3.77	2.26
43	Brain metastases	17 / 1	16.73	10.04	19	30 / 5	23.29	13.97	Brainstem	40.02	24.01
44	Brain metastases	24 / 1	2.91	1.75	11	30 / 10	62.16	37.29	Brainstem	65.07	39.04
45	Brain	50 / 25 + 10 / 5	85.66	51.39	17	35 / 10	0.33	0.20	Brainstem	85.99	51.59
46	Brain	46 / 23 + 14 / 7	97.28	58.37	26	35 / 10	1.62	0.97	Brainstem	98.90	59.34
47	Brain metastases	30 / 5	22.21	13.33	7	30 / 10	66.30	39.78	Brainstem	88.51	53.10
48	Brain	55 / 30	90.69	54.42	45	35 / 10	42.04	25.22	Brainstem	132.73	79.64
49	Brain	48 / 24 + 10 / 5	84.54	50.73	40	35 / 10	46.17	27.70	Brainstem	130.71	78.43
50	Brain	70 / 33	36.64	21.98	40	60 / 30	42.50	25.50	Brainstem	79.14	47.48
51	Brain	46 / 23 + 14 / 7	72.54	43.53	17	35 / 10	7.79	4.68	Brainstem	80.34	48.20
52	Brain	60 / 30	30.43	18.26	15	35 / 10	10.96	6.58	Brainstem	41.39	24.83

Abbreviations: RT - Radiotherapy, Gy - Gray, Gy_3 - Gray unit for alpha beta of 3 Gy, fx - fractions, BED - Biologically Effective Dose, EQD_2 - Dose Equivalent in Fractions of 2 Gy, cBED - Cumulative Biologically Effective Dose, $cEQD_2$ - Cumulative Dose Equivalent in Fractions of 2 Gy.

Continuation of Table 11 – Group II cases: characteristics of the first and second treatment courses.

Patient	Tumor region	1st RT treatment			Time between 1st and 2nd RT (months)	2nd RT treatment			Overlap region	cBED	$cEQD_2$
		Prescription Gy / fx	BED Brainstem Gy_3	EQD_2 Brainstem Gy_3		Prescription Gy / fx	BED Brainstem Gy_3	EQD_2 Brainstem Gy_3			
53	Brain metastases	30 / 10	62.02	37.21	9	20 / 10	34.13	20.48	Brainstem	96.15	57.69
54	Brain metastases	30 / 12	42.38	25.43	20	23 / 9	45.20	27.12	Brainstem	87.58	52.55
55	Head and neck	55 / 33	68.81	41.29	35	30 / 10	22.96	13.78	Brainstem	91.77	55.06
56	Brain metastases	30 / 10	62.61	37.57	6	20 / 10	22.86	13.72	Brainstem	85.48	51.29
57	Brain metastases	30 / 10	61.01	36.60	35	18 / 1	62.66	37.59	Brainstem	123.66	74.20
58	Brain	25 / 10	46.85	28.11	22	30 / 10	53.83	32.30	Brainstem	100.68	60.41
59	Brain metastases	30 / 10	59.04	35.42	11	20 / 10	33.75	20.25	Brainstem	92.79	55.67
60	Brain metastases	30 / 10	62.47	37.48	12	20 / 10	35.41	21.25	Brainstem	97.88	58.73
61	Brain metastases	30 / 10	61.26	36.75	18	30 / 5	21.98	13.19	Brainstem	83.24	49.94
62	Brain metastases	30 / 10	60.81	36.48	11	20 / 10	34.04	20.42	Brainstem	94.84	56.91
63	Brain metastases	30 / 10	59.85	35.91	22	20 / 10	33.14	19.89	Brainstem	92.99	55.79
64	Brain	25 / 10	46.53	27.92	8	30 / 10	54.03	32.42	Brainstem	100.56	60.34
65	Brain metastases	30 / 10	61.23	36.74	12	20 / 10	34.72	20.83	Brainstem	95.96	57.57
66	Brain metastases	20 / 5	49.44	29.66	15	25 / 10	46.97	28.18	Brainstem	96.40	57.84
67	Brain metastases	30 / 10	61.48	36.89	15	20 / 10	34.37	20.62	Brainstem	95.85	57.51
68	Brain metastases	30 / 10	60.02	36.01	39	30 / 10	60.76	36.46	Brainstem	120.78	72.47
69	Brain metastases	30 / 10	61.28	36.77	37	25 / 10	41.49	24.89	Brainstem	102.76	61.66
70	Brain	50 / 25 + 10 /5	60.70	36.42	61	40 / 10	1.69	1.01	Brainstem	62.77	37.66
71	Brain metastases	23 / 1	44.42	26.65	12	32 / 5	0.21	0.13	Brainstem	86.02	51.61
72	Brain metastases	20 / 5	46.56	27.93	23	25 / 10	49.88	29.93	Brainstem	96.43	57.86
73	Brain	60 / 30	83.04	49.82	61	35 / 10	7.30	4.38	Brainstem	90.34	54.20

Abbreviations: RT - Radiotherapy, Gy - Gray, Gy_3 - Gray unit for alpha beta of 3 Gy, fx - fractions, BED - Biologically Effective Dose, EQD_2 - Dose Equivalent in Fractions of 2 Gy, cBED - Cumulative Biologically Effective Dose, $cEQD_2$ - Cumulative Dose Equivalent in Fractions of 2 Gy.

Table 12 – Group III cases: characteristics of the first and second treatment courses.

Patient	Tumor region	1st RT treatment			Time between 1st and 2nd RT (months)	2nd RT treatment			Overlap region	cBED	$cEQD_2$
		Prescription Gy / fx	BED Spinal Cord Gy_2	EQD_2 Spinal Cord Gy_2		Prescription Gy / fx	BED Spinal Cord Gy_2	EQD_2 Spinal Cord Gy_2			
74	Spinal metastases	30 / 10	80.18	40.09	35	8 / 1	43.79	21.90	T4 – T8	123.97	61.99
75	Spinal metastases	20 / 5	63.48	31.74	23	20 / 5	66.45	33.23	L1 – L5	129.94	64.97
76	Spinal metastases	30 / 10	76.13	38.07	3	8 / 1	41.85	20.92	T6 – T8	117.98	58.99
77	Spinal metastases	50 / 25	93.33	46.67	40	8 / 1	40.73	20.37	L4 – L5	134.06	67.03
78	Spinal metastases	48 / 24 + 25 / 12	78.26	39.13	78	8 / 1	41.18	20.59	C1 – C4	119.44	59.72
79	Spinal metastases	30 / 10	79.19	39.59	5	20 / 5	62.19	31.10	T10 – T12 and L3 – L5	182.78	91.39
80	Spinal metastases	20 / 5	63.02	31.51	5	8 / 1	42.11	21.06	T8 – T11	105.14	52.57
81	Spinal metastases	20 / 5	61.54	30.77	33	20 / 5	64.24	32.12	T4 – T8	125.78	62.89
82	Spinal metastases	20 / 5	61.18	30.59	10	8 / 1	40.47	20.23	T12 – L3	101.65	50.82
83	Spinal metastases	8 / 1	41.48	20.74	3	8 / 1	41.70	20.85	L2 – L4	83.18	41.59
84	Spinal metastases	20 / 5	63.61	31.80	11	20 / 5	60.11	30.06	T11 – L2	123.72	61.86
85	Spinal metastases	20 / 5	66.42	33.21	10	20 / 5	66.63	33.31	C5 – T6	133.04	66.52
86	Spinal metastases	20 / 5	61.58	30.79	12	8 / 1	40.98	20.49	T9 – T11	102.56	51.28
87	Spinal metastases	20 / 5	64.28	32.14	11	20 / 5	62.10	31.05	L2 – L5	126.38	63.19
88	Spinal metastases	30 / 10	77.76	38.88	7	8 / 1	41.54	20.77	T6 – T9	119.30	59.65
89	Spinal metastases	30 / 10	76.87	38.43	7	20 / 5	63.79	31.90	L1 – L3	140.66	70.33
90	Spinal metastases	8 / 1	42.77	21.39	4	8 / 1	46.18	23.09	L2 – L4	88.95	44.48
91	Spinal metastases	20 / 5	65.42	32.71	4	20 / 5	60.80	30.40	L2 – L5	245.59	122.79

Abbreviations: RT - Radiotherapy, Gy - Gray, Gy_2 - Gray unit for α/β of 2 Gy, fx - fractions, BED - Biologically Effective Dose, EQD_2 - Dose Equivalent in Fractions of 2 Gy, cBED - Cumulative Biologically Effective Dose, $cEQD_2$ - Cumulative Dose Equivalent in Fractions of 2 Gy, C - Cervical Region, T - Thoracic Region, L - Lumbar Region.

Table 13 summarizes the cases of the different groups that received three and four RT treatments. The prescription dose for each treatment is presented, and the BED and EQD_2 calculations were performed in the same way.

Table 13 – Cases of the different groups received three and four RT treatments.

Patient	Group	OAR irradiated	Time between 2nd and 3rd RT (months)	3rd RT treatment			Time between 3rd and 4th RT (months)	4th RT treatment		
				Prescription Gy / fx	BED Gy_2	EQD_2 Gy_2		Prescription Gy / fx	BED Gy_2	EQD_2 Gy_2
10	I	Spinal Cord	10	30 / 10	14.03	7.01	–	–	–	–
19	I	Spinal Cord	3	8 / 1	5.97	2.98	–	–	–	–
21	I	Spinal Cord	3	8 / 1	3.05	1.53	–	–	–	–
24	I	Spinal Cord	8	36 / 12	28.35	14.18	–	–	–	–
26	I	Spinal Cord	13	8 / 1	30.37	15.19	–	–	–	–
31	I	Spinal Cord	9	20 / 5	54.77	27.38	–	–	–	–
40	II	Brainstem	15	30 / 5	45.61 Gy_3	27.36 Gy_3	–	–	–	–
71	II	Brainstem	13	35 / 10	0.38 Gy_3	0.23 Gy_3	–	–	–	–
72	II	Brainstem	11	35 / 10	41.39 Gy_3	24.83 Gy_3	–	–	–	–
79	III	Spinal Cord	13	8 / 1	41.40	20.70	–	–	–	–
91	III	Spinal Cord	6	20 / 5	56.20	28.10	10	20 / 5	63.16	31.58

Abbreviations: RT - Radiotherapy, Gy - Gray, Gy_2 - Gray unit for α/β of 2 Gy, Gy_3 - Gray unit for α/β of 3 Gy, fx - fractions, BED - Biologically Effective Dose, EQD_2 - Dose Equivalent in Fractions of 2 Gy.

The second re–irradiation occurred up to six months after the first course in six patients (18.75%) in group I, three patients (7.32%) in group II, and seven patients (38.89%) in group III. Twenty–four months after the first irradiation, treatment courses were performed in fourteen patients (43.75%) in group I, fourteen patients (34.15%) in group II, and four patients (22.22%) in group III.

In the first course of treatment, the median BED of the spinal cord for groups I and III was 48.60 (0.29 – 84.74) Gy_2 and 64.85 (41.48 – 93.33) Gy_2, respectively. For the brainstem, the median BED in the first course was 60.81 (2.91 – 102.81) Gy_3.

In the second course, the median BED for the spinal cord was 11.56 (0.48 – 66.99) Gy_2 and 44.99 (40.47 – 66.63) Gy_2 for groups I and III, respectively. For the brainstem, the median BED of the second course was 26.78 (0.21 – 39.78) Gy_3. For the third and fourth course of treatment, a median value was not calculated due to the small number of cases, however, these values can be observed individually for each case in Table 13. The cumulative BED values for the spinal cord taking into account all treatments performed were 76.49 (0.77 – 179.66) Gy_2 and 123.85 (83.18 – 245.59) Gy_2 for groups I and III, respectively. For the brainstem, the cumulative BED was 92.79 (3.77 – 132.73) Gy_3. Table 14 details these values and the corresponding EQD_2.

Table 14 – BED and EQD_2 values for each study group and corresponding cumulative values.

	Group I n = 32	Group II n = 41	Group III n = 18
1st course			
BED	48.60 (0.29 – 84.74) Gy_2	60.81 (2.91 – 102.81) Gy_3	64.85 (41.48 – 93.33) Gy_2
EQD_2	24.30 (0.15 – 42.37) Gy_2	36.48 (1.75 – 61.69) Gy_3	32.43 (20.74 – 46.67) Gy_2
2nd course			
BED	11.56 (0.48 – 66.99) Gy_2	26.78 (0.21 – 66.30) Gy_3	44.99 (40.47 – 66.63) Gy_2
EQD_2	5.78 (0.24 – 33.49) Gy_2	16.07 (0.13 – 39.78) Gy_3	22.49 (20.23 – 33.31) Gy_2
Cumulative			
cBED	76.49 (0.77 – 179.66) Gy_2	92.79 (3.77 – 132.73) Gy_3	123.85 (83.18 – 245.59) Gy_2
$cEQD_2$	38.25 (0.39 – 89.83) Gy_2	55.67 (2.26 – 79.64) Gy_3	61.92 (41.59 – 122.79) Gy_2

Abbreviations: BED – Biologically Effective Dose, EQD_2 – Dose Equivalent in Fractions of 2 Gy, cBED – Cumulative Biologically Effective Dose, $cEQD_2$ – Cumulative Dose Equivalent in Fractions of 2 Gy, Gy_2 – Gray unit for alpha beta of 2 Gy, Gy_3 – Gray unit for alpha beta of 3 Gy.

The doses administered to the spinal cord and brainstem depended on the distance from the target volume of these organs. Supplementary Table 2 of Appendix I describes the median doses for each course of treatment for each group. It is important to note that in group III all target volumes were overlapping with the spinal cord.

The region of dose overlap of all treatments was evaluated and categorized in Table 15. In group I, the thoracic region was the most frequently involved in 43.75% of the cases, followed by the cervical region with 37.50% of the cases. These two regions were irradiated in the same treatment (corresponding to the distal cervical and proximal thoracic regions) in 12.50% of the cases in this group.

In group III, the lumbar region was the most frequently irradiated in 38.88% of the cases, followed by the thoracic region with 33.33%, these two regions were irradiated in the same treatment in 16.67% of the cases in this group, corresponding to the irradiation of the distal thoracic and proximal region. Dose overlap was observed in the brainstem for all cases included in group II.

Table 15 – Dose overlap region in the spinal cord and brainstem for the different groups.

	Group I n = 32	Group II n = 41	Group III n = 18
Overlapping region all treatments			
Spinal cord			
Cervical	12 (37.50%)	0 (0.00%)	1 (5.56%)
Thoracic	14 (43.75%)	0 (0.00%)	6 (33.33%)
Lumbar	1 (3.12%)	0 (0.00%)	7 (38.88%)
Cervical + Thoracic	4 (12.50%)	0 (0.00%)	1 (5.56%)
Thoracic + Lumbar	1 (3.12%)	0 (0.00%)	3 (16.67%)
Brainstem	0 (0.00%)	41 (100%)	0 (0.00%)

In the search and evaluation of the cases included in this study, three benign cases corresponding to re–irradiations were found. These cases were excluded from our analysis, however, the following parameters were collected and calculated: the benign tumor type and location, dose prescription, BED and EQD_2 for each treatment and cumulative values, overlapping region. This information is summarized in Supplementary Table 3 of Appendix I. It is important to mention that the cases were thymoma, trigeminal neuralgia and pituitary macroadenoma, all of which received two courses of RT treatment at the institution. Follow–up time varied from 27 months to 38 months. At the time of this study two of the patients are alive with stable disease. No adverse effects have been reported in these patients.

iii. Survival analysis

Median overall survival was 32.00 (95% CI: 25.07 – 38.93) months. For group I median overall survival was 32.00 (95% CI: 30.63 – 33.38) months, for group II it was 42.00 (95% CI: 21.13 – 62.87) months, and for group III it was 18.00 (95% CI: 11.80 – 24.20) months. Overall survival at 12 and 24 months was: 90.6% and 71.9% for group I, 95.1% and 73.2% for group II, and 72.2% and 38.9% for group III.

Figure 6 shows the survival curves for the three groups. The p–value of the log–rank test was 0.044, which means that there are statistically significant differences between the survival curves of the three groups.

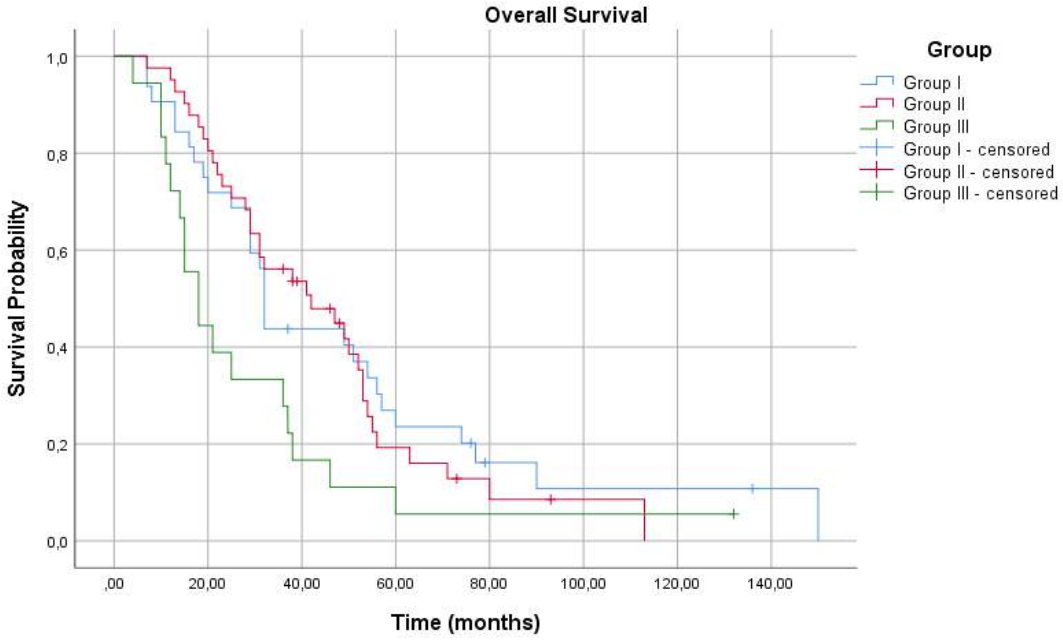


Figure 6 – Overall survival curves for the three groups under study.

Median follow–up after second course of RT treatment was 11.5 (2 – 61) months, 11 (5 – 53) months, 7 (1 – 51) months, for group I, II and III, respectively.

In the end of the present study, eleven patients were alive (ten with stable disease four from group I, five from group II and one from group III) and one patient has disease progression, as identified by imaging methods.

In the search for side effects in the medical records of each patient, no effects associated with radiation–induced myelitis, brainstem necrosis or other toxicities have been reported. However, toxicities were reported in other OARs in three cases: patient number 2 in group I presented left cerebral radionecrosis (17 months after the second treatment), patient number 7 in group I – fracture of the tenth right costal arch (19 months after the first treatment), and patient 18 of group I – radiation–induced pneumonitis (5 months after the second treatment).

2. SECOND PHASE

In the second phase, 71 cases were included. The number of cases included in groups I, II and III was 25, 29 and 17, respectively. Initially, 149 plans were evaluated with the AAA algorithm and the dose variables for the OAR (spinal cord or brainstem) and the target volume were collected. To evaluate the AXB algorithm, 149 plans were replicated and recalculated. The same variables were collected to compare the algorithms. Comparison between the plans is show in the Tables 16 and 17.

Table 16 summarizes the median values of each dosimetric parameter under evaluation for the OARs of both the AAA and AXB algorithms.

Table 16 – Dosimetric parameter results comparisons between AAA and AXB algorithms for the spinal cord and brainstem organ at risk.

Evaluated dose parameter	AAA (Gy)	AXB (Gy)	P - value
Group I			
Doses to spinal cord			
Dmin 1st course	0.18 (0.00-1.05)	0.19 (0.00-1.05)	**0.022**
Dmax 1st course	25.77 (4.11-45.84)	24.90 (4.58-43.90)	0.145
Dmed 1st course	7.58 (0.54-27.90)	8.41 (0.51-26.91)	0.242
D2% 1st course	24.50 (2.77-43.24)	23.51 (3.28-42.49)	0.109
D2cm^3 1st course	20.58 (2.64-42.94)	20.41 (3.12-42.12)	0.696
Dmin 2nd course	0.07 (0.00-1.07)	0.09 (0.00-1.13)	**0.017**
Dmax 2nd course	8.97 (1.83-34.05)	8.72 (2.06-34.75)	0.051
Dmed 2nd course	2.10 (0.56-16.13)	2.15 (0.56-16.03)	**0.012**
D2% 2nd course	7.32 (1.77-29.58)	6.85 (1.91-29.35)	**0.012**
D2cm^3 2nd course	7.28 (1.75-28.12)	6.44 (1.83-27.86)	**0.010**
Group II			
Doses to brainstem			
Dmin 1st course	19.03 (0.37-47.53)	18.88 (0.33-47.98)	**0.014**
Dmax 1st course	30.42 (2.96-58.83)	30.78 (2.84-59.22)	0.080
Dmed 1st course	25.31 (1.40-55.06)	24.92 (1.38-55.11)	0.737
D2% 1st course	30.27 (2.66-56.91)	30.43 (2.58-57.05)	0.206
D2cm^3 1st course	30.10 (2.34-55.73)	30.27 (2.31-55.73)	0.854
Dmin 2nd course	0.40 (0.04-28.88)	0.34 (0.04-28.94)	0.125
Dmax 2nd course	15.18 (0.33-31.48)	14.98 (0.33-31.25)	0.449
Dmed 2nd course	3.35 (0.14-29.78)	3.47 (0.13-29.96)	0.304
D2% 2nd course	12.01 (0.27-30.10)	12.60 (0.27-30.68)	0.393
D2cm^3 2nd course	8.96 (0.24-29.96)	9.35 (0.23-30.17)	0.336
Group III			
Doses to spinal cord			
Dmin 1st course	0.59 (0.05-2.29)	0.52 (0.05-2.30)	**0.015**
Dmax 1st course	20.84 (8.16-47.74)	21.79 (8.22-49.21)	**<0.001**
Dmed 1st course	16.85 (2.99-28.87)	17.12 (2.99-30.40)	0.096
D2% 1st course	20.70 (8.15-47.07)	21.41 (8.16-48.17)	**0.001**
D2cm^3 1st course	20.61 (8.11-44.85)	21.19 (8.12-46.40)	**0.001**
Dmin 2nd course	0.49 (0.13-2.06)	0.48 (0.13-1.86)	**0.004**
Dmax 2nd course	8.45 (8.05-21.29)	8.76 (8.20-23.14)	**<0.001**
Dmed 2nd course	6.74 (4.83-18.85)	6.82 (4.84-20.37)	0.221
D2% 2nd course	8.40 (7.98-21.19)	8.54 (8.02-22.65)	**0.001**
D2cm^3 2nd course	8.36 (7.91-20.98)	8.48 (7.92-22.25)	**0.001**

Abbreviations: AAA – Anisotropic Analytic Algorithm, AXB – Acuros XB Dose calculation algorithm, Min – Minimum, Max – Maximum, Gy – Gray, 1st – first, 2nd – second, D_{min} – minimum dose, D_{max} – maximum dose, D_{med} – mean dose, $D_{2\%}$ – two percent of the dose, D_{2cm3} – dose in two cubic centimetres of the organ.

For group I, there were statistically significant differences in the comparison of the two algorithms for the values of minimum dose of the first and second course, mean dose, two percent of the dose and dose in two cubic centimetres of the spinal cord volume.

In group II, only the minimum dose of the first course was statistically significant when comparing the two algorithms.

In group III several dosimetric parameters showed statistically significant differences. In the evaluation of the median dose calculated with the two algorithms, it is possible to observe that in this group the dosimetric values calculated with AXB were higher than those calculated with AAA. For example, the median value of the maximum dose (D_{max}) in the spinal cord in the first course of treatment for the AAA algorithm was 20.84 (8.16 – 47.74) Gy, while for the AXB algorithm it was 21.79 (8.22 – 49.21) Gy.

This evaluation was carried out for each treatment course. However, the statistical comparison was only performed for the parameters of the first and second treatment courses, since all cases received two RT treatments. As only five of the cases included in this phase performed the third course of treatment and only one the fourth course, the statistical comparison for these courses was not performed.

For the sum of the dose administered in the spinal cord and brainstem, the same parameters were evaluated. Table 17 summarizes the median values of the dose calculated by the two algorithms for each evaluation parameter. Only in group III, statistically significant differences in the doses calculated by the two algorithms were observed. The median values of D_{max} in the sum for the AAA algorithm was 39.06 (16.18 – 59.61) Gy whereas in the AXB algorithm it assumes a median value of 39.36 (16.56 – 60.85) Gy. The median dose values in two percent ($D_{2\%}$) and two cubic centimetres (D_{2cm3}) were higher in the AXB algorithm compared to AAA.

Table 17 – Dosimetric parameters results comparison between AAA and AXB algorithms in the sum of plans delivered.

Evaluated dose parameter	AAA (Gy)	AXB (Gy)	P - value
Group I			
Doses to spinal cord			
Dmin sum	0.39 (0.00-36.14)	0.42 (0.00-35.57)	0.097
Dmax sum	32.43 (7.15-53.53)	33.09 (7.49-51.93)	0.353
Dmed sum	15.28 (1.26-42.53)	14.85 (1.25-41.95)	0.326
D2% sum	27.69 (5.86-48.68)	27.95 (6.59-47.83)	0.527
$D2cm^3$ sum	25.59 (5.76-48.21)	26.10 (6.49-47.40)	0.104
Group II			
Doses to brainstem			
Dmin sum	23.27 (0.50-57.69)	24.25 (0.37-57.72)	0.456
Dmax sum	50.78 (3.47-76.95)	51.23 (5.99-78.89)	0.068
Dmed sum	36.14 (1.72-59.35)	35.54 (1.68-59.76)	0.897
D2% sum	49.40 (3.15-67.62)	49.75 (3.67-68.41)	0.157
$D2cm^3$ sum	46.83 (2.83-64.55)	46.77 (3.01-65.04)	0.705
Group III			
Doses to spinal cord			
Dmin sum	0.66 (0.21-20.94)	0.64 (0.21-20.75)	0.345
Dmax sum	39.06 (16.18-59.61)	39.36 (16.56-60.85)	**<0.001**
Dmed sum	22.50 (9.69-39.03)	22.80 (9.86-39.71)	0.311
D2% sum	38.52 (16.12-58.80)	38.92 (16.16-59.27)	**0.002**
$D2cm^3$ sum	38.24 (16.09-57.42)	38.38 (16.12-57.77)	**0.028**

Abbreviations: AAA – Anisotropic Analytic Algorithm, AXB – Acuros XB Dose calculation algorithm, Min – Minimum, Max – Maximum, Gy – Gray, D_{min} – minimum dose, D_{max} – maximum dose, D_{med} – mean dose, $D_{2\%}$ – two percent of the dose, D_{2cm3} – dose in two cubic centimetres of the organ.

Two important parameters for dose assessment in the spinal cord and brainstem are the D_{max} and D_{2cm3}.

Figures 7a and 7c show the difference in D_{max} in the spinal cord for groups I and III for the first and second courses, respectively. Figures 7b and 7d show the difference in maximum dose for group II, for the first and second courses, respectively. These figures support the conclusions drawn from Table 16.

Figures 8a and 8c show the difference in D_{2cm3} in the spinal cord for groups I and III for the first and second courses, respectively. Figures 7b and 7d show the difference in D_{2cm3} for group II, for the first and second courses, respectively. These figures support the conclusions drawn from Table 16.

The differences in D_{max} and D_{2cm3} for each case were illustrated in Figure 9. Graph a) and b) correspond to the difference in maximum dose for the first and second courses, respectively. While graphs c) and d) correspond to the difference of D_{2cm3} for the first and second treatment courses, respectively. In these graphs it is possible to observe that in group II the difference values are close to 0 Gy for the vast majority of cases.

In Figure 9, is possible observe that in group I, some non–zero values are observed for several cases, supporting the statistically significant differences observed in some of these parameters. However, these values do not assume a pattern, observing values of negative and positive differences within the same group. In group III, the difference values tend to be mostly greater than zero, demonstrating that the AXB algorithm for these parameters calculated higher doses compared to AAA.

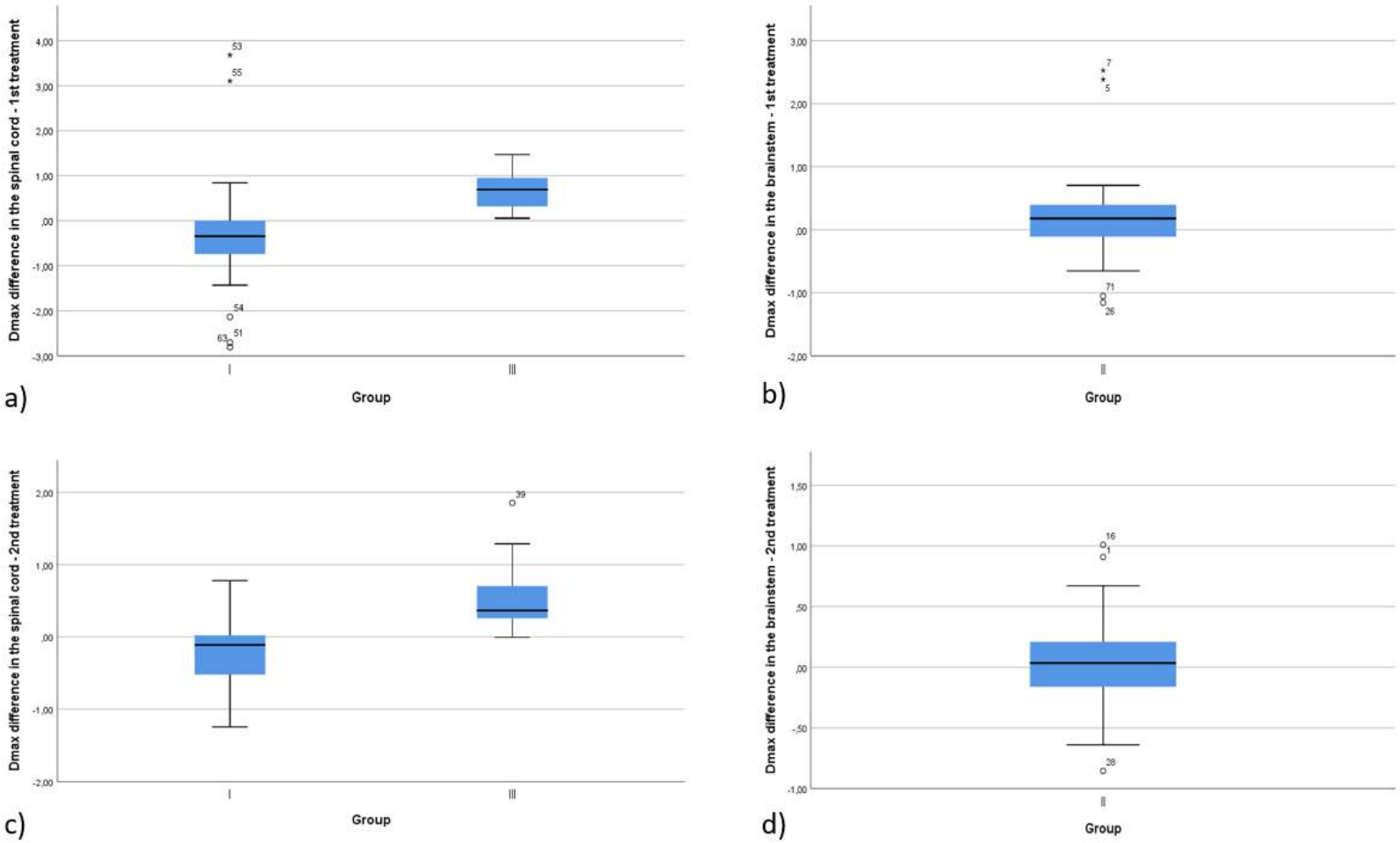


Figure 7 - Boxplot charts for the difference in maximum dose calculated between the two algorithms in the spinal cord and brainstem for the first and second course.

a) and b) boxplot for the difference in maximum dose calculated by the two algorithms in the spinal cord and brainstem for the first treatment, respectively. c) and d) boxplot for the second course. Graph a) and c) illustrate the boxplots for groups I and III. Graph b) and d) for group II.

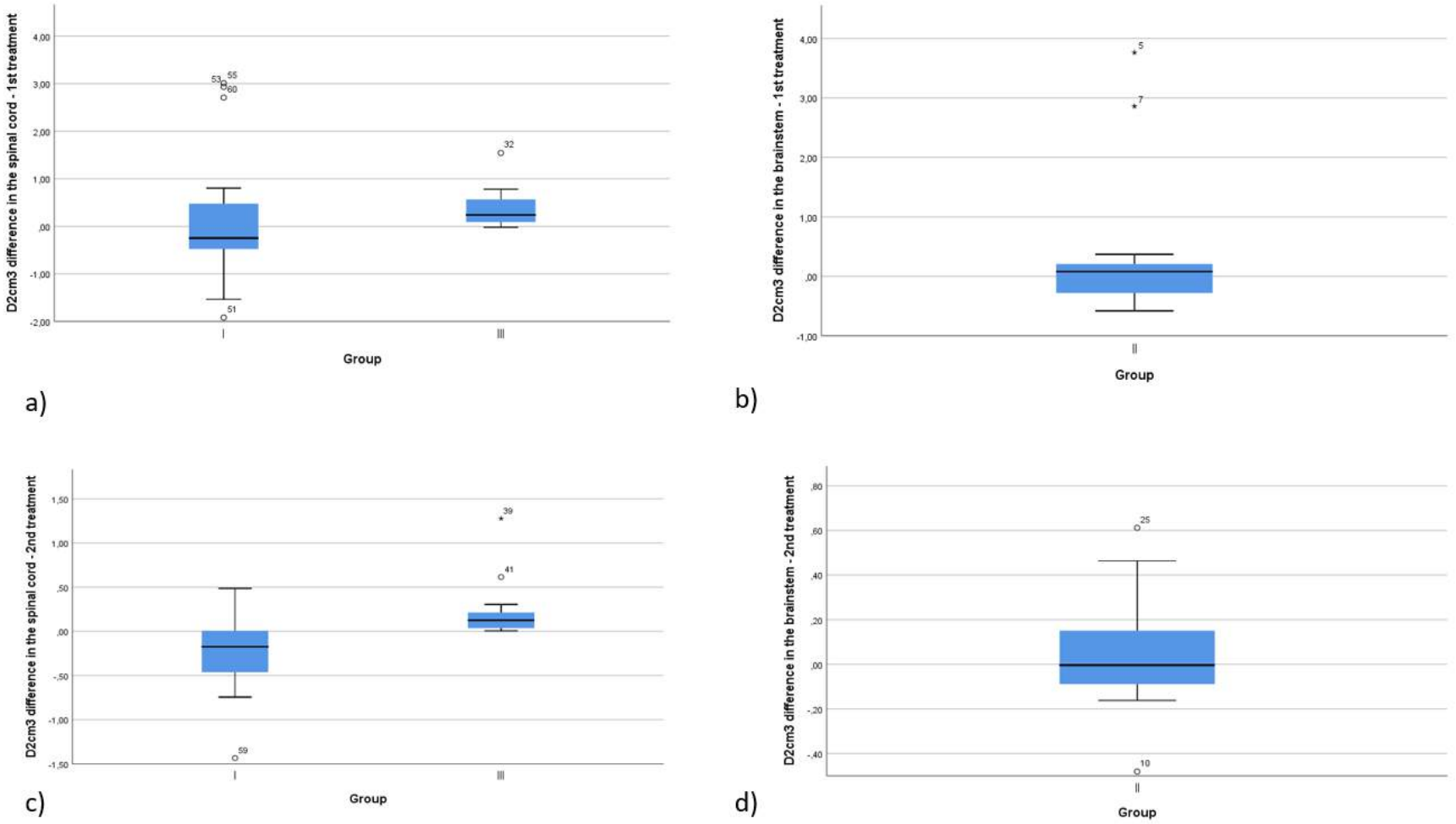


Figure 8 – Boxplot charts for the difference in D_{2cm3} dose calculated between the two algorithms in the spinal cord and brainstem for the first and second course. a) and b) boxplot for the difference in D_{2cm3} dose calculated by the two algorithms in the spinal cord and brainstem for the first treatment, respectively. c) and d) boxplot for the second course. Graph a) and c) illustrate the boxplots for groups I and III. Graph b) and d) for group II.

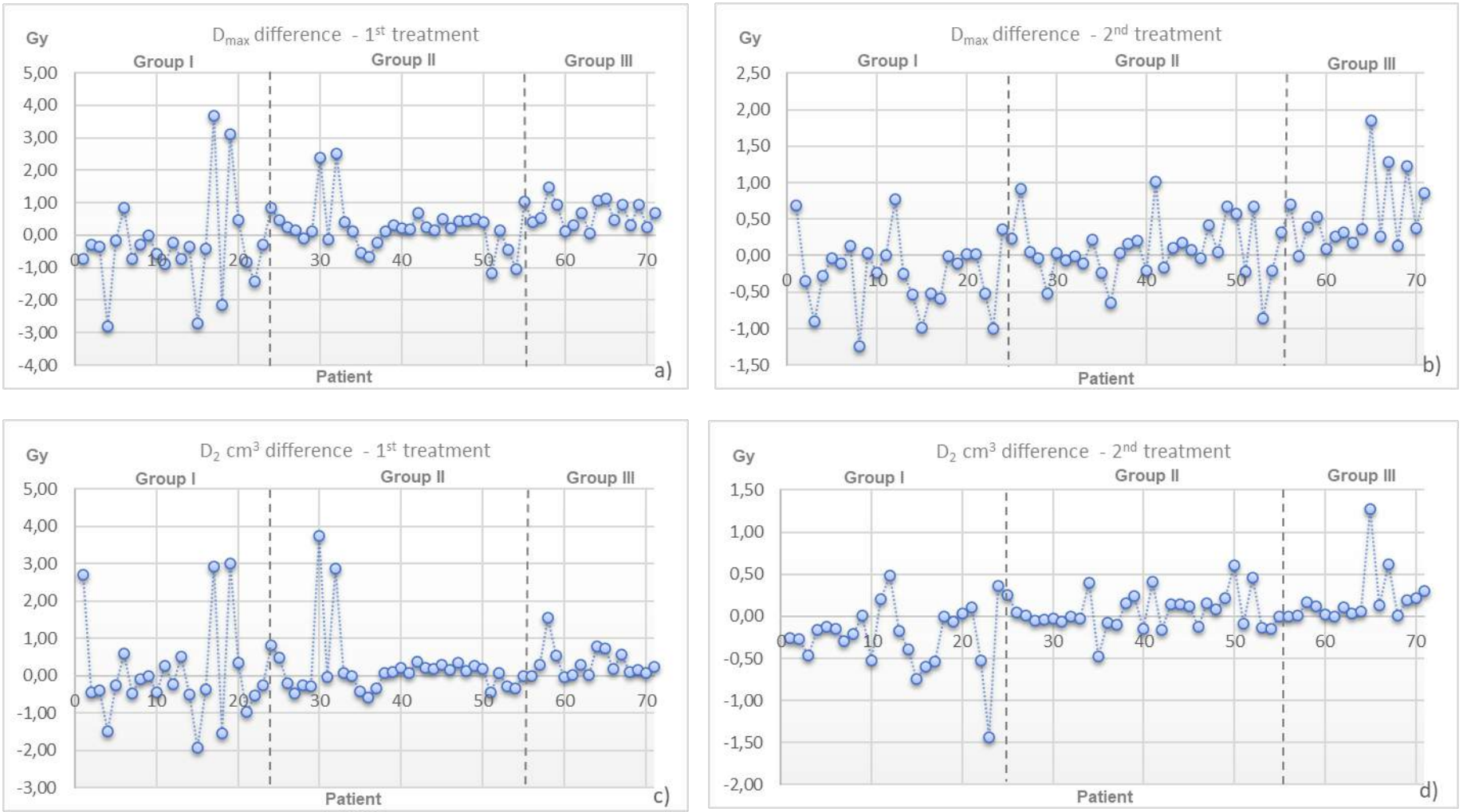


Figure 9 - Differences in maximum dose and D_{2cm3} of the first and second courses for each patient included in the study.
a) and b) graphs of the D_{max} difference calculated with the two algorithms for the first and second courses, respectively. c) and d) graphs of the D_{2cm3} difference calculated with the two algorithms for the first and second courses, respectively.

Group I include cases of target volumes from different anatomical regions, such as head and neck tumors (n = 11) and lung tumors (n = 14). Table 18 shows the median values calculated by the two algorithms for each dose evaluation parameter. Head and neck cases do not have any statistically significant dose parameters. On the other hand, the cases of irradiation in the lung region showed statistically significant differences between the calculation of dose of AAA and AXB algorithm for the following parameters, minimum dose in both courses, maximum dose, average and D_{2cm3} of the second course.

Table 18 - Dosimetric parameters results comparison between AAA and AXB algorithms – lung and head and neck cases.

Evaluated dose parameter	AAA (Gy)	AXB (Gy)	P - value
Group I – Lung Cases			
Doses to spinal cord			
Dmin 1st course	0.34 (0.01 – 1.05)	0.42 (0.01 – 1.05)	**0.009**
Dmax 1st course	26.99 (6.40 – 44.64)	26.41 (5.98 – 43.90)	0.198
Dmed 1st course	8.14 (0.54 – 15.92)	8.70 (0.51 – 17.36)	0.300
D2% 1st course	25.44 (5.40 – 42.93)	24.82 (4.88 – 42.49)	0.221
D2cm^3 1st course	24.96 (3.81 – 42.57)	24.36 (3.45 – 42.12)	0.594
Dmin 2nd course	0.05 (0.01 – 1.07)	0.08 (0.01 – 1.06)	**0.036**
Dmax 2nd course	9.63 (2.93 – 19.81)	9.58 (2.41 – 19.82)	**0.048**
Dmed 2nd course	2.33 (0.62 – 11.14)	2.26 (0.64 – 11.19)	**0.021**
D2% 2nd course	8.05 (2.46 – 19.55)	7.86 (1.91 – 19.64)	0.064
Dcm^3 2nd course	7.59 (2.36 – 18.69)	7.03 (1.83 – 18.89)	**0.041**
Dmin sum	0.22 (0.01 – 4.95)	0.35 (0.01 – 3.23)	0.101
Dmax sum	32.99 (13.86 – 53.53)	31.88(12.66 – 51.93)	0.124
Dmed sum	14.53 (2.12 – 27.34)	12.98 (2.26 – 26.43)	0.594
D2% sum	29.18 (11.87 – 48.68)	28.11 (10.76 – 47.83)	0.158
D2cm^3 sum	26.45 (9.25 – 48.21)	26.86 (8.53 – 47.40)	0.221
Group I – Head and Neck Cases			
Doses to spinal cord			
Dmin 1st course	0.16 (0.08 – 0.79)	0.15 (0.01 – 0.83)	0.689
Dmax 1st course	21.87 (4.11 – 45.84)	21.59 (4.58 – 43.04)	0.575
Dmed 1st course	7.07(1.57 – 27.90)	7.51 (1.58 – 26.91)	0.424
D2% 1st course	20.87 (2.77 – 43.24)	20.59 (3.28 – 42.44)	0.424
D2cm^3 1st course	15.07 (2.64 – 42.94)	17.78 (3.12 – 41.45)	0.929
Dmin 2nd course	0.20 (0.01 – 0.95)	0.18 (0.01 – 1.13)	0.169
Dmax 2nd course	6.69 (1.83 – 34.05)	5.77 (2.06 – 34.75)	0.594
Dmed 2nd course	2.03 (0.56 – 16.13)	1.93 (0.56 – 16.03)	0.248
D2% 2nd course	4.52 (1.78 – 29.58)	4.35 (2.02 – 29.35)	0.213
Dcm^3 2nd course	3.38 (1.75 – 28.12)	3.22 (1.99 – 27.86)	0.155
Dmin sum	0.44 (0.01 – 36.14)	0.50 (0.01– 35.57)	0.534
Dmax sum	32.15 (7.15 – 51.42)	33.79 (7.79 – 50.85)	0.424
Dmed sum	15.34 (1.26 – 42.53)	15.55 (1.25 – 41.95)	0.328
D2% sum	26.18 (5.86 – 47.24)	25.86 (6.59 – 46.39)	0.328
D2cm^3 sum	25.59 (5.76 – 45.04)	25.15 (6.50 – 44.10)	0.328

Abbreviations: AAA – Anisotropic Analytic Algorithm, AXB – Acuros XB Dose calculation algorithm, Min – Minimum, Max – Maximum, Gy – Gray, 1st – first, 2nd – second, D_{min} – minimum dose, D_{max} – maximum dose, D_{med} – mean dose, $D_{2\%}$ – two percent of the dose, D_{2cm3} – dose in two cubic centimetres of the organ.

The same comparison was performed additionally for dose assessment parameters of the target volume. Table 19 summarizes the median values calculated with the two algorithms. For group I, the D_{max} for the first and second courses was statistically significant. For groups II and III, the difference in the calculation with the two algorithms was statistically significant for several parameters. The median values calculated with the AXB were higher compared to those obtained with the AAA algorithm.

Table 19 – Dosimetric parameters results comparison between AAA and AXB algorithms for the target volume.

Evaluated dose parameter	AAA (Gy)	AXB (Gy)	P - value
Group I			
Doses to Target Volume			
Dmin 1st course	44.31 (3.44-64.04)	43.35 (0.28-62.02)	0.304
Dmax 1st course	65.55 (8.71-78.00)	67.16 (9.81-78.96)	**0.001**
Dmed 1st course	60.60 (8.14-71.40)	60.60 (8.51-71.40)	0.374
Dmin 2nd course	27.95 (5.96-55.12)	29.21 (6.03-54.71)	0.476
Dmax 2nd course	53.48 (8.47-67.78)	53.80 (8.65-70.94)	**0.002**
Dmed 2nd course	46.28 (8.00-61.20)	46.63 (8.00-61.20)	0.594
Group II			
Doses to Target Volume			
Dmin 1st course	41.65 (3.38-61.57)	42.26 (2.95-62.17)	**0.004**
Dmax 1st course	57.11 (21.52-77.98)	58.47 (22.55-77.75)	**0.001**
Dmed 1st course	54.00 (20.00-70.00)	54.00 (20.00-70.00)	0.123
Dmin 2nd course	26.23 (2.67-46.82)	25.56 (2.27-43.36)	**0.003**
Dmax 2nd course	32.22 (18.99-64.89)	32.94 (19.73-66.49)	**0.015**
Dmed 2nd course	30.00 (17.23-60.00)	30.00 (18.00-60.00)	**0.002**
Group III			
Doses to Target Volume			
Dmin 1st course	15.77 (0.00-47.04)	16.77 (0.00-46.08)	0.756
Dmax 1st course	21.39 (8.55-52.24)	22.35 (8.68-53.11)	**<0.001**
Dmed 1st course	20.10 (8.00-50.00)	20.53 (8.00-50.00)	**0.046**
Dmin 2nd course	7.45 (4.20-17.93)	7.10 (4.58-17.94)	0.554
Dmax 2nd course	8.86 (8.34-22.26)	9.22 (8.65-24.67)	**<0.001**
Dmed 2nd course	8.27 (8.00-20.32)	8.38 (8.00-21.53)	**0.046**

Abbreviations: AAA – Anisotropic Analytic Algorithm, AXB – Acuros XB Dose calculation algorithm, Min – Minimum, Max – Maximum, Gy – Gray, 1st – first, 2nd – second, D_{min} – minimum dose, D_{max} – maximum dose, D_{med} – mean dose.

As an example, in Figure 10, course two of case 85 of group III is shown, where it is possible to observe the differences in the dose distribution of AAA with AXB in the spinal cord region. AXB dose distributions justify the higher values calculated for D_{max} and D_{2cm3} for the spinal cord.

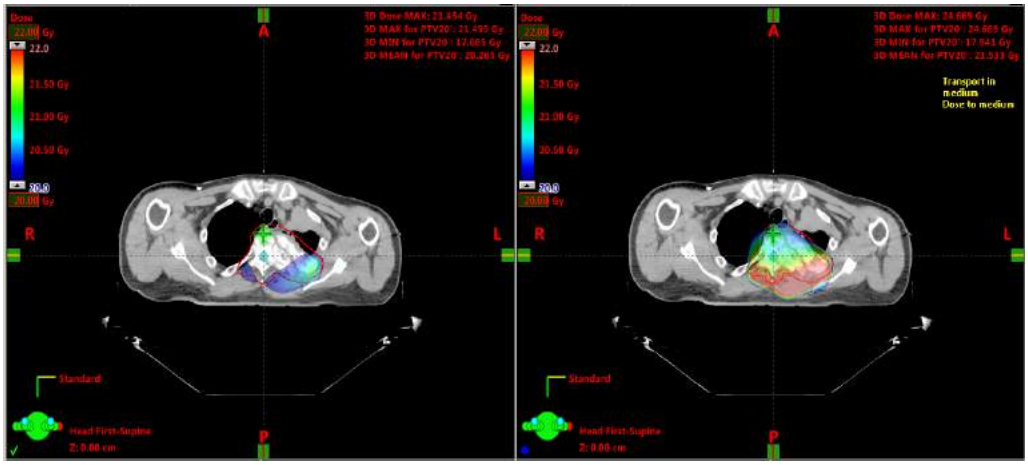


Figure 10 – Dose distribution (range 20Gy – 22Gy) illustrating the difference observed in D_{2cm3} and D_{max} for the spinal cord: on the left: calculation with AAA; on the right: calculation with AXB.

For the same patient, Figure 11 shows the DVH of the same course of treatment for the spinal cord. The triangle curve corresponds to the dose calculated with AAA, while the curve with squares corresponds to the dose calculated with AXB. It is possible to observe the differences mentioned above, the AXB algorithm calculates higher doses for the spinal cord for group III cases.

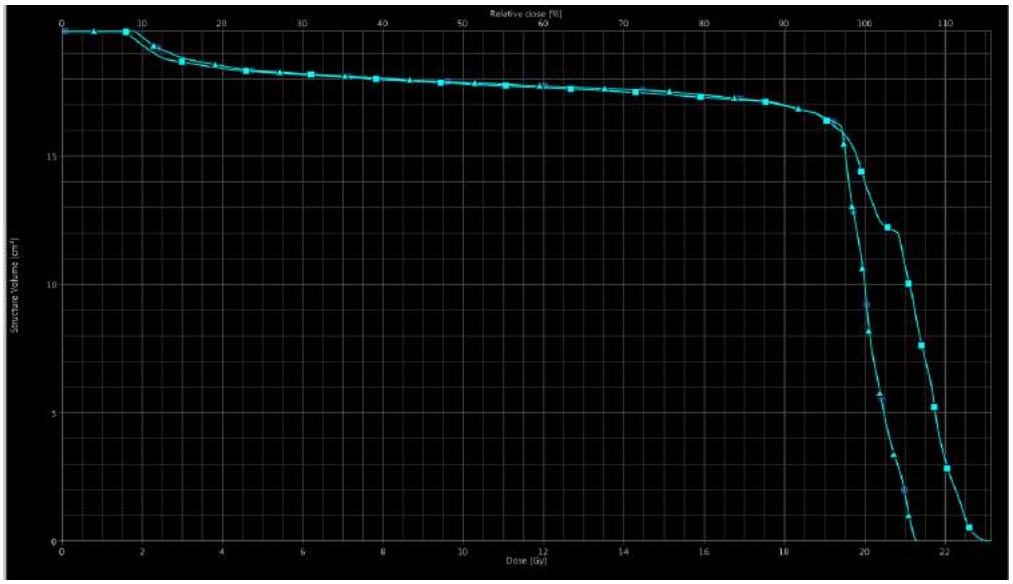


Figure 11 – Dose–Volume Histogram of the spinal cord course irradiation of this case. Curve with triangles refer to the AAA and squares to the AXB calculation.

V. DISCUSSION

Re–irradiation of local recurrences, metastases or second tumors is an increasingly common reality in the clinical practice of radiation treatments. Planning for the treatment of RT at previously irradiated sites is more complex due to the cumulative dose administered to normal tissues (68).

In the first phase of this study, data on various Radiotherapy (RT) courses were collected retrospectively. All the cases collected had the particularity of overlapping the irradiated region in all treatments performed.

Of the total of 91 patients included, all were treated with at least two RT courses. The first RT treatment was curative in 49 of the patients included in this study. Two cases corresponded to prophylactic cerebral RT, while the remaining cases corresponded to palliative treatment.

Palliative radiotherapy is used to relieve symptoms associated with the disease and/or its progression, such as pain associated with bone metastases, brain metastases and superior vena cava syndrome. The dose fractionation schemes used vary, some examples are 30 Gy in ten fractions, 20 Gy in five fractions and 8 Gy in a single fraction (69).

Patients were divided into three different groups, group I and II corresponding to the irradiation of the spinal cord and brainstem, respectively, when the target volume is close to these organs. Group III corresponds to the spinal cord irradiation when the target volume is spinal metastases.

The overall survival of the patients included in this study was 32.00 (95% CI: 25.07 – 38.93) months. Of the three groups under study, in group III, the lowest overall survival of 18.00 (95% CI: 11.80 – 24.20) months was observed. It is important to note that all patients included in this group corresponded to spinal metastases treatments.

In cases of this study, different fractionation schemes were used, depending on the intention of the RT treatment and the technique. Fractions such as those previously mentioned in methods were observed in all study groups, however, we emphasize that in group III, since they depicted cases of spinal metastases, total dose used were equal to or less than 30 Gy in ten fractions.

An important parameter of evaluation when referring to cases of re–irradiation is the time that elapses between treatments. In this study, median time between the first and the second treatment was 20.5 (1 – 129) months, 18 (5 – 80) months, and 10 (3 – 78) months for groups I, II and III, respectively. For patients who received third treatment, the median time between the second and third course was 8.75 (3 – 13) months, 13 (11 – 15) months, and 9.5 (6 – 13) months for the group I, II and III, respectively. It would be expected that the time between RT treatments would be shorter, since all patients included in this study correspond to cases of disease progression.

In the study about re–irradiations of brain metastases developed by Scharp *et al.* (2014) the median time interval between the first and the second treatment was 13.4 (3.4 – 58.8) months (70). Comparatively, group II of this study obtained a time between the first and the second course of RT higher than that observed by these authors.

The time interval between RT treatments is an important factor, since it allows the repair of normal adjacent tissues previously irradiated. For the spinal cord and brainstem, the effects caused by radiation are late, and can manifest from six months to years after irradiation (17). For this reason, the time between treatments plays a crucial role to avoid the accumulation of doses in these organs that can lead to irreversible damage.

Recommendations for the time that must elapse between treatments are made by several authors. Cerebral and spinal cord re–irradiation should be avoided within six months after the first RT treatment. Ideally, re–irradiation should only occur after twelve months, especially when higher doses are used in the first treatment (41, 70). Brenner *et al.* (2008) considers that for a total dose of 34 Gy in the spinal cord, 76% and 85% damage to cells is recovered after one and two years, respectively (11).

For Nieder *et al.* (2018) suggest that for the time interval of one and three years between the treatment courses, retreatment with higher doses is possible. For example, an initial exposure equivalent to 50 Gy in 2 Gy fractions might be followed by an additional 25 Gy in 2 Gy fractions 1 or 2 years later is possible for a low risk of developing myelopathy (71).

In the present study, the second re–irradiation occurred up to six months after the first course in six patients (18.75%) in group I, three patients (7.32%) in group II, and seven patients (38.89%) in group III.

In cases of palliative RT, the time between treatment is weighted between several factors such as the quality of life that the patient can benefit from the treatment. The shortest time between treatments observed was one month, in a group I patient who received three

RT courses for stomach cancer, the treatments were palliative, so the prescription dose was 8 Gy in a single fraction for each treatment. The short time between treatments in this case is not limiting since the dose administered is low and the goal of improving symptoms of disease progression is the main goal of treatment.

Due to the different fractionations used in RT treatments, the conversion of doses into Biologically Effective Dose (BED) is crucial (14). In this study by BED of organ at risk (spinal cord or brainstem) was calculated using the maximum dose for that organ, collected in the planning system.

According to Nieder *et al.* (2005) the risk of cumulative BED myelopathy of ≤135.5Gy_2 is low when the interval between treatments was not less than six months and the treatment dose of the first treatment ≤98 Gy_2, close to the tolerance dose recognized for the spinal cord of 50 Gy in fractions of 2 Gy, using 5 daily fractions per week corresponding to 100 Gy_2 (34).

Therefore, in the first course of treatment, the median BED of the spinal cord for groups I and III was 48.60 Gy_2 (range: 0.29 – 84.74 Gy_2) and 64.85 Gy_2 (range: 41.48 – 93.33 Gy_2), respectively. In other words, no value is above 98 Gy_2 referred to as a threshold for the first treatment.

In the second course, the median BED for the spinal cord was 11.56 Gy_2 (range: 0.48 – 66.99 Gy_2) and 44.99 Gy_2 (range: 40.47 – 66.63 Gy_2) for groups I and III, respectively. The cumulative BED values for the spinal cord taking into account all treatments performed were 76.49 Gy_2 (range: 0.77 – 179.66 Gy_2) and 123.85 Gy_2 (range: 83.18 – 245.59 Gy_2) for groups I and III, respectively. Through the cumulative BED range values observed in this study it is possible to verify that there are cases with a value greater than 135.5Gy_2

This threshold value defined by Nieder et al. (2005) corresponds to the cumulative value for two RT treatments. Three cases resulted in cumulative BED greater than the threshold value in our study. One of them, patient 31 of group I, underwent three RT treatments and obtained a cumulative BED of 179.66 Gy_2. Another example is patient 89 in group III whose cumulative BED was 140.66 Gy_2. This patient underwent only two RT treatments however, he belongs to the group in which the target volume is spinal metastases, thus reaching higher doses than the spinal cord. Finally, patient 91 in group III received a cumulative BED of 245.59 Gy_2. This was the only case where there were four irradiations to overlapping regions included in this study, in addition, all treatments were spinal metastases with higher doses being administered to the spinal cord since the target volume is overlapping.

In this retrospective study, no serious side effects for spinal cord and brainstem were observed. It is important to note that the diagnosis of these effects is complex, the symptoms of their development can be associated with possible disease progression. Factors such as low doses and longer time between treatments are associated with a lower risk of developing adverse effects. For cases where the effect could occur years later, it may not have been observed due to the early patient's death.

Regarding the development of adverse effects on the Organs At Risk (OARs) under study, the following effects were observed in three cases: left cerebral radionecrosis (17 months after the second treatment), fracture of the tenth right costal arch (19 months after the first treatment), and radiation–induced pneumonitis (5 months after the second treatment). Studies targeting other organs at risk present in re–irradiated regions that receive cumulative doses should be carried out to assess and correlate these effects.

According to the study developed by Binkley *et al.* (2016), which assesses the dosimetric and toxicity factors of chest re–irradiation, overlapping courses of re–irradiation can be administered safely and with acceptable toxicity. They observed rib fracture in two patients who received cumulative doses of 81.5 and 117.2 Gy (72).

In the case of the spinal cord, it can be irradiated throughout its length, depending on the location of the irradiated target volume. Authors describe the possibility that there are regions of the spinal cord that are more sensitive to radiation. They consider the thoracic region to be more sensitive to radiation due to the insufficient vascularization particular to this region and the greater amount of white matter (20, 23). Smoking and systematic treatments can also influence the sensitivity of the spinal cord (20).

In our study, different regions of the spinal cord were re–irradiated. In group I, the thoracic region was the most involved in 43.75% of the patients, followed by the cervical region with 37.50% of the patients. In group III, the lumbar region was commonly irradiated in 38.88% of the cases, followed by the thoracic region with 33.33%.

There are suggestions for different $^{\alpha}/_{\beta}$ values for different regions (for example, 2 Gy for the cervical region and 4 Gy for the thoracic region). Different $^{\alpha}/_{\beta}$ values change the BED and calculated EQD_2, which may influence the prediction of possible adverse effects correctly (23). Studies that assess the differences in sensitivity of the spinal cord regions and the possible correlation to adverse effects are needed.

The number of treatment courses has been studied, the study by Xu *et al.* (2020) evaluated the safety efficacy of three or more radiotherapy courses in 33 cases of head and neck cancer. They verified that the repetition of re–irradiation for this pathology is feasible,

however, it brings significant risks of toxicities that must be considered by the multidisciplinary team. They highlighted that the intention was palliative in 52% of cases in the second course of treatment (73).

Another aspect that has been increasingly studied is the prophylactic cerebral RT. This treatment is delivered because mainly cases of primary lung tumors due to the high probability of metastasizing to the brain. However, prophylaxis is questioned due to the potential risk of developing side effects to treatment such as neurological toxicity (74).

In this study, the two patients who initially underwent prophylactic RT, later developed brain metastases requiring re–treatment. This phenomenon was also observed in the study developed by Scharp *et al.* (2014) in which six patients initially underwent prophylactic RT and were subsequently re–irradiated. Thus, it is important to evaluate the doses in these cases, since re–irradiation may be necessary (70).

As a curiosity, three benign cases were reported in Appendix I that were not included in this study but were identified as re–irradiations. According to Binks et al. (2018), although on a small scale, there are increasingly cases of re–irradiation of benign tumors, such as trigemial neuralgia. In their study 22 cases were re–treated with stereotactic radiosurgery, being considered effective and safe treatments, with minimal toxicities (75). In our study, two of the three patients re–irradiated for benign tumors are alive and without reported toxicities associated with RT treatment.

In the second phase of this study, we investigated the dosimetric differences between the Acuros External Beam (AXB) and Anisotropic Analytic Algorithm (AAA) algorithms for the 71 patients included in the three groups.

Initially, dosimetric parameters for the spinal cord and brainstem were compared. For group I, where the spinal cord is irradiated in the treatment of anatomically close target volumes, statistically significant differences were observed. We point out that in parameter $D_{2\%}$ of spinal cord volume and D_{2cm3} of the second course of treatment, the AXB algorithm calculated, apparently lower dose values. However, with the observation of the graphs in Figure 9, it is possible to observe that there is no difference pattern below 0 Gy of values calculated between the two planes, which would be expected considering only the calculated median values.

One possible reason for this event is in the different regions irradiated in this group, such as cases of irradiation of the lung and head and neck. Therefore, we evaluated the same parameters taking into account the irradiated region, lung and head and neck. As can

be seen in Table 18, no statistically significant differences were observed in the irradiation of the spinal cord in the head and neck region. However, for cases in which radiation to the lung region occurs, differences between the calculations of the two algorithms were found.

These results can be justified by the density of the structures surrounding the spinal cord. In the head and neck region, the difference in density between the soft tissues and the spine surrounding the spinal cord is smaller than the difference between the densities of lung and spine in the cases of lung irradiation. In the former there is soft tissue – bone– soft tissue interface, whereas at the later there is lung – bone – soft tissue interface.

Since the AXB algorithm takes into account the dose in the medium, it is expected that it calculates different doses from those of the AAA for regions with different densities. However, it is important to note that according to Bassi *et al.* (2020) the interface regions of very different densities can induce errors in the calculation of the AXB algorithm since there are voxels with large differences in densities (58). Therefore, improved studies are needed to correctly assess the differences observed between these regions.

In group III, corresponding to the spinal cord irradiation in the treatment of spinal metastases, there were more statistically significant differences in the evaluated parameters. We emphasize the parameters of D_{max} and D_{2cm3} since they are important for the evaluation of plans and important for the development of possible side effects. These parameters were statistically significant in the two treatment courses. In the graphs of Figure 9, it is possible to verify that the difference in dose calculation between AXB and AAA tends to have positive values, which means that AXB calculates statistically significant higher doses compared to AAA. For cases in which spinal cord re–irradiation occurs, the possible underestimation of the dose in this organ can be problematic since high cumulative doses are administered.

For group II, corresponding to irradiated brainstem as OAR, no statistically significant results were found between the doses calculated with the two algorithms, for the two treatment courses under evaluation (except the minimum dose value of the first course). Kamaleldin *et al.* (2018) for the same risk organ did not find statistically significant differences when comparing the doses calculated by AXB and AAA for different RT techniques (76).

Since brain structures, such as the brainstem, have densities close to that of water when compared to other tissues such as bone and air. For this reason, the difference in the calculation with the two algorithms may not be different. Kamaleldin *et al.* (2018) there were also no significant differences in regions of densities similar to water (76).

The comparisons between the algorithms were also performed for the dosimetric parameters corresponding to the sum of the treatment plans carried out for each patient. The difference between the doses calculated with the algorithms were significant for the group III dosimetric parameters. However, the results obtained must be carefully analyzed since the sum of the treatment plans implies the overlapping of different computed tomography sets, which causes an inherent error of correct overlapping of the anatomy of each patient especially when substantially different immobilization devices or patient positioning are used in each course.

For the target volume, comparisons between doses calculated by the algorithms were significant for dosimetric parameters of the three groups. Taking into account the median values, the AXB algorithm calculated higher doses compared to the AAA. In the study developed by Ong *et al.* (2017), for lung tumors, the comparison of the maximum dose in the target planning volume calculated by the same algorithms was statistically significant, showing a median value of 54.61 (51.39 – 59.34) for the AAA and 55.52 (52.44 – 59.71) for AXB. The value calculated with the AXB was also higher for this parameter, so the authors refer to an underestimation of the maximum dose of the target volume with the AAA algorithm (77).

However, the results of this study correspond to different target volumes, in locations of different densities and doses of non–identical prescription. Thus, studies restricted to a population of patients with the same tumor type, location and dose prescription should be performed in order to properly use the calculation algorithms for the target volume.

In this way, the calculation with AXB algorithm for cases in which the region to be irradiated there are structures with different densities provides doses taking into account the differences of that medium, calculating a dose significantly different from the AAA algorithm.

It is important to note that within the same group there are differences in the calculated dose inter–patient for the different dosimetric parameters evaluated. This study suggests that for cases in which the irradiated region has structures of different densities, comparing the doses of the AAA and AXB algorithm is important, since it provides important tools for the evaluation of the treatment plan.

In the first phase of this study, no side effects on the spinal cord and brainstem were observed. However, effects on other OAR have been reported, such as fracture of the tenth costal arch and radiation–induced pneumonitis. Since bone and lung are structures with different densities, it is important to develop studies that compare the doses calculated by

the algorithms in order to assess whether there are differences and possibly correlate with high doses in these OARs that could be underestimated initially.

Concluding, as in all situations where there is a change of the calculation algorithm used clinically, also the transition between the use of the algorithm AAA and AXB should be particularly careful in assessing the situations in which the target volume and / or OAR are in areas or close to the interface between regions of very different densities.

This study had limitations, namely: the low number of patients included in each group under evaluation; within group I there are a low number of head and neck and lung cases; different anatomical locations with different densities and the impossibility of evaluations according to the technique and beam energy used.

VI. CONCLUSION AND FUTURE PERSPECTIVES

In conclusion, in our retrospective study including re–irradiated patients in the spinal cord and brainstem region, no side effects were seen in these organs, suggesting that, for observed cumulative BED values, re–treatment involving these organs is safe.

To define the risk of myelopathy, large–scale institutional studies are needed, focusing on the dosimetric data of patients with and without reported effects, so that, in this way, it is possible to estimate a real risk in relation to the dose, allowing to assist and direct the planning of re–treatments.

With the comparison of the calculation algorithms it was found that in group III, where treatment is performed on spinal metastases, there are more dosimetric parameters evaluated with significant differences in the calculation of the two algorithms.

For cases where irradiation of heterogeneous density structures occurs, the AXB algorithm calculates higher doses compared to AAA, with a benefit in the calculation with this algorithm since doses in the risk organs are important parameters of evaluation to minimize possible side effects. The most real assessment possible of the doses that are administered to the organs at risk is essential considering that some patients may benefit from re–treatments.

Considering our findings, in further work, a larger number of cases should be included in order to allow stratification by pathology/anatomical region, treatment technique and beam energy, which would enable the assessment of AXB behaviour in those cases and seeking to correlate administered doses and the adverse effects caused by re–treatments.

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VIII. APPENDIX

APPENDIX I – CHARACTERISTICS OF RT TREATMENTS

Supplementary Table 1. Other characteristics of treatments: modality of RT treatments and complementary treatments.

	Group I n = 32	Group II n = 41	Group III n = 18
Modality 1st course			
3DCRT	16 (50.00%)	23 (56.10%)	18 (100%)
IMRT	6 (18.75%)	6 (14.63%)	0 (0.00%)
VMAT	8 (25.00%)	9 (21.95%)	0 (0.00%)
SBRT	2 (6.25%)	3 (7.32%)	0 (0.00%)
Modality 2nd course			
3DCRT	14 (43.75%)	12 (29.27%)	17 (94.44%)
IMRT	2 (6.25%)	2 (4.88%)	0 (0.00%)
VMAT	14 (43.75%)	16 (39.02%)	1 (5.56%)
SBRT	2 (6.25%)	11 (26.83%)	0 (0.00%)
Modality 3rd course			
3DCRT	3 (50.00%)	0 (0.00%)	2 (100%)
VMAT	3 (50.00%)	3 (100%)	0 (0.00%)
Modality 4th course			
3DCRT	0 (0.00%)	0 (0.00%)	1 (100%)
Other treatments in 1st course			
Chemotherapy	11 (34.37%)	15 (36.59%)	11 (61.11%)
Chemotherapy and surgery	11 (34.37%)	16 (39.02%)	3 (16.67%)
Surgery	2 (6.25%)	4 (9.76%)	2 (11.11%)
Hormone therapy	1 (3.13%)	0 (0.00%)	0 (0.00%)
Immunotherapy	0 (0.00%)	1 (2.44%)	0 (0.00%)
None	7 (21.88%)	5 (12.19%)	2 (11.11%)
Other treatments in 2nd course			
Chemotherapy	13 (40.62%)	20 (48.78%)	11 (61.11%)
Chemotherapy and surgery	3 (9.38%)	5 (12.19%)	0 (0.00%)
Surgery	1 (3.13%)	3 (7.32%)	0 (0.00%)
Hormone therapy	0 (0.00%)	1 (2.44%)	1 (5.56%)
Immunotherapy	0 (0.00%)	1 (2.44%)	1 (5.56%)
None	15 (46.87%)	11 (26.83%)	5 (27.77%)
Other treatments in 3rd course			
Chemotherapy	4 (66.67%)	2 (66.67%)	0 (0.00%)
None	2 (33.33%)	1 (33.33%)	2 (100%)
Other treatments in 4th course			
None	0 (0.00%)	0 (0.00%)	1 (100%)

Abbreviations: 3DCRT – Three-Dimensional Conformal Radiotherapy, IMRT – Intensity Modulated Radiotherapy, VMAT – Volumetric-Modulated Arc Therapy, SBRT – Stereotactic Body Radiotherapy.

Supplementary Table 2. Mean distance from the target volume irradiated to the spinal cord or brainstem for each course of treatment for the different groups.

	Group I n = 32	Group II n = 41	Group III n = 18
Distance from target volume to OAR (1st course)			
Spinal cord (cm)	2.02 (0.37 – 6.95)		Overlapping
Brainstem (cm)		0.03 (0.01 – 3.26)	
Distance from target volume to OAR (2nd course)			
Spinal cord (cm)	2.23 (0.11 – 6.92)		Overlapping
Brainstem (cm)		0.33 (0.01 – 5.56)	
Distance from target volume to OAR (3rd course)			
Spinal cord (cm)	3.09 (0.11 – 12.34)		Overlapping
Brainstem (cm)		2.56 (0.08 – 3.91)	

Abbreviations: OAR – Organ at Risk, cm – centimetres.

Supplementary Table 3. Three benign re-irradiated cases observed in the collection of the remaining cases. The three cases received two courses of RT treatment. The same variables were collected and calculated as in malignant cases.

ID	Benign tumor	1st RT treatment			Time between 1st and 2nd RT months	2nd RT treatment			Overlap region	cBED Gy_3	$cEQD_2$ Gy_3
		Prescription Gy / fx	BED Gy_3	EQD_2 Gy_3		Prescription Gy / fx	BED Gy_3	EQD_2 Gy_3			
a	Timoma	20 / 5	19.80 Gy_2	9.90 Gy_2	22	30 / 10	17.84 Gy_2	8.92 Gy_2	T1 –T4	37.64 Gy_2	18.82 Gy_2
b	Trigeminal neuralgia	80 / 1	130.11	78.07	31	60 / 1	21.73	13.04	B	151.84	91.11
c	Pituitary macroadenoma	46 / 25	62.35	37.41	113	19 / 1	31.08	18.65	B	93.43	56.06

Abbreviations: ID - sequential alphabet of each case included in the study, RT - Radiotherapy, Gy - Gray unit, Gy_2 - Gray unit for α/β of 2 Gy, fx - fractions, BED - Biologically Effective Dose, EQD_2 - Dose Equivalent in Fractions of 2 Gy, Gy_3 - Gray unit for alpha beta of 3 Gy, cBED - Cumulative Biologically Effective Dose, $cEQD_2$ - Cumulative Dose Equivalent in Fractions of 2 Gy, T - Thoracic Region, B – Brainstem.