U. PORTO

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ReSCue: Re-irradiation of the Spinal Cord – Radiobiological, Dosimetric Data and Outcomes

Catarina Conceição da Costa Ribeiro

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INSTITUTO DE CIÊNCIAS BIOMÉDICAS ABEL SALAZAR

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ReSCue: Re-irradiation of the Spinal Cord – Radiobiological, Dosimetric Data and Outcomes.

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Para a minha Mãe

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RESUMO

Introdução: A metastização está associada a mais de 90% das mortes relacionadas com cancro, principalmente em tumores da próstata, pulmão e mama. A medula espinhal é o principal órgão de risco no tratamento de metástases da coluna vertebral porque, 20% dos doentes com metástases ósseas necessitam de tratamento de reirradiação para controlo da doença, alívio dos sintomas e melhoria da qualidade de vida. Parâmetros radiobiológicos, como a Dose Biologicamente Efetiva (BED) e a Dose Equivalente em frações de 2 Gy (EQD2), permitem a comparação entre diferentes esquemas de fracionamento.

Objetivo: Avaliar os parâmetros radiobiológicos e dosimétricos em doentes submetidos a re-irradiação da medula espinhal, após o diagnóstico de metástases da coluna vertebral, e o seu impacto na sobrevivência global e no desenvolvimento de mielopatia.

Materiais e métodos: Este estudo de coorte retrospetivo incluiu 42 doentes re-irradiados no IPO Porto entre janeiro de 2018 e dezembro de 2023. Os doentes tinham metástases da coluna vertebral e foram submetidos a re-irradiação na mesma região.

Resultados: Esta amostra incluiu 24 homens (57%) e 18 mulheres (43%), com uma mediana de idades de 62 anos. As regiões lombar (33%) e torácica (31%) foram as mais afetadas. Antes e após a primeira irradiação, predominou o ECOG 1; após a re-irradiação, 24 doentes mantiveram o score, 6 melhoraram e 12 pioraram. A mediana entre os tratamentos foi de 10 meses. Primeira irradiação: 20 Gy / 5 frações (57%) e 8 Gy / fração única (34%), 3D-CRT (96%). Re-irradiação: 8 Gy / fração única (55%) e 20 Gy / 5 frações (45%), 3D-CRT (83%). Mediana de BED/EQD2: 60/30 Gy_2 (primeira irradiação) e 40/20 Gy_2 (re-irradiação); cumulativa: 100/50 Gy_2. A maioria dos pacientes apresentava risco baixo/intermediário de mielopatia; um paciente apresentava risco alto. Não ocorreu mielopatia em nenhum doente. Mediana da sobrevida global: 15,4 meses (primeira irradiação) e 3,5 meses (re-irradiação).

Conclusão: As doses totais, os valores de BED e EQD2 estavam dentro dos limites recomendados, sem ocorrência de mielopatia. Apesar da sobrevivência global limitada, a re-irradiação demonstra valor clínico para cuidados paliativos, destacando a necessidade de mais pesquisas em doentes com melhor estado funcional.

ABSTRACT

Introduction: Metastatic cancer is associated with more than 90% of cancer-related deaths. Bone is one of the most common regions affected by metastatic site, mainly by prostate, lung and breast cancers. The spinal cord is the main organ at risk in the treatment of metastases because 20% of patients with bone metastases require reirradiation treatment to control the disease, relieve symptoms, and improve patients' quality of life. Radiobiological parameters, such as the biologically effective dose (BED) and the equivalent dose in fractions of 2 Gy (EQD2), allow comparison between different fractionation schemes.

Aim: To evaluate the impact of radiobiological and dosimetric parameters in patients who underwent re-irradiation of the spinal cord following a diagnosis of spinal metastases and its impact in the overall survival and myelopathy development.

Materials and Methods: This retrospective cohort study included 42 patients re-treated at IPO Porto between January 2018 and December 2023. Patients had spinal metastases and underwent re-irradiation in the same spinal region.

Results: The cohort included 24 men (57%) and 18 women (43%), median age 62. Lumbar (33%) and thoracic (31%) regions were most affected. Before and after the first irradiation, ECOG 1 predominated; after re-irradiation, 24 maintained baseline, 6 improved, 12 worsened. Median interval between treatments was 10 months. First irradiation: 20 Gy / 5 fractions (57%) and 8 G / single fraction (34%), 3D-CRT (96%). Re-irradiation: 8 Gy / single fraction (55%) and 20 Gy / 5 fractions (45%), 3D-CRT (83%). Median BED/EQD2: 60/30 Gy_2 (first) and 40/20 Gy_2 (re-irradiation); cumulative: 100/50 Gy_2. Most patients had low/intermediate myelopathy risk; one patient was high risk. No myelopathy occurred. Median overall survival: 15,4 months (first irradiation) and 3,5 months (re-irradiation).

Conclusion: Total doses, BED, and EQD2 values were within recommended limits, with no occurrence of myelopathy. Despite limited survival, re-irradiation demonstrates clinical value for palliative care, highlighting the need for further research in patients with better functional status.

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LIST OF ABBREVIATIONS

2D - Two-dimensional

3D-CRT - Three-dimensional Conformal Radiotherapy

ASTRO - American Society for Radiation Oncology

BED - Biologically Effective Dose

CT – Computer Tomography

D2% - Percentage of the prescribed dose received by 2% of the PTV volume

D98% - Percentage of the prescribed dose received by 98% of the PTV volume

Dmax - Maximum Dose

DVH - Dose–Volume Histogram

EBRT - External beam radiation therapy

ECOG-PS - Eastern Cooperative Oncology Group Performance Scale

EQD2 - Equivalent Dose in fractions of 2 Gy

ESCC - the Epidural Spinal Cord Compression

ESTRO - European Society for Radiotherapy and Oncolog

FSU - Functional Subunit

Gy – Gray

HyTEC - Hypofractionated Treatment Effects in the Clinic

ICRU - International Commission on Radiation Units and Measurements

IMRT - Intensity-modulated Radiotherapy

KPS - Karnofsky Performance Status

LQ - Linear-Quadratic

MRI - Magnetic Resonance Imaging

NCDS - Noncommunicable Disease

NOMS - Neurological, Oncological, Mechanical, Systemic Framework

NTCP - Complications in Normal Tissues Probability

OARs - Organ at Risk

PET - Positron Emission Tomography

PTV - Planning Target Volume

QUANTEC - Quantitative Analysis of Normal Tissue Effects in the Clinic

RT – Radiotherapy

SBRT - Stereotactic Body Radiotherapy

SINS - Spinal Instability Neoplastic Score

SRS – Radiosurgery

TCP - Tumour Control Probability

TD5/5 - The radiation dose that is expected to produce a severe complication in 5% of patients within 5 years.

TD50/5 - The radiation dose that is expected to produce a severe complication in 50% of patients within 5 years.

TME - Tumour Microenvironment

V95% - % of the PTV is covered by the 95% isodose

VMAT - Volumetric Modulated Arc Therapy

I. INTRODUCTION

1. CANCER: A GLOBAL CHALLENGE AND A MULTIFACTOR PROCESS

Nowadays, cancer with approximately 20 million of new cases diagnosed in 2022, is one of the most important noncommunicable diseases (NCDs) worldwide, with a global estimated 9.7 million of deaths. In the next few years, the estimates indicate a continuous increase in the global incidence of cancer, attributing to demographic changes rather than to significant variations in exposure to risk factors (1, 2).

Hanahan and Weinberg identified the hallmarks of cancer, including sustaining proliferative signalling, evading growth suppressors, resisting cell death, enabling replicative immortality, inducing angiogenesis, activating invasion and metastasis, genome instability and mutation, tumour-promoting inflammation, reprogramming energy metabolism, and evading immune destruction (3, 4).

Metastatic cancer is associated with more than 90% of cancer-related deaths and leads to an impact on 5-year survival rates in patients. Metastasis is a complex and multistep process that englobes angiogenesis, invasion, immune escape, and the ability to colonize distant organs (5). Bone is one of the most common regions affected by metastasis, mainly by prostate, lung and breast cancers. The spine is the most common site to the development of bone metastasis, representing about 70% of all of them (6).

2. VERTEBRAL COLUMN AND SPINAL CORD: THE IMPORTANCE IN CANCER TREATMENT

Metastatic spine disease has increased in prevalence, affecting a complex and heterogeneous group of patients. The spine is a common site for metastasis in cancer, only surpassed by lung and liver. Thus, a multidisciplinary approach to treating these patients is becoming increasingly necessary to achieve a global therapeutic decision based in different areas (7, 8).

The vertebral column described as spinal column or spine, forms the central axis of the body skeleton. Superiorly extends from the base of the skull (in the occipital bone) to end caudally at the coccyx, next to the anus, articulating on each side, with corresponding hip bone. The spine encompasses 33 vertebrae divided for five distinct regions, all of them with distinct morphological and functional characteristics. In a cephalocaudal direction spine is divided in seven cervical vertebrae, twelve thoracic vertebrae, five lumbar vertebrae, five sacral and four coccygeal. It is very strong and flexible, representing a significant part of body height in adults, contains and protects the spinal cord and its meningeal coverings in the vertebral canal. The nerve roots exist of spinal cord through the intervertebral foramen of the spine to their anatomical locations. In the sagittal plane, it is possible to see two lordosis (cervical, lumbar) and two kyphosis (thoracic, sacral) (figure 1) (9-11).

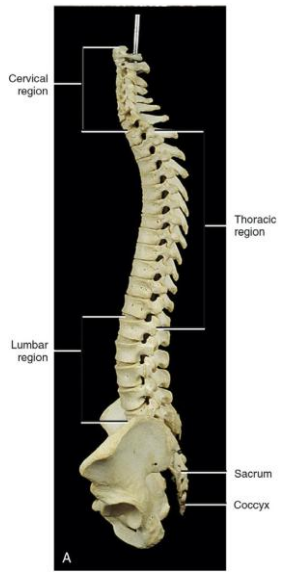

Figure 1- Spinal column in lateral view with cervical and lumbar lordosis; and thoracic and sacral kyphosis (figure taken from Kandahari *et al.* (9)).

The spinal cord is a major component of the central nervous system, measuring approximately 45 cm in length and 1 cm in diameter. It serves as a conduit for neural signals, facilitating the transmission of sensory information from organs and the peripheral receptors to the brain and the motor information from the brain to internal and peripheral effectors

organs. The spinal cord lies within the vertebral canal and extends from the foramen magnum at the base of the skull, above C1, to approximately the level of the second lumbar vertebra, where it terminates in a tapered structure known as the conus medullaris (12-14).

The spinal cord is segmented according to its connection with spinal nerves, comprising 31 segments (Figure 2): eight cervical, twelve thoracic, five lumbar, five sacral, and typically one coccygeal. In clinical radiotherapy practice, however, treatment fields may encompass transitional regions between spinal cord segments, with irradiation extending across adjacent vertebral levels (e.g., D11 to L3 – dorsolumbar region), reflecting both the anatomical continuity of the spinal cord and disease-related target volume requirements. There are two enlargements of the spinal cord, which reflect increased number of neurons in these regions: the cervical enlargement (brachial plexus) and the lumbosacral enlargement (lumbosacral plexus) (12, 13).

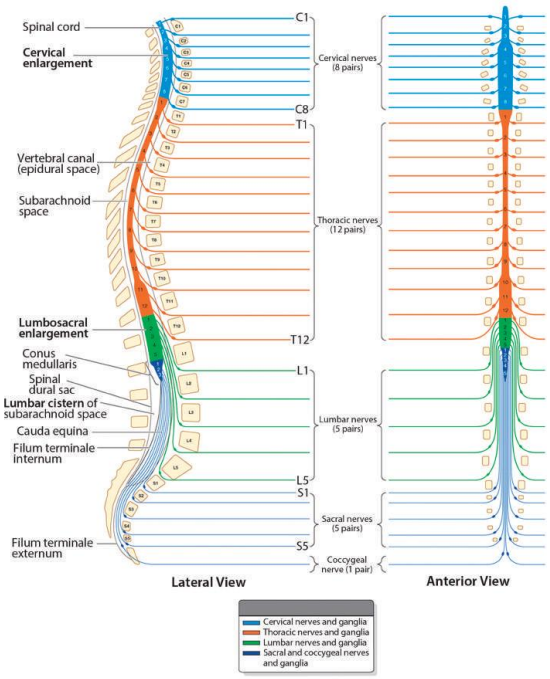

Figure 2- Segmentation of the spinal cord (figure taken from Hardy T. (13)).

2.1 Vertebral Column: Cancer Insights in metastasis process

The increased survival rates of patients with primary tumours have led to a corresponding rise in the incidence of metastatic disease. Bone metastases significantly impact patients' quality of life and are associated with a worse prognosis. This reduction in quality of life is mainly due to pain, loss of mobility, and decreased independence. The management of bone metastases should involve a multidisciplinary team to reduce morbidity and mortality while preserving the patient's quality of life (8, 15-17).

Spinal metastases most commonly originate from primary tumours of the lung, breast, prostate, and gastrointestinal tract, among others, affecting mainly thoracic spine. Wewel and O'Toole (15) stated that up to 70% of all bone metastases are localized in this region with long-term survival estimates for patients with spinal metastases ranging from 10% to 20% at two years. Van den Brande *et al.* (17) report that the overall survival of patients with spinal metastases is approximately six months; however, this varies significantly depending on the histological type of the primary tumour: patients with breast cancer have a median survival of 11–22 months, those with prostate cancer 16–38 months, while patients with lung cancer exhibit the poorest outcomes, with survival ranging from only 2 to 5 months (15-17).

2.1.1 Development process of metastasis

The process of metastasis is complex and depends on several factors. It is possible for metastasis to occur even before the primary tumour becomes clinically detectable. Tumour cells create a premetastatic niche that facilitates colonization (18, 19).

The occurrence of metastasis also relies on the tumour cells' ability to invade the blood or lymphatic circulation and be attracted to metastatic niches. From these haematopoietic or perivascular niches, the tumour cells can disseminate to other anatomical locations. Following their dissemination to the bone marrow, tumour cells may either develop into metastases or enter a dormant state. Once reactivated, tumour cells retain their proliferative capacity, potentially leading to the development of metastatic disease (18, 19).

Bone is one of the primary sites for metastasis due to the abundance of red bone marrow. According to data of Pipola *et al.* (20) it is estimated that more than 10% of cancer patients develop symptomatic spine metastasis and around 70% present metastasis at the

time of death. This strong presence of metastases in the spine is related to its strong vascularization, especially in the vertebral bodies (18, 20).

Bone is a connective tissue composed of several cell types, including osteoclasts and osteoblasts. The presence of tumour cells disrupts this balance, resulting in lytic, osteosclerotic lesions or mixed bone lesion. Osteoblasts are associated with the induction and maintenance of dormancy, while osteoclasts are linked to the reactivation of dormant tumour cells (18, 19).

2.2.2 Diagnosis, Treatment and Prognosis

The presence of metastases in the spine represents not only a significant loss of quality of life but also a reduction in the life expectancy of cancer patients. Treatment requires a multidisciplinary approach, the heterogeneity of primary tumours makes treatment guidelines difficult to standardize (20).

The most common clinical presentation in patients with spinal metastases is pain — especially at night and may have a radicular component. The pain is usually associated with one of two mechanisms: bone expansion or neural compression, which can lead to pain, pathological fractures, neurological deficits bowel and urinary dysfunction, motor and sensory deficits , or paraplegia (8, 20).

Patients with spinal metastases often have poor performance status, frequently associated with cachexia. Diagnosis should be based on a complete medical history, through neurological and physical examination, and complementary diagnostic methods. These complementary methods may include imaging, biochemical, and pathological assessments. Imaging modalities - as plain radiographs, computed tomography (CT), magnetic resonance imaging (MRI), bone scan (99mTc-MDP), and positron emission tomography (PET), are crucial. (8, 16, 20, 21).

Once the diagnosis is confirmed, therapeutic decisions depend on tumour biology, spread pattern, patient condition, and treatment sensitivity. The primary objective is to prevent disease progression, control pain, stabilize spine, preserve function and preserving the patient’s quality of life. Prognosis factors are determined by three main patient-related factors: quality of life, performance status, and life expectancy (8, 22-24).

To support clinical decisions, various scoring systems are employed to support an integrated approach - Neurological, Oncological, Mechanical, Systemic Framework (NOMS), the Spinal Instability Neoplastic Score (SINS), the Epidural Spinal Cord Compression scale (ESCC), the Tokuhashi Score, the Tomita Score, modified Bauer

Karnofsky Performance Status (KPS) and Eastern Cooperative Oncology Group Performance Scale (ECOG-PS) (8, 22-24).

Following a full evaluation of the patient's overall condition, therapeutic options include systemic therapy (hormonal, chemotherapy, targeted, immunotherapy), bone-targeted agents, surgery, and radiotherapy (22, 25).

The therapeutic decision-making process in patients with spinal metastases is influenced by several factors, including patient, tumour, and spine-related factors (age, comorbidities, histology, molecular profile, extent of disease, spinal stability, degree of compression). Surgery is indicated for mechanical instability or neural compression, unless widespread disease or poor performance status contraindicate (22, 25, 26).

External beam radiation therapy (EBRT) is one of the main treatment modalities for spinal metastases. It can be used alone or in combination with other therapies, contributing to improved clinical outcomes and quality of life for patients. This therapy is, therefore, a valuable tool in managing the symptoms associated with spinal metastases (26).

3. THE ROLE OF RADIATION THERAPY IN THE TREATMENT OF SPINE METASTASIS: AN OVERVIEW

In the last decades, radiotherapy has become an important piece in the palliative treatment of spinal metastases. In general, treatment is well tolerated by patients and allows for pain relief, local tumour control, and the recovery of neurological function, leading to an improvement in quality of life (26).

3.1 Biological mechanisms and Clinical indications of Radiotherapy

Ionising radiation penetrates in tissues, causing the ionisation of atoms or molecules, interacting with DNA structures, causing breaks in chemical bonds and biological damage to cells. The interaction of radiation with tissues occurs by direct or indirect effect. In direct effect, radiation is absorbed by matter, leading to several primary processes, such as excitation. In this effect, a direct interaction between a radiation particle and a cellular component leads to the destruction of chemical bonds and damage to biomolecules. In the indirect impact, biological damage caused by the chemical reactions within cells occurs due to free radicals formed through the radiolysis of water molecules (27).

So, these effects cause exogenous damage to DNA structure due to the interactions between radiation particles and cellular components. The main types of DNA damage include breaks of single-strand and double-strand. Tumour cells often have deficiencies in repairing double-strand break mechanisms, depending on alternative repair mechanisms. These mechanisms can be therapeutically targeted through specific inhibitors by enabling tumour cells to lose the ability to repair damage and consequently causing their death (27).

Radiotherapy (RT) can be used as primary treatment for local disease control in patients with radiosensitive tumours. However, these patients cannot have spine instability or spinal cord compression. Additionally, RT may be effective for pain relief in patients with tumour progression; isolated epidural spinal cord compression (ESCC) without bone involvement; those who are not surgical candidates and have a median life expectancy of less than three months; or in cases of severe neurological deficits lasting more than 48 hours. This treatment is indicated for patients with multiple segments or extensive compromise of vertebral elements (24).

Figure 3 illustrates the role of radiotherapy in the treatment of symptomatic bone metastasis, as outlined in the American Society for Radiation Oncology (ASTRO) Clinical Practice Guidelines in 2024 (28).

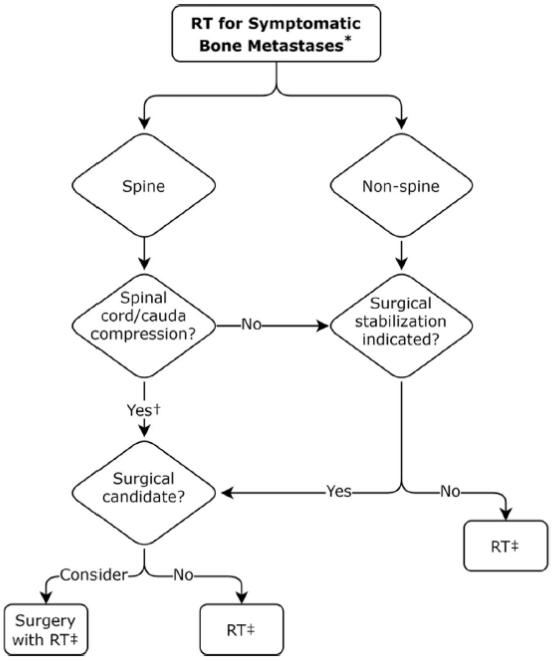

Figure 3 - EBRT for Symptomatic Bone Metastasis (figure taken from Alcorn *et al.* (28)).

3.2 Planning and Treatment Techniques of Radiotherapy

Radiotherapy is widely used in the treatment of spinal metastases. However, considering the increase in patient survival, a guidance to treatment techniques and prescribed doses is essential. The spinal cord is the main organ at risk (OAR) in the treatment of these patients and limiting doses that can be used. It is necessary to consider possible re-irradiation scenarios when prescribing treatment, to minimise side effects on adjacent tissues and without compromising the improvement of the patient's quality of life (26, 29, 30).

Planning techniques have undergone several advances over time, allowing modulation of radiation beams and the administration of higher doses without compromising treatment parameters, while protecting organs at risk. In the past, the conventional two-dimensional (2D) technique was considered the standard for palliative irradiation of the spine. However, the major need to consider possible re-irradiation and the spinal cord dose tolerances has made this technique at a disadvantage (29, 30).

Advances in imaging systems and computer technology have made possible the development of strategies to maximise local control rates and minimise adverse effects related to radiation. With this technological evolution, more advanced techniques of planning appear, such as three-dimensional conformal radiotherapy (3D-CRT), which uses three-dimensional imaging to allow a better evaluation of the treatment volume and a better

precision in radiation planning and delivery. This made it possible to deliver higher doses to the target and minimise exposure to adjacent healthy tissues, such as the spinal cord. So, this technique has become the standard treatment for spinal metastases in many hospitals. (23).

The development of other more advanced techniques of planning, such as intensity-modulated radiotherapy (IMRT) and volumetric modulated arc therapy (VMAT), has allowed for the associated use of stereotactic body radiotherapy (SBRT). This technique can be defined as hypofractionated, highly conformal, image-guided radiation therapy. It allows for the administration of at least one biologically equivalent dose to that administered using conventional fractionated treatment regimens, in one or a few fractions, to an extracranial location. As a result, the spinal cord is no longer a major limiting factor in dose escalation when using more precise options (29, 31).

SBRT can be particularly beneficial in patients with oligometastatic disease, minimal or no epidural involvement, a stabilised spine, and in those who have previously received radiotherapy selectively after surgery. In a selection of patients, the benefits of this technique include reduced exposure of normal tissues to excessive doses, shorter overall treatment times, effective re-irradiation, improved control of radioresistant tumours, and longer pain relief through (26, 29).

All the mentioned techniques have their advantages, and different evaluations and parameters must be considered for each patient. Although 3D-CRT remains a standard technique, more complex and precise options have been developed to improve the therapeutic results in more difficult situations. Thus, IMRT, VMAT, and SBRT are important in difficult cases, especially those involving complex geometric volumes, dose escalation, or the delivery of high doses per fraction. These advanced techniques allow a treatment without compromising treatment efficacy or the safety of surrounding healthy tissues (32).

3.3 Dose prescription options in Palliative Radiotherapy

Advances in planning and treatment techniques have led to better efficacy in the radiotherapy (RT) delivery. These progresses have made the implementation of different fractionation schemes, according to various factors related to the patients, as the topography of the primary tumour, the anatomical location of metastases, previous history of irradiation, risk of pathological fractures, and the life expectancy of the patient. The use of radiobiological principles is also essential to determining the most appropriate treatment scheme for each clinical situation (29).

3.3.1 Concept terms of Radiobiology

Radiobiology is associated with essential concepts as tumour control and normal tissue toxicity. Usually healthy and tumour cells have similar sensitivity to radiation, but in some cases, such as very radiosensitive or radioresistant tumours, that is not the case. The DNA damage caused by radiation is not repaired with the same efficiency in both, since tumour cells in general, exhibit impaired DNA repair capacity when compared to healthy cells. Thus, in RT radiation is delivered in small fractions, which allows healthy tissues to better recover from damage, but tumour cells are less capable of repairing, resulting in more damage (33).

The principle of biological efficacy is represented by tumour control probability (TCP) compared to the risk of damage to healthy tissues. This probability is influenced by several parameters in dose fractionation schemes, including (33):

- Total dose.
- Dose per fraction.
- Time between fractions.
- Total time of the treatment.

In addition, tumour control also depends on tumour heterogeneity, oxygenation state before and during the RT treatment, vascularisation, and presence and recruitment of immune cells, among other factors. Considering these parameters, the main goal of RT is to achieve the optimal balance between tumour control and the risk of toxicity in healthy tissues. (33)

3.3.2 Acute and late tissue response: the therapeutic window and ratio

Normal tissues can be divided into acute-response tissues and late-response tissues. The initial biological effects of radiation result from responses to DNA damage, which activate DNA repair mechanisms, cell cycle checkpoints, and cell death pathways, and may depend on the cell type (33).

Acute-response tissues include tissues with an active cell proliferation compartment, for example, the intestinal mucosa, hematopoietic system, skin, and gonads, which can result in apoptosis or mitotic death within days after irradiation. Furthermore, acute-response tissues are associated with acute radiation-induced toxicity, which usually

appears during treatment or shortly thereafter, and may present as mucositis, nausea, or diarrhoea. These toxicities are generally reversible (33, 34).

On the other hand, late-response tissues do not have an active cell proliferation compartment, being characterised by slower rates of cell renewal, such as nervous and glandular tissues. These tissues are associated with late radiation-induced toxicity, which may be chronic and may appear months or even years after treatment. Examples of late effects can include hormonal dysfunction, neurocognitive impairment, gastrointestinal dysfunction, heart failure, and secondary primary tumours (33, 34).

Radiation constraints vary according to the type of normal tissue and the technique used. Considering these constraints, it is essential to minimise the risk of severe toxicity to healthy tissues in the RT treatment. The tolerance dose of normal tissues influences the maximum dose that can be safely delivered to the target volumes. The term therapeutic window refers to a conceptual range between the two probabilities: the tumour control and the complications in normal tissues (NTCP). Thus, the goal of treatment is to achieve a large therapeutic window, where risks and benefits are balanced, increasing the probability of efficacy and safety of the treatment. Additionally, the concept of therapeutic ratio is also essential in treatment planning. This concept is defined as the relationship between the TCP curve and the NTCP curve, i.e., for example, the efficacy/toxicity ratio (33).

3.3.3 7 R's: the hallmarks of radiobiology

The effectiveness of radiotherapy treatment is determined by the balance between the tumour control rate (whether palliative or curative) and the complication rate in normal tissues. The most important biological factors influencing the response of tumours and normal tissues to fractionated treatment are referred to as the R's of radiobiology (33).

Initially, Withers (35) defined four essential concepts of tissue response to fractionated radiotherapy in his 1975 paper: sublethal damage repair, reoxygenation, redistribution, and regeneration. In 1989, Steel, McMillan and Peacock (36) observing different slopes in the survival curves of tumour cells in response to 2 Gray (Gy) fractions, added a new concept—the fifth R—radiosensitivity. Since then, two further updates have been made to what are considered the hallmarks of radiobiology.

In 2019, Boustani *et al.* (37) introduced immune response reactivation as the sixth R. Advances in the field have demonstrated that RT can modify the tumour microenvironment and inducing both local and systemic immune responses (including the abscopal effect),

which influence tumour radioresistance. The fractionation and dose used can, therefore, have an immunomodulatory effect on the biological properties of radiotherapy.

More recently, Taghizadeh-Hesary (38) refers the concept of “Reinforcement by tumour microenvironment ” which completes the R's of radiobiology, presently. Recent findings have shown that the response of tumour cells to radiation can be influenced by surrounding cellular and non-cellular components, together referred to as the tumour microenvironment (TME). This influences survival, progression, and metastasis, and contributes to resistance to cancer treatments. Thus, the term *“Reinforcement”* summarises the role of the TME in supporting tumour cells against the effects of radiation.

The concepts of radiobiology have evolved over time (figure 4), reflecting a better understanding of the interaction between radiation and both tumour and healthy cells, as well as the current role of radiotherapy in cancer treatment.

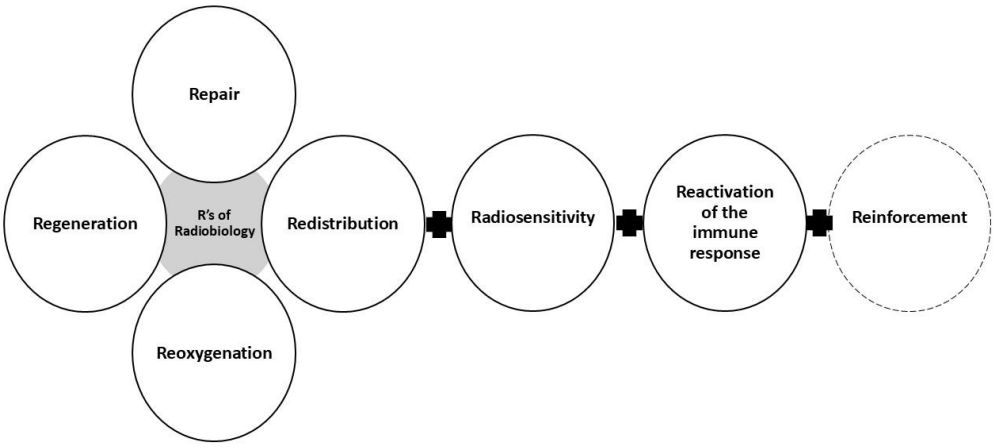

Figure 4 - Illustrative diagram of the evolution of the Rs of Radiobiology.

3.3.4 Fractionated radiotherapy

Henri Coutard introduced fractionated radiotherapy in the 1920s, and, in 1935, Hayes Martin reinforced this method in his work. Radiation oncologists discovered that the delivery of multiple versus single fractions produced better outcomes between tumour control and healthy tissue complications. Currently, fractionated RT remains a basic principle, suffering an update with significant advances in imaging, radiation delivery and technology knowledge that allow the use of higher doses per fraction without compromising efficacy and safety. The basic principles are based on two essential rules: the size of each fraction and the total duration of treatment. The main goal remains to be the creation of a therapeutic

window that takes advantage of the biological differences between normal and tumour tissues (33, 39).

The biological factors of radiobiology help to explain the different responses of normal and tumour tissues to different RT fractionation schemes. During treatment, tumour cells become more radiosensitive due to the redistribution within the cell cycle and reoxygenation. These processes increase cellular damage and lead to more cell death. In normal cells, over the total fractionated treatment time, repair of sublethal damage and regeneration of the tissues occur. With prolonged total treatment time, reoxygenation also contributes to better outcome (33, 39).

In acute-response tissues, the intensity of effects depends on both dose per fraction and number of fractions administered per week. However, late effects in normal tissues largely depend on the size of each fraction, and total treatment time has a limited relevance (33).

Thus, when the dose per fraction is higher and total treatment time is shortened (hypofractionation), late effects can be more severe. However, total treatment time affects both acute effects and tumour control. If the overall duration is prolonged, this has a sparing effect on acute-response tissues, without affecting late-response tissues significantly. The interval between fractions is also an important parameter, with a minimum of 8 hours recommended for most tissues (33).

An ideal fractionation treatment balances radiobiological issues, as re-sensitisation, regrowth, and the beginning of tumour resistance, with the repair advantages of normal tissue (39).

3.3.5 Linear Quadratic (LQ) Model

With constant advances in the field of radiobiology, numerous mathematical models have been proposed to predict tissue response to radiation. Among them, the Linear-Quadratic (LQ) model has been the most thoroughly validated through both experimental and clinical data. Its simplicity has contributed to its sustained use over time, and it remains the standard model in clinical practice. Clinically, the LQ model is applied to a range of problems, including compensating for missed treatment days, comparing different fractionation schemes, and designing new regimens within clinical trial settings (33, 39, 40).

The basic LQ model describes the surviving fraction (SF) of stem cells as a function of the radiation dose (D):

$$\boldsymbol{SF} = \boldsymbol{e}^{(-\alpha d - \beta d^2)}$$ from Ghaderi *et al.* (39).

The main parameters in this equation are the alpha and beta values, which represent the radiosensitivity of irradiated cells. In this model, α represents lethal, irreparable damage, and β represents sublethal, reparable damage. Thus, since the α/β ratio reflects the intrinsic radiosensitivity higher α/β value indicate greater sensitivity to radiation. The α/β ratio differs between normal tissues, depending on the type of response to radiation. After DNA damage occurs, if sublethal damage repair takes place, this ratio decreases, and cell survival increases. However, when damage repair does not occur, the α/β ratio increases, resulting in decreased cell survival (40-42).

In summary, in normal acute-response tissues, the α/β value is higher (less sensitive to fraction size), and lower in normal late-response tissues (more sensitive to fraction size) (40-42).

The Biologically Effective Dose (BED) offers a straightforward method for comparing doses across different fractionation schemes, each associated with distinct biological effects. By applying BED, clinicians can overcome the challenge of estimating the total dose when the dose per fraction is altered. In the BED formula, the α/β ratio reflects the tissue's sensitivity: for acutely responding tissues, this ratio typically ranges between 7 and 20 Gy, whereas for late-responding tissues it is generally between 0,5 and 6 Gy. Consequently, increases in BED are more pronounced in late-responding tissues compared to acute-responding ones (43, 44).

In a fractionated dose context, the total dose (**D**) is administered using **n** equal and consecutive fractions of dose **d**. Based on the LQ model, the Biologically Effective Dose (BED) is useful in directly comparing different fractionation schemes that result in the same surviving fraction of cells (SF) (39).

$$\boldsymbol{BED} = \frac{\boldsymbol{nd}}{\boldsymbol{1+\frac{d}{\alpha/\beta}}}\ (\boldsymbol{Gy})$$ from Ghaderi *et al.* (39).

In this scenario, the α/β ratio allows conclusions to be drawn about the sensitivity of tissues to fractionation. Cells with a higher α/β ratio are less sensitive to the tissue-sparing effect associated with a fractionated regimen (41).

The LQ model has been applied in clinical practice using BED, which allows not only accurately quantifying the sparing effect of fractionated treatment, but also for comparison

between different regimens. Conceptually, BED is the total dose required to produce a specific effect with infinitely small dose fractions (33, 45).

Equivalent dose in fractions of 2 Gy (EQD2) is used as an isoeffective descriptor of any radiotherapy treatment regimen. It is often suggested as a better alternative, even though all its derivations are based on the BED concept. EQD2 allows any treatment regimen to be expressed in terms of total isoeffective dose, as if it was administered in fractions of 2 Gy. This metric has been recommended in clinical practice because it allows for an evaluation of the effectiveness of relatively new fractionation regimens. Additionally, it allows for the standardization of different fractionation schemes to evaluate and classify them, as well as to assess the impact of changes in treatment prescriptions. The equation used to calculate EQD2 for normal tissues with delayed response is as follows (44)**:**

$$\boldsymbol{EQD2 = Dref.\frac{dref+(\frac{\alpha}{\beta})}{2+\alpha/\beta}\ (Gy)}$$ from Dale and Plataniotis (44).

Where **Dref** and **dref** are the total dose and fraction dose used in the reference scheme.

3.3.6 The different schemes of fractionation in Palliative Radiotherapy

The application of radiobiology in a clinical context, through BED and EQD2, allows better comparison between different fractionation schemes, particularly in the context of palliative treatments. It is important to understand which treatment scheme allows the administration of the same iso-effective dose while considering the purpose and general condition of each patient (33).

Palliative radiotherapy, unlike curative radiotherapy, has the main objective of slowing tumour growth, preventing or treating symptoms, and improving the patient's quality of life. As a rule, this type of treatment is used in cases of bleeding, obstruction, and pain. It is particularly applied in patients with bone pain associated with bone metastases, although it is also widely employed to relieve neurological symptoms in brain and spinal cord metastases. The biological effects of RT in terms of pain relief are still poorly understood but are associated with modulation of cytokines. However, this type of treatment usually involves shorter fractionation schemes, hypofractionation, or single-fraction

schemes (8 Gy), which can induce radiobiological effects different from those that occur with conventional fractionation (33).

Palliative treatment of spinal metastases should consider the characteristics of each patient. However, parameters such as total dose and fractionation scheme are debatable to keep the total treatment time as short as possible. Many authors have shown that RT in lower doses is equivalent to higher radiation doses and that short course treatment should be preferred (32).

The American Society for Radiation Oncology (ASTRO) published a systematic review incorporating emerging evidence regarding the treatment of symptomatic bone metastases. Thus, in 2024, ASTRO recommended that for patients with bone metastases treated with RT, the use of a single fraction of 8 Gy, multifraction regimen of 20 Gy in 5 fractions, 24 Gy in 6 fractions, or 30 Gy in 10 fractions was most appropriate (28, 46).

In situations where there is clinical evidence of spinal cord or cauda equina compression, without indication for surgical decompression, RT with a single fraction of 8 Gy, or multifraction regimens of 16 Gy in 2 fractions, 20 Gy in 5 fractions, or 30 Gy in 10 fractions is recommended. However, in selected cases, the use of SBRT technique allows higher doses per fraction, enabling alternative regimens for spinal and non-spinal metastases. Thus, doses of 12–16 Gy in a single fraction (for non-spinal metastases) and 24 Gy in 2 fractions (for spinal metastases) are recommended. Alternative SBRT schemes with similar BED values (3-5 fractions) may also be used depending on the patient's tumour characteristics, the factors related to surrounding normal tissues, and the experience of the medical team(28).

In 2022, the European Society for Radiotherapy and Oncology (ESTRO) published therapeutic guidelines for the treatment of bone metastases. These guidelines are divided into two documents, which distinguish between the most appropriate clinical recommendations for uncomplicated bone metastases and complicated bone metastases (47, 48).

In the case of patients with uncomplicated bone metastases, a single fraction of 8 Gy is recommended over a multifraction regimen. Regarding the use of SBRT in these cases, it is argued that there are no randomised studies supporting its routine use in the treatment of patients with this diagnosis (47).

Cases of complicated bone metastases include all those with spinal cord compression, pathological fractures, metastases with associated soft tissue mass, or neurological deficits. In this situation, ESTRO recommendations consider the different

associated complications. Thus, in cases of spinal cord compression that are not eligible for surgery, a single fraction of 8–10 Gy is recommended, with SBRT being discouraged outside the context of a clinical trial. In patients presenting with neuropathic pain, a single fraction of 8 Gy is also recommended, using techniques other than SBRT. However, concomitant use with pharmacological treatments and neurostimulators is recommended (48).

Liakouli *et al.* (49) studied the impact of different fractionation schemes in a sample of patients diagnosed with osteolytic bone metastases. The results presented indicated that the use of multiple fractions (10 fractions) was more beneficial for bone remineralization in these patients.

Therefore, according to the literature and the various published guidelines, the main fractionation regimens for the treatment of bone metastases, including spinal metastases, are outlined in Diagram of figure 5.

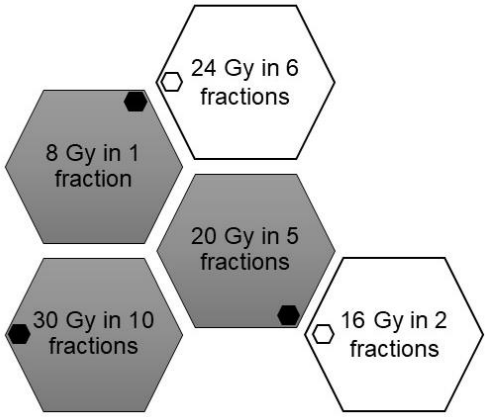

Figure 5 - Diagram of possible fractionation schemes, referenced in the literature, for the treatment of bone metastases (except with the SBRT technique).

4. THE SPINAL CORD: THE DOSE-LIMITING ORGAN IN RADIOTHERAPY

The spinal cord is one of the main dose-limiting organs in radiotherapy, being at risk in several primary tumours and especially in the case of spinal metastases. Depending on the structures of the spinal cord that are affected and the severity of the radiation damage, the side effects can range from sensory deficits and pain to loss of motor function and paralysis. Generally, late effects on normal tissues occur at least 60 days after irradiation. The mechanisms involved in this type of response are related to damage to the vasculature, fibrosis, and damage to the organ's parenchymal cells. Late damage usually occurs in tissues that do not undergo rapid cell renewal and cannot be completely repaired (33, 34, 42).

In short, there are two types of cells in irradiated tissue: stem cells that are dividing and undergo cell death, and functional cells that do not divide and suffer almost no damage. Thus, the time for tissue dysfunction to become apparent — the latency time — depends on the lifespan of the functional cell. Stem cells are then responsible for tissue regeneration, although each cell is only capable of regenerating a certain volume of the organ. This volume is called a functional subunit (FSU). Thus, a structurally defined FSU forms an anatomical structure that defines a group of cells in an organ (42).

With tumour progression being the most common cause of myelopathy and neurological morbidity, radiation-induced spinal cord myelopathy remains a rare side effect. However, cases such as re-irradiation of the spinal cord using conventional fractionation External Beam Radiation Therapy (EBRT); re-irradiation of the spinal cord after previous treatment with traditional fractionation EBRT; and irradiation of the spinal cord using the SBRT technique can increase the likelihood of developing radiation-induced myelopathy (50, 51).

Radiation-induced myelopathy can be of two types: transient myelopathy and chronic progressive myelopathy. Transient myelopathy occurs 2 to 6 months after radiotherapy, is self-limiting and reversible, and Lhermitte's sign is a clinical presentation of this type of myelopathy. This is characterised by the appearance of numbness, tingling, and shock sensations that radiate to the hands and feet after bending the neck. Although its aetiology is not completely understood, it may be related to transient demyelination mediated by a lesion in the oligodendrocytes. This syndrome is transient and occurs over a period of weeks (51).

On the other hand, chronic progressive or delayed myelopathy can occur within a period of months or years after radiotherapy treatment. This is characterised by progressive neurological symptoms such as paraesthesia, motor weakness, and loss of pain and

temperature sensation. In more advanced stages, patients lose bowel and bladder motor control, with total motor and sensory loss. Late chronic myelopathy can occur in two temporal peaks, which are associated with different biological processes. The first peak is associated with demyelination of the white matter because of a lesion. A later peak may be associated with a lesion in the microvasculature of the spinal cord. It should be noted, however, that chronic late myelopathy is a very rare side effect, mainly associated with conventional fractionation and adequate time intervals between treatments (51).

4.1 Tolerance Doses of spinal cord

The spinal cord is the main dose-limiting organ in the treatment of spinal metastases. The occurrence of chronic late myelopathy is a rare effect that is influenced by the total dose, dose per fraction, irradiated volume, and concomitant chemotherapy. However, inter-fraction interval is also an important factor. This interval should exceed six hours, as total dose constraints to the spinal cord may need to be reduced when two fractions are administered on the same day, since incomplete repair of sublethal damage may occur. Although initial studies suggested differences in radiosensitivity among regions of the spinal cord, more recent data do not support this distinction. Nevertheless, the total irradiated volume (or length) of the cord has been linked to the risk of radiation injury, with longer segments being associated with a higher risk of myelopathy (33, 51).

In the treatment of spinal metastases for palliative purposes, hypofractionated schemes with larger fraction sizes (e.g., 8 Gy) are commonly used, which biologically cause more damage than an equivalent dose delivered in 2 Gy fractions. Therefore, to compare different treatment regimens, BED (Biologically Effective Dose) and EQD2 (equivalent dose in fractions of 2 Gy) calculations are employed. These calculations also consider the α/β ratio of both tumours and adjacent organs at risk (OARs). Accordingly, late-responding tissues, such as the spinal cord, are typically assigned α/β values between 2 and 4 Gy (51).

There has always been a need to establish guidelines that clearly define the tolerance doses for organs at risk, particularly the spinal cord. These guidelines made it possible to determine the doses that each normal tissue can safely receive, as well as the probability of complications developing in these tissues. Thus, the evaluation of any dosimetric plan is based on the analysis of the Dose-Volume Histogram (DVH), primarily for the Planning Target Volume (PTV) and the organs at risk. The quality of the plan is associated with the TCP/NTCP balance - its complexity, robustness, and dose distribution - as well as compliance with the tolerance limits of each OAR (33, 52, 53).

Historically, the tolerance dose for the spinal cord has been limited to values between 45 and 50 Gy at the maximum point, for conventional fractionation of 1.8 to 2 Gy per day. However, earlier studies reported other tolerance values in a study involving 1,112 patients treated with various fractionation schemes and total doses - without concomitant chemotherapy - identified only two cases of myelopathy in patients who received less than 50 Gy to the spinal cord. The authors suggest that a total dose of 55 Gy, delivered in fractions of up to 2 Gy/day or 1.2 Gy twice daily, is considered safe (52).

One of the pioneering studies in the field was conducted by Emami *et al.* in 1991 (54), and it defined spinal cord tolerance doses based on the length of the irradiated segment. This study showed that the spinal cord could tolerate different maximum doses depending on the irradiated volume (i.e., length). In summary, the dose associated to the risk of 5% of the patient developing myelopathy within 5 years (TD 5/5) was 50 Gy for 10 cm segment. However, if the irradiated length increased to 20 cm, the maximum dose decreased to 47 Gy. The study also presented data for the dose associated to the risk of 50% of the patient developing myelopathy within 5 years (TD 50/5).

Following Emami's study, other studies emerged with the aim of updating research on spinal cord tolerance doses, considering new techniques and clinical practices. In 2010, Kirkpatrick, van der Kogel, and Schultheiss (50) presented tolerance doses of 50 Gy, 60 Gy, and 69 Gy for the spinal cord, associated with probabilities of developing myelopathy of 0.2%, 6%, and 50%, respectively. However, with the advent of modern planning techniques—characterised by steep dose gradients near the spinal cord— these constraints, originally based on full cross-sectional irradiation, may not directly apply to current high-precision techniques. However, this study was used as a reference for the spinal cord in *Quantitative Analysis of Normal Tissue Effects in the Clinic* (QUANTEC) project in 2010.

The QUANTEC project aimed to review the data published in recent years on tolerance values for various critical organs and the effects associated with their irradiation. This study consists of two introductory articles and 16 organ-specific reviews, including one focused on the spinal cord. However, the values presented in QUANTEC are based on treatment planning using techniques such as 3D-CRT, and do not incorporate data from more modern modalities such as VMAT or SBRT. For techniques like SBRT, which employ hypofractionated schemes and relatively small target volumes, updated guidelines have since been published, in 2021, notably in the *Hypofractionated Treatment Effects in the Clinic* (HyTEC) project (33, 55).

Bisello *et al.* (53) created the *Dose-Volume Constraints fOr oRganS At risk In Radiotherapy* (CORSAIR). This review compiles, in a single document, the tolerance doses for different organs at risk and across various fractionation schemes. In the specific case of the spinal cord, this project cites authors previously mentioned in this text, concluding that the maximum dose should range between 45–50 Gy for conventional fractionation. However, the authors also mention the tolerance doses to be considered when using hypofractionation of 1 to 8 fractions, in smaller treatment volumes (53, 56). In summary (figure 6), according to several authors, the maximum dose in the spinal cord should vary between 45-50 Gy to ensure safe treatment with minimal probability of developing myelopathy.

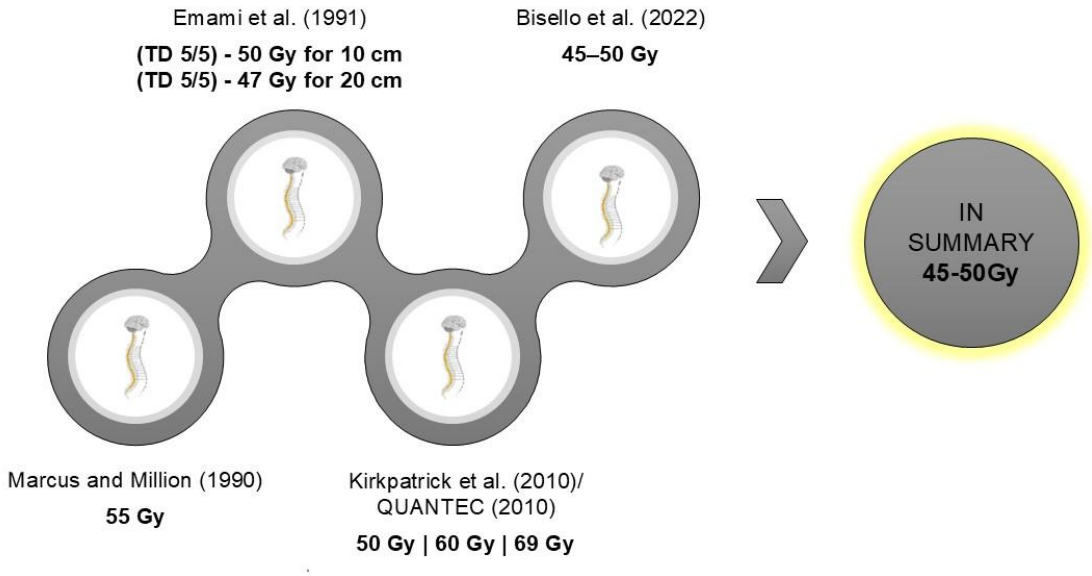

Figure 6 - Diagram summarising tolerance doses for the spinal cord, as described in the literature.

5. RE-IRRADIATION IN SPINE METASTASIS: THE CASE OF SPINAL CORD

In recent years, the number of patients who need a second course of radiation therapy has largely increased, due to improved cancer survival associated with more effective systemic and local treatments. However, a longer survival in these patients is also associated with a higher incidence of recurrences and second malignancies in previously irradiated areas. This has become a challenge, and it has emphasised the critical need for standardised guidelines to define the term re-irradiation, establish evidence-based clinical criteria, and ensure consistency in the nomenclature used in reported cases. Consequently, publications from systematic literature reviews and expert consensus have contributed to a more precise and rigorous definition of the term re-irradiation (57-59).

5.1 Definition and principles of re-irradiation

The definition of **re-irradiation** is based on three key criteria: the administration of a new course of RT, overlap with previously irradiated volumes, or concerns regarding toxicity due to cumulative radiation doses. Re-irradiation is a term that refers to the delivery of an additional course of RT to a previously irradiated region, either with or without geometric overlap, if there is a potential risk of cumulative dose-related toxicity. This classification includes two distinct scenarios (58, 59):

- **Type 1 re-irradiation** involves any new course of radiotherapy that geometrically overlaps with a previously irradiated volume.
- **Type 2 re-irradiation** refers to a new course of radiotherapy administered to a region without direct geometric overlap but with concerns about toxicity due to cumulative radiation exposure.

Re-irradiation is used for recurrent, metastatic, or second primary malignancies in previously irradiated anatomical locations. The balance between tumour control and the risk of complications in normal tissues due cumulative radiation doses to previously irradiated organs is the crucial point in re-irradiation (57-59).

Advances in RT techniques improve the precision of treatment planning and delivery, reducing doses to organs at risk while maintaining adequate target coverage. The improved availability of more precise data from before radiation doses, using CT-based treatment planning and advanced dose calculation algorithms, allows for a more accurate evaluation of cumulative doses and overlaps with previous radiation fields. Furthermore, new schemes with higher doses become possible the delivery of ablative doses for tumours that have recurred after RT or are located adjacent to previously irradiated areas (58, 59).

The goal of treatment may be different to each patient, encompassing symptom palliation and prevention up to local ablation and potential remission. For this, several available RT techniques can be used for re-irradiation. These can include external beam photon radiotherapy and particle therapy (such as proton therapy), resorting to the use of advanced modalities such as intensity-modulated radiotherapy (IMRT), volumetric-modulated arc therapy (VMAT), and brachytherapy. External beam radiotherapy techniques also allow the delivery of radiosurgery (SRS) and stereotactic body radiotherapy (SBRT), which can use high-doses in a focal treatment of resistant or recurrent lesions enabling focal, high-dose treatment of resistant or recurrent lesions. (58, 59).

In re-irradiation treatment patients, it is important to determine the tolerance doses of normal tissues from the prior treatment and possible complications that can arise from that treatment. This provides essential data for estimating the ideal biologically equivalent dose. In this context, the response of previously irradiated normal tissues remains the better indicator to guide therapeutic decisions in re-irradiation. On the other hand, the response of the tumour to the first treatment should also be considered. The occurrence of recurrence in early and late stages probably indicates radioresistance of the tumour and/or the patient. Therefore, when the treatment intent is curative, the dose administered during re-irradiation should be at least equivalent (in biological terms, if applicable) to that used in the initial treatment (60).

Currently, there are no recommendations about tolerance doses for normal tissues in re-irradiation cases. However, it is assumed that these tissues are more susceptible to higher levels of toxicity, regardless of the dose received during the initial treatment. Organs with a serial functional organisation (such as the spinal cord) present a significantly different risk profile compared to those with a parallel organisation. Special attention is therefore required for this group of structures, as high cumulative doses may lead to serious side effects, such as radiation-induced myelopathy (60).

5.2 General considerations in re-irradiation of Spinal Cord

The spinal cord is the main organ at risk in spinal metastases treatment, which has gained high importance because about 20% of patients with bone metastases require re-irradiation treatment to control disease or for symptom relief. Thus, compliance with the tissue tolerance allows a decrease in the probability of developing radiation-induced myelopathy, even of re-irradiation. Furthermore, there are essential points that must be considered when therapeutic decisions in these cases are made, namely total dose/ dose

per fraction; volume and region of the spinal cord irradiated in the first RT treatment and time interval between the two treatments (43, 60, 61):

The biological effects of the dose on tissues depend on their radiobiological characteristics (both in the first irradiation and in the re-irradiation), such as the total dose and the fractionation scheme (43, 60).

Doi *et al.* (62) demonstrated that limiting re-irradiation doses to guide tolerance is not always possible, and sometimes a higher re-irradiation dose is needed in special treatment cases. Thus, they have proposed a simple method for calculating spinal cord tolerance to re-irradiation, assuming there is recovery over time from sublethal damage in the spinal cord. The authors reported that 25% of the damage from the initial irradiation is considered recovered after 6 months, and 50% after 12 months. This results in tolerance doses of 125% and 150%, respectively, in spinal cord re-irradiation.

The safety of re-irradiation treatment with conventional methods for myelopathy remains low if the time between treatments exceeds six months and both treatments have a BED less than 98 Gy_2, and the cumulative BED stays below 135 Gy_2. Nieder *et al.* (63) reported no myelopathy cases when cumulative BED levels reached 120 Gy_2 or lower, and present a table that summarises the risk score for development of myelopathy based on the parameters mentioned above (table 1). This table can serve as a useful aid in special clinical decisions, in which the tolerance doses for re-irradiation do not allow for the desired outcome in terms of either efficacy or local control (43, 63, 64).

Table 1 - Risk score for development of myelopathy in BED. Low risk: point sum ≤3, intermediate risk: point sum 4–6, high risk: point sum >6. Taken from Nieder et al. (63)

Factor	**0 points**	**1 point**	**2 points**	**3 Points**	**4 points**	**5 Points**	**6 Points**	**7 points**	**8 points**	**9 points**
Cumulative BED in Gy_2	≤120	120,1 -130	130,1 -140	140,1 -150	150,1 - 160	160,1 - 170	170,1 -180	180,1 - 190	190,1 - 200	>200
Interval <6 months					X (4,5)					
BED of one course ≥102 Gy_2					X (4,5)					

In summary, the evidence indicates that recovery in spinal cord occurs after first treatment, and the extent of recovery is influenced by several factors — the most important being the initial damage as a percentage of spinal cord tolerance (43).

5.3 Clinical Evidence and Outcomes

Over the years, given the growing need for re-irradiation, several hospital-based studies and reviews have been conducted. They aimed to analyse the response of the patients to re-irradiation, through evaluation of efficacy, local control and probability of developing myelopathy.

Nieder *et al.* (65) published a systematic review of a total of 40 patients. This review allows a combined analysis of all published clinical data, making it possible to create a base for future studies, which can help in therapeutic decisions regarding spinal cord re-irradiation. In this work, the authors, based on the data in the literature, suggest that the risk of myelopathy appears to be low for doses <135.5 Gy_2 when the interval between treatments is not less than 6 months and the dose for each course is <98 Gy_2. However, it is proposed that more prospective data be collected to evaluate the administration of BED doses in the range of 136 to 150 Gy_2 to assess their safety in cases where dose limits may compromise local control.

Nieder *et al.* (63), updating this study with the prospective collection of data from 38 additional patients, obtained the confirmation of prior recommendations. They also evaluated the work of other authors that contained important new observations about spinal cord re-irradiation and added indications to palliative and curative re-irradiation, with the spinal cord as the main organ at risk. With this study, they reaffirm the same indications to doses and time intervals of their previous study, emphasising that the influence of more pronounced dose gradients with stereotactic and intensity-modulated approaches requires further evaluation.

Following these two studies, Doi *et al.* (62) conducted an update of the data, with more recent clinical information on spinal cord re-irradiation. In this study, the results indicate that even patients treated with higher cumulative doses or with an associated risk of myelopathy have not developed clinical evidence of this side effect. However, two main points must be recognised: a longer follow-up period is necessary in living patients to exclude the development of myelopathy. Furthermore, in specific clinical cases that deviate from the established pattern, an individualised clinical decision and informed consent from the patient are essential.

Kawashiro *et al.* (66) evaluated the efficacy and safety of the IMRT (intensity-modulated radiation therapy) technique in the re-irradiation treatment of patients with spinal metastases. A sample of 23 patients was analysed in this retrospective study, concluding that re-irradiation treatment using this technique is safe, with results in pain relief, and with

an improvement and/or prevention of paresis. These results were also associated with a reduced risk of myelopathy.

In another study, Amraee *et al.* (67) conducted a meta-analysis to determine a safe dose of BED, the cumulative dose, and the interval between treatments, which can be associated with the prevention or reduction of risk of development of myelopathy. At the same time, the authors evaluated whether these optimal parameters achieve pain control in re-irradiated spinal cord patients. A total of 17 studies were included, revealing that the use of appropriate BED doses in the first and second treatments, and a safe interval between irradiations, can reduce the effects of myelopathy and achieve regional pain control in spinal cord re-irradiation.

More recently, Ayadi *et al.* (68) presented a survey that aimed to show the experience of institutions on re-irradiation. Data from 48 institutions was obtained, revealing that there are several approaches and tools that can be used in re-irradiation treatment.

II. AIMS

Considering technological advancements and clinical challenges in recent years, data collection and approaches to treating re-irradiated patients have become increasingly important. With notable improvements in oncology treatments, there has been a significant increase in patient survival rates. However, this longer life expectancy often leads to the need for multiple courses of irradiation.

In palliative patients, in whom the primary disease has progressed and invaded other organs, bone metastases account for the highest percentage. Furthermore, among patients with bone metastases, the spine is the region most affected by tumour progression.

The treatment of this group of patient's regions. This presents a challenge due to limited tolerance to radiation.

In summary, the aims of this project are:

Main aim:

- To evaluate the impact of radiobiological and dosimetric parameters in patients who underwent re-irradiation of the spinal cord following a diagnosis of spinal metastases and its impact in the overall survival and myelopathy development.

Specific aims:

- Characterize the study sample in terms of demographic and clinical features, including the time interval between treatments.
- Analyse fractionation schemes, techniques, and radiobiological/ dosimetric data used in first irradiation and re-irradiation.
- Calculate BED, EQD2, and cumulative doses, and evaluate overall survival following first irradiation and re-irradiation.

III. MATERIALS 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 (Ref. CES.090_25)).

1. Type of study

This research project is a retrospective cohort study that was conducted at the Radiotherapy Department of the IPO Porto.

2. Population and sample

This project involved the population of patients that were re-irradiated at the Radiotherapy Department of IPO Porto. The selection was made using the department database, using the keyword “re-irradiation” in a temporal search that included the period from January 2018 to December 2023.

In selecting patients, the **inclusion criteria** for the study were defined as:

- Patients diagnosed with bone metastases in the spine, treated at the Radiotherapy Department.
- Patients had undergone at least two irradiations in the same region of the spine (i.e., overlapping treated areas – Re-irradiation Type I).

Exclusion criteria were defined as:

- Patients with disease located outside the spine, with diagnoses other than those already specified (e.g., spinal cord metastases, bone involvement by soft tissue tumours).
- Patients who did not undergo at least two radiotherapy (RT) treatment.
- Patients in which there was no overlap in the re-irradiated regions.

Using re-irradiation term, a sample of 641 patients was obtained, designated in the system by radiation oncologists as re-irradiations. This search was refined to obtain a sample of patients diagnosed with bone metastases, whose treatment objective was palliative and reirradiation occurred in the spine. Within the anatomical location, all designations such as “cervical,” “dorsal,” “lumbar,” “sacral,” and their variants were considered. This research yielded a sample of 107 patients.

Of these 107 cases, after a more detailed analysis of each one, a total of 51 patients were **excluded** for four reasons:

- Repetition of the same patient in the database.
- Registration of only one treatment in the system.
- No direct irradiation of the spine, and no Type I re-irradiation.

Thus, after this more detailed analysis, a sample of **56 patients was obtained**.

Subsequently, after a further analysis of the remaining sample, during the collection of variables, 14 more patients were excluded. The reasons for exclusion are partly like those of the first analysis, i.e., no direct irradiation of the spine and no occurrence of Type I re-irradiation. However, patients who did not treat bone metastases (bone involvement by soft tissue tumours) were also excluded, as well as others due to non-completion of re-irradiation treatment.

In summary, after careful selection according to the previously defined inclusion and exclusion criteria, a sample of **42 patients** was obtained, as shown in the flowchart in Figure 7.

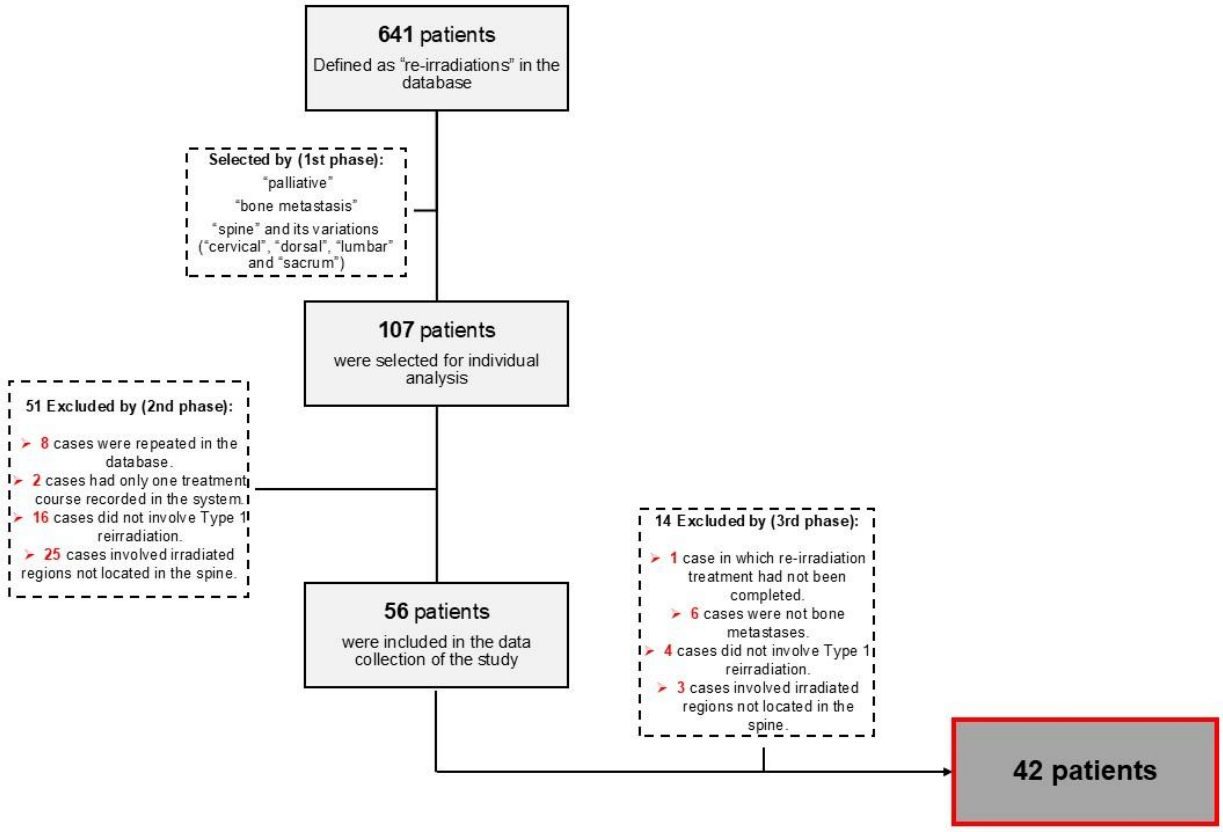

Figure 7 - Flowchart illustrating the selection of the study sample.

All patients in the study were referred to the RT Department either through internal referral during multidisciplinary group consultations or through external referral from other institutions. All patients underwent treatment at the IPO Porto Radiotherapy Department; however, not all had follow-up consultations at the institution, as some were followed up at other hospitals. Nevertheless, all patients received medical follow-up before and after treatment, which allowed their clinical status to be assessed throughout the study period.

3. Study variables and data collection

Data collection was carried out using sources such as medical consultations (multidisciplinary group consultations, medical oncology consultations, radiation oncology consultations, among others), nursing consultations, and hospital admission notes available on the internal hospital network.

Data related to the dosimetric treatment plan were collected using Varian's ARIA® Radiotherapy Information System and Eclipse™ treatment planning system (Varian Medical Systems, Palo Alto) version 13.5.

Given the workflow that takes place in the RT Department of IPO Porto, Figure 8 summarises the patient's journey after referral to the service (whether from within the same institution or from external institutions). For patients undergoing palliative treatment, some steps in this workflow may overlap or be omitted. In cases where only a single fraction of RT is prescribed, the start and end of treatment occur on the same date. Consequently, there is only one consultation with the radiation oncologist, rather than one at the beginning and another at the end of treatment. This applies only to treatments involving more than one fraction. After treatment ends, patients continue follow-up with medical oncology, regardless of whether they are inpatients or outpatients.

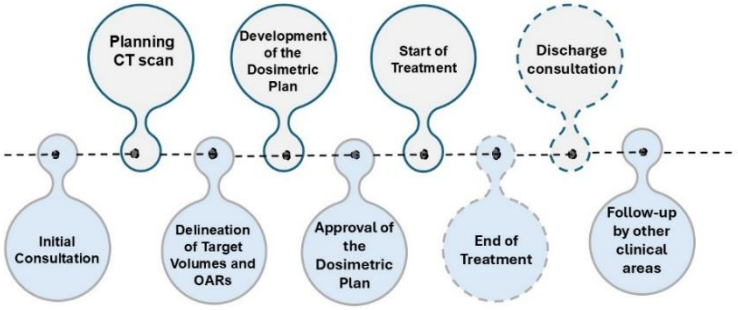

Figure 8 - Workflow of RT Department of IPO Porto.

The variables studied were divided into four main categories:

- Patient demographics.
- Patient clinical data.
- Treatment and dosimetric data.
- Follow-up Data.

A summary of all variables under study is presented in Table 2. A more detailed explanation of some of the variables collected is provided below.

Table 2 - Study variables.

<table>
<tr><th colspan="5">Study variables</th></tr>
<tr><th>Patient Data</th><th>Clinical Data</th><th colspan="2">Treatment and dosimetric Data</th><th>Follow-up Data</th></tr>
<tr><td>Age</td><td>Date of diagnosis of primary tumour</td><td>Date of first treatment</td><td>Treatment technique</td><td>Time of death</td></tr>
<tr><td>Gender</td><td>Primary Tumour</td><td rowspan="2">Date of re-irradiation</td><td>For Target: Dmax (Gy); $V_{95\%}$; $D_{2\%}$ e $D_{98\%}$</td><td>Last appointment date</td></tr>
<tr><td rowspan="3"></td><td>Location of metastases in the spine</td><td>For OAR - spinal cord: Dmax (Gy)</td><td>Side Effects</td></tr>
<tr><td rowspan="2">Performance status (ECOG-PS)</td><td>Total dose (Gy)</td><td rowspan="3">BED and EQD2 (Gy) values and their cumulatives</td><td rowspan="3">Disease control</td></tr>
<tr><td>Dose per fraction (Gy)</td></tr>
<tr><td>Other treatments performed (Therapeutic state in re-irradiation)</td><td>Interval between treatments (months)</td></tr>
</table>

Abbreviations: Gray (Gy); Dmax (maximum dose); $v_{95\%}$ (volume that receives 95% of the dose); $D_{2\%}$ (dose received by 2% of the volume); $D_{98\%}$ (dose received by 98% of the volume).

3.1 Patient and Clinical Data

The variable “age” was calculated based on the date of the first radiation treatment analysed.

The variable “performance status” was assessed according to the Eastern Cooperative Oncology Group Performance Scale (ECOG-PS), using values available in each patient's records. The timing of collection was defined as “before” and “after” treatment. “Before” refers to the assessment made at the first consultation at the

radiotherapy department. “After” refers to a period between two and five weeks following the end of treatment (according to the timing of the consultations performed). This collection was performed before and after each irradiation that was studied.

The variable “Location of metastases in the spine” was coded with six designations: “cervical”, “dorsal”, “dorsolumbar”, “lumbar”, “lumbosacral”, and “sacrum.” This allowed for more detailed analysis according to spine region. The terms “dorsolumbar” and “lumbosacral” refer to irradiated areas that include a transition zone in the spine regions.

Regarding additional treatments, a variable “Therapeutic state in re-irradiation” was created. This variable is a nominal qualitative variable, whose main purpose is to group patients in the sample into two distinct categories at the time of re-irradiation: those who were still undergoing active systemic treatment (chemotherapy or immunotherapy) – **In systematic treatment**, and those who had already been referred for palliative care - **Referred for palliative care**.

3.2 Treatment and Dosimetric Data

The variables “total dose,” “dose per fraction,” and “interval” were collected to analyse the fractionation schemes used and to obtain data for calculating the Biologically Effective Dose (BED) and Equivalent dose in fractions of 2 Gy (EQD2) and their cumulative totals. These parameters are essential for the radiobiological evaluation of treatment plans and the equations used for the calculations were as follows (previously presented in **section 3.3.4 of the Introduction**:

$$\boldsymbol{BED = \frac{nd}{1 + \frac{d}{\alpha/\beta}}\ (Gy_2)}$$

$$\boldsymbol{EQD2 = Dref.\frac{dref + (\frac{\alpha}{\beta})}{2 + \alpha/\beta}\ (Gy_2)}$$

Note: the α/β value used in the calculations was **2**Gy, according to Jones, Klinge and Hopewell (69).

Among the variables related to the dosimetric plan, it should be noted that the maximum doses in target volume were evaluated. Generally, is the Planning Target Volume (PTV to which the dose is prescribed.

Regarding the dosimetric parameters relating to the planning techniques, some of the parameters collected vary according to the technique used. For the evaluation of treatments using the three-dimensional conformal radiotherapy (3D-CRT) technique, the standards of

the International Commission on Radiation Units and Measurements (ICRU) 62 (70) are used. According to these standards, the treatment plan is evaluated to ensure that 100% of the PTV is covered by the 95% isodose—i.e., 100% of the PTV receives 95% of the prescribed dose. For this purpose, the variable $\mathbf{V_{95\%}}$ was created.

When using intensity-modulated radiotherapy (IMRT) and volumetric modulated arc therapy (VMAT) techniques, treatment plans are evaluated according to ICRU 83 (71) standards. In these standards, the evaluation of the dosimetric plan is based on the premise that 2% of the PTV volume receives a dose equal to or less than 107% of the prescribed dose ($\mathbf{D_{2\%}}$). Furthermore, 98% of the target volume receives a dose equal to or greater than 95% of the prescribed dose ($\mathbf{D_{98\%}}$).

The assessment of organs at risk (OARs) was performed only for the spinal cord. This organ is a serial organ, and as already described in **section 4 of the introduction**, its assessment considers the maximum dose received by the organ (**Dmax**).

3.4 Follow-up Data

The follow-up dates were updated to the last day of data collection, **June 13, 2025**. The side effect analysed in each patient's medical history was the possible development of myelopathy and the variable disease control as classified as **Alive With Disease (AWD)**, **Death With Disease (DWD)**, **Alive No Evidence of Disease (ANED)** and **Death No Evidence of Disease (DNED)**.

4. Statistical analysis

Continuous variables are presented with their median, maximum and minimum values. For categorical variables, the values are expressed as frequencies and percentages.

The age variable was obtained by subtracting the date of birth from the date of the first irradiation studied. The interval between irradiations was calculated as the difference between the first day of re-irradiation treatment and the last day of the previous irradiation treatment.

The follow-up time for patients was not defined as a fixed period, considering the clinical status and treatment intent of the patients in the sample. Thus, the follow-up time was considered as the period between the last day of the last irradiation studied and the date of death or the last consultation recorded in the patient's medical history.

Overall survival was calculated for two different periods: from the end of the first treatment and from the end of the last treatment studied, each compared with the date of death. Survival curves were estimated using the Kaplan–Meier method. Statistical analysis was performed using **R** (version 4.5.1; R Core Team, 2024, Vienna, Austria) within **RStudio** (version 2025.05.1 Build 513; Boston, MA, USA).

IV. RESULTS

1. Characterization of the sample study

The sample encompasses a total of 42 patients, 24 male and 18 female with a median age of 62 (43-81) years. In the study, different primary tumours were found. The most frequent were lung and bronchus (n=10), breast (n=6) and prostate (n=5). The table below (table 3) shows de frequencies for gender and primary tumour variable, as well the median, minimum and maximum for age variable.

Table 3 - Characterisation of gender, age and primary tumour variables.

Variable		n (%) / Median [Min-Max]
Gender		
-	Male	24 (57%)
-	Female	18 (43%)
Age (years)		62 [43-81]
Primary tumour		
-	Lung and bronchus	10 (24%)
-	Breast	6 (14%)
-	Prostate	5 (12%)
-	Colon	4 (10%)
-	Kidney	4 (10%)
-	Others	13 (30%)
Total		42 (100%)

For a more detailed analysis of the sample, the spine was divided into six distinct regions. The data obtained revealed a higher number of cases located in the lumbar spine (n=14) (33%) and in the thoracic spine (n=13) (31%). The remaining patients in the sample (n=15) (36%) developed metastases in other regions of the spine, with a very similar distribution, as can be seen in Figure 9.

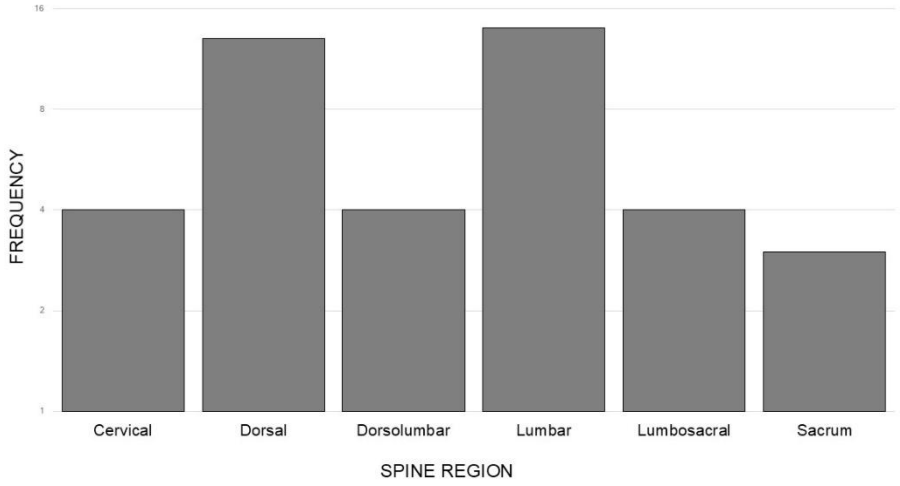

Figure 9 - Distribution of the patients by location of metastases in the spine.

The sample was then divided into two groups based on the variable “Therapeutic state in re-irradiation”. This division resulted in one patient group designated as “In systemic treatment” with a total of 35 patients (83%) and another group designated as “Referred for palliative care” with 7 patients (17%), as shown in Figure 10.

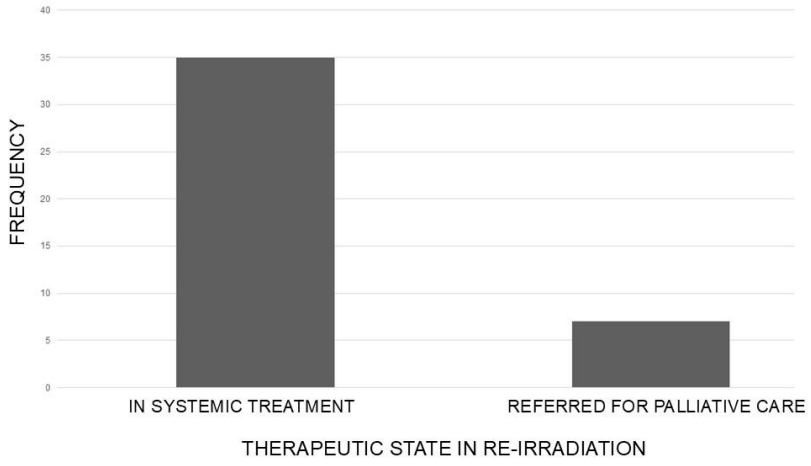

Figure 10 - Distribution of the patients by status at re-irradiation.

1.1 Performance status (ECOG scale) overall and by group

OVERALL

From the initial sample of 42 patients, ECOG scores were analysed at two time points for each irradiation: before and after the first RT treatment, and before and after re-irradiation.

Figures 11 and 12 show the distribution of ECOG scores before and after the **first irradiation**. ECOG 1 was the most frequent score at both time points, followed by ECOG 2. Most of the patients maintained the same score after treatment, with only minor variations observed: of the two patients with ECOG 0, one progressed to ECOG 1; among the 25 with ECOG 1, one improved to ECOG 0 and one worsened to ECOG 2. Of the 11 patients with ECOG 2, nine remained stable, one improved to ECOG 1, and one deteriorated to ECOG 3. Of the four patients with ECOG 3, three remained unchanged and one improved to ECOG 1.

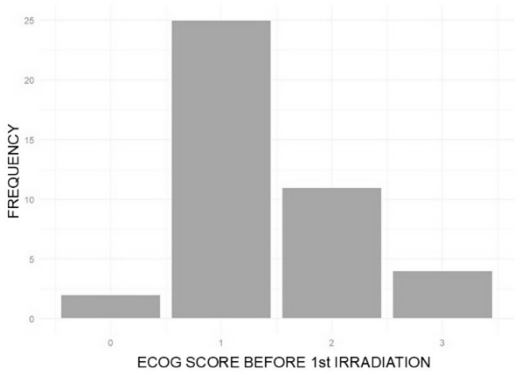

Figure 11 - Distribution of the patients by ECOG score before the first irradiation treatment.

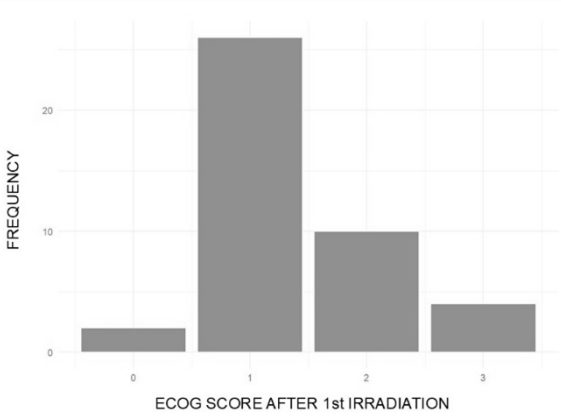

Figure 12 - Distribution of the patients by ECOG score after the first irradiation treatment.

Figures 13 and 14 show the distribution of ECOG scores before and after **re-irradiation**. These charts highlight that all ECOG values from 0 to 4 were represented at both time points. No single value predominated, although ECOG 4 was the least frequent: 4 patients (10%) before and 7 patients (17%) after re-irradiation. Notably, ECOG 0 was observed in only 1 patient (2%) after re-irradiation.

Among the 13 patients with ECOG 1 before treatment, eight remained stable, four deteriorated to ECOG 2, and one improved to ECOG 0. Of the 13 patients with ECOG 2, five showed no change, three improved to ECOG 1, and five progressed to ECOG 3. In the

group of 12 patients with ECOG 3, seven remained stable, two improved (one to ECOG 1 and one to ECOG 2), and three deteriorated to ECOG 4. All four patients with ECOG 4 at baseline maintained this score.

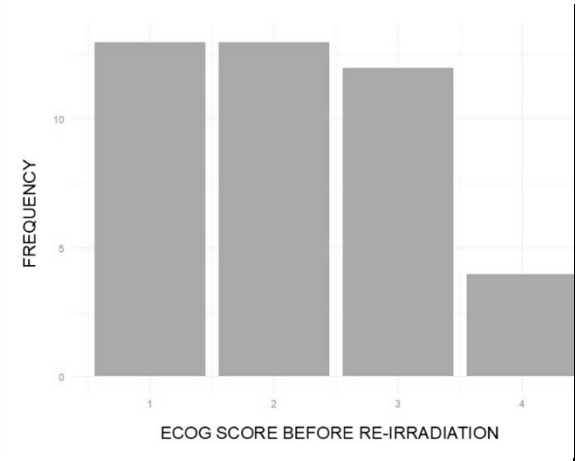

Figure 13- Distribution of the patients by ECOG score before re-irradiation.

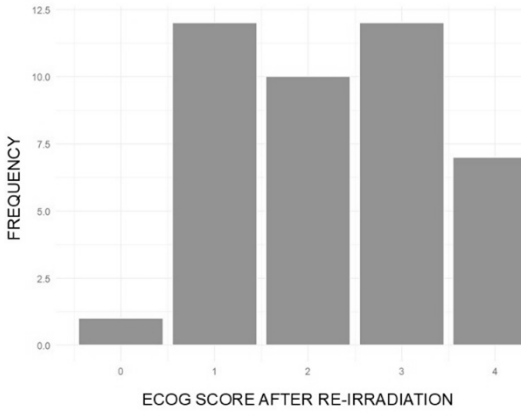

Figure 14 - Distribution of the patients by ECOG score after re-irradiation.

BY GROUP ("In systemic treatment" and "Referred for palliative care")

After dividing the sample into two groups of patients ("In systemic treatment" and "Referred for palliative care"), a comparative analysis of performance status (ECOG-PS) was conducted. These groups were defined for evaluation during the re-irradiation period, and ECOG scores were collected at two distinct time points: before and after radiotherapy.

Before re-irradiation, in the "In systemic treatment" group, 13 patients had ECOG 1 (37%), 12 had ECOG 2 (34%), 8 had ECOG 3 (23%), and 2 had ECOG 4 (6%). In contrast, in the "Referred for palliative care" group, ECOG scores ranged only between 2 and 4: 1 patient had ECOG 2 (14%), 4 patients had ECOG 3 (57%), and 2 patients had ECOG 4 (29%). Figure 15 illustrates the comparison of ECOG distributions between the two groups, also before treatment.

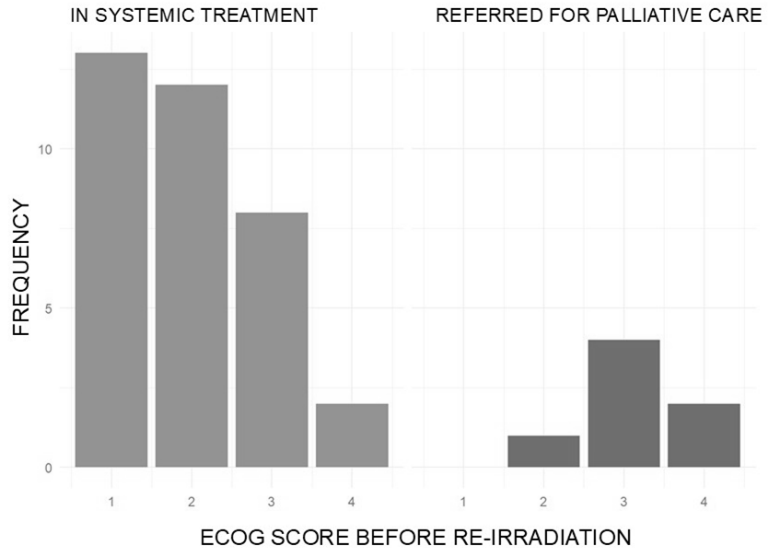

Figure 15- Comparison of the distribution of patients by ECOG score in two groups before re-irradiation.

Analysis of the data collected **after re-irradiation** showed that, in the “In systemic treatment” group, 1 patient had ECOG 0 (3%), 12 had ECOG 1 (34%), 10 had ECOG 2 (29%), 8 had ECOG 3 (23%), and 4 had ECOG 4 (11%).

In contrast, in the “Referred for palliative care” group, ECOG scores were limited to higher values: 4 patients had ECOG 3 (57%) and 3 had ECOG 4 (43%). Figure 16 illustrates the comparison of ECOG scores between the two groups during the same period.

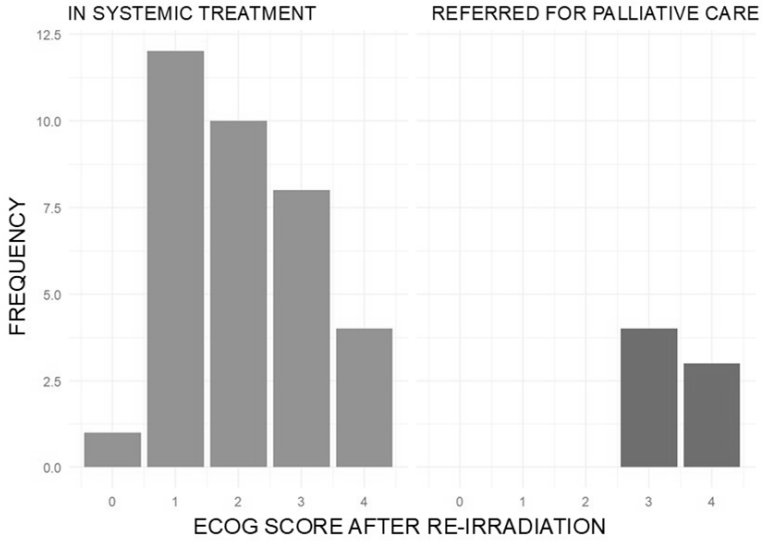

Figure 16- Comparison of the distribution of patients by ECOG score in two groups after re-irradiation.

2. Time interval between treatments

The time interval between treatments was analysed, considering the end date of the first irradiation and the start date of the re-irradiation. The results showed a median interval of 10 months (range: 3-56 months).

To further explore this, the sample was stratified into three groups based on clinically relevant time cut-offs: less than 6 months, between 6 and 12 months, and more than 12 months (Figure 17, Table 4). The distribution of cases across the three groups was relatively balanced, although the interval of ≥12 months included the largest number of patients, with a total of 16 cases.

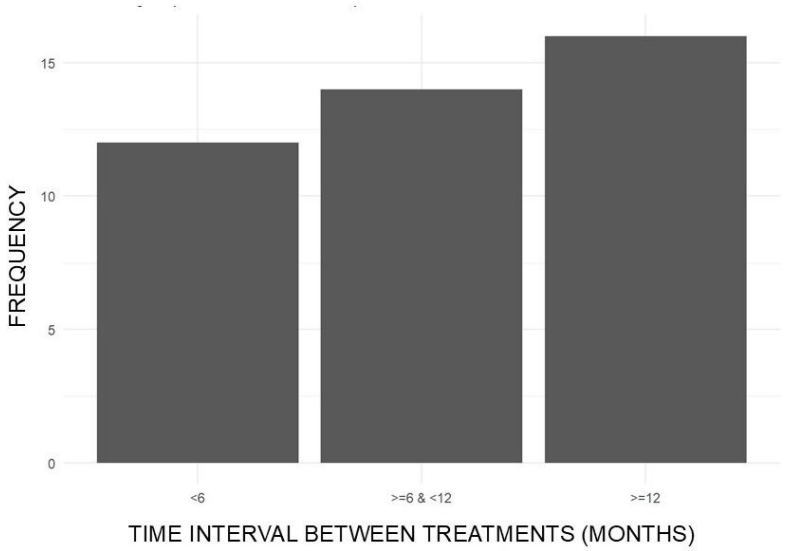

Figure 17 - Distribution of time interval between treatments, based in three-time cut-off: <6months; ≥6 and <12 months; ≥12 months.

Table 4 - Statistic description for intervals between treatments.

Variable		**n (%) / Median [Min-Max]**
Interval between treatments		
Overall		42 (100%) / 10 [3-56]
-	< 6 months	12 (29%)
-	≥6 and <12 months	14 (33%)
-	≥12 months	16 (38%)
Total		42 (100%)

3. Fractionation Schemes and Techniques

In the **first irradiation**, four fractionation schemes were used, most frequently 20 Gy in 5 fractions (57%) and 8 Gy in a single fraction (34%). Less common regimens included 30 Gy in 10 fractions (7%) and 36 Gy in 12 fractions (2%) (Table 5). In **re-irradiation**, only two schemes were adopted: 20 Gy in 5 fractions (45%) and 8 Gy in a single fraction (55%) (Table 6).

Table 5 - Frequencies and percentages for Fractionation Scheme and Technique variables (first treatment).

Variable	n (%)
First Irradiation	
Fractionation Scheme	
• **20Gy / 5fx**	24 (57%)
• **8 Gy / 1 fx**	14 (34%)
• **30 Gy / 10 fx**	3 (7%)
• **36 Gy / 12 fx**	1 (2%)
Techniques	
• **3D-CRT**	40 (96%)
• **IMRT**	1 (2%)
• **VMAT**	1 (2%)
TOTAL	42 (100%)

Abbreviations - fx= fractions

Table 6 - Frequencies and percentages for Fractionation Scheme and Technique variables (re-irradiation treatment).

Variable	n (%)
Re-irradiation	
Fractionation Scheme	
• **20Gy / 5fx**	19 (45%)
• **8 Gy / 1 fx**	23 (55%)
Techniques	
• **3D-CRT**	35 (83%)
• **IMRT**	2 (5%)
• **VMAT**	5 (12%)
TOTAL	42 (100%)

Abbreviations – fx= fractions

Overall, most patients were treated with hypofractionated schemes, and most of the treatment plans employed 3D-CRT, both in the initial and re-irradiation phases.

4. Other Dosimetric and Radiobiological Data

For this study, other dosimetric parameters were collected to assist in the evaluation of the treatment plan. To evaluate the dosimetric plan, the maximum dose (Dmax) in the target volume was recorded, as well as other variables in accordance with ICRU Report 62 (for 3D-CRT), ICRU Report 83 (for IMRT and VMAT) and the maximum dose in spinal cord.

In the **first irradiation**, Dmax values in the target and spinal cord were consistently slightly above the prescribed dose across all fractionation schemes. The V95% variable, which evaluates the dose coverage in 3D-CRT plans (n=40), had a median value of 98%. This means that, in median, 95% of the prescribed dose covered 98% of the target volume. When IMRT (n=1) and VMAT (n=1) techniques were used, the D2% and D98% parameters were applied instead. In this irradiation, D2% and D98% have a median value of 106,6% and 96,5%, respectively. This it confirmed adequate dose homogeneity and coverage.

During **re-irradiation**, results were similar: target and spinal cord Dmax remained close to but slightly higher than the prescription dose. Coverage parameters showed a median V95% of 98,6% for 3D-CRT plans, while IMRT and VMAT presented results with D2% and D98% medians of 104,9% and 95,9%, respectively.

Overall, the dosimetric evaluation demonstrated consistent dose distributions, with adequate target coverage and acceptable spinal cord doses in both treatment phases. Detailed values are summarized in Table 7 and supplementary Table 1.

Table 7 - Median, minimum and maximum for dosimetric parameters in first irradiation and re-irradiation.

Variable	Median [minimum, maximum] (Gy)
First Irradiation	
Target Dmax	
• **20 Gy / 5 fx**	21,4 [18,6 – 21,9]
• **30 Gy/ 10 fx**	31,6 [31,3 – 32,6]
• **8 Gy/ 1 fx**	8,6 [8,3 – 8,8]
Spinal cord Dmax	
• **20 Gy / 5 fx**	20,8 [20,1 – 21,4]
• **30 Gy/ 10 fx**	30,8 [30,7 – 32,4]
• **8 Gy/ 1 fx**	8,3 [8,2 – 8,6]
V95%	98,0 [89,2 – 100,0]
D2%	106,6 [106,4 – 106,8]
D98%	96,5 [95,0 – 98,0]

Re-irradiation	
Target Dmax	
• **20 Gy / 5 fractions**	21,4 [20,7 – 22,3]
• **8 Gy / 1 fraction**	8,5 [8,2 – 8,6]
Spinal cord Dmax	
• **20 Gy / 5 fractions**	20,5 [20,0 – 21,2]
• **8 Gy / 1 fraction**	8,3 [8,1 – 8,5]
V95%	98,6 [90,2 – 99,9]
D2%	104,9 [101,7 – 108,3]
D98%	95,9 [95,0 – 99,0]

Abbreviations – fx= fractions

4.1 Calculation of BED and EQD2 and their cumulative values

Based on the data collected on the prescribed dose, the corresponding Biologically Effective Dose (BED) and Equivalent Dose in 2 Gy fractions (EQD2) were calculated. BED and EQD2 values were determined according to the formulas presented in the **Materials and Methods section**, using an **α/β ratio of 2 Gy** for the spinal cord.

In the **first irradiation**, the median BED was 60 (40-90) Gy_2. Among the 42 patients in the study, 24 (57%) had a BED of 60 Gy_2, 14 (34%) had 40 Gy_2, 3 (7%) had 75 Gy_2, and only 1 (2%) had 90 Gy_2. The median EQD2 was 30 (20-45) Gy_2 and within the 42 patients, 24 (57%) had EQD2 values of 30 Gy_2, 14 (34%) had 20 Gy_2, 3 (7%) had 37,5 Gy_2 and only 1 (2%) had 45 Gy_2. The distributions of these two parameters are shown in Figures 18 and 19.

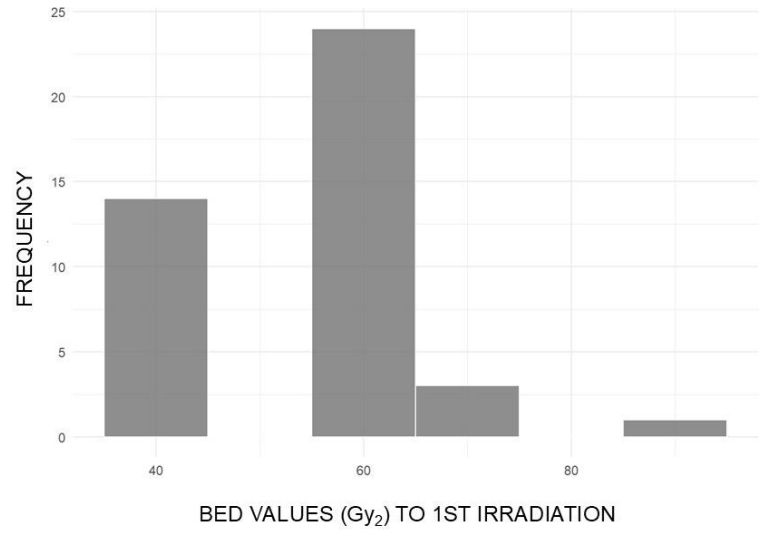

Figure 18 - Distribution of BED values in first irradiation.

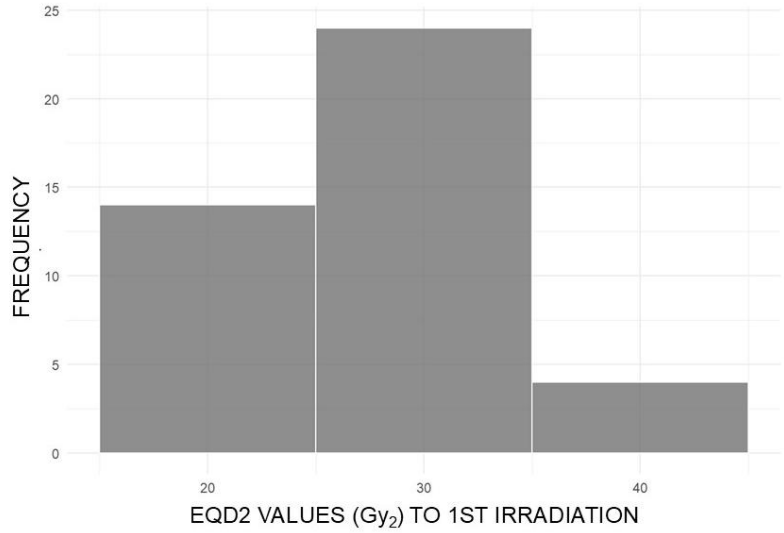

Figure 19 - Distribution of EDQ2 values in first irradiation.

The distribution of BED and EQD2 values for **re-irradiation** treatment is shown in Figures 20 and 21. According to the calculations performed, the median BED for re-irradiation was 40 (40-60) Gy_2, where 19 patients (45%) had a BED of 60 Gy_2, while the remaining 23 (55%) had 40 Gy_2. In contrast, the median EQD2 for this treatment was 20 (20-30) Gy_2. Of the patients evaluated, 19 (45%) had an EQD2 of 30 Gy_2, and the remaining 23 (55%) had 20 Gy_2.

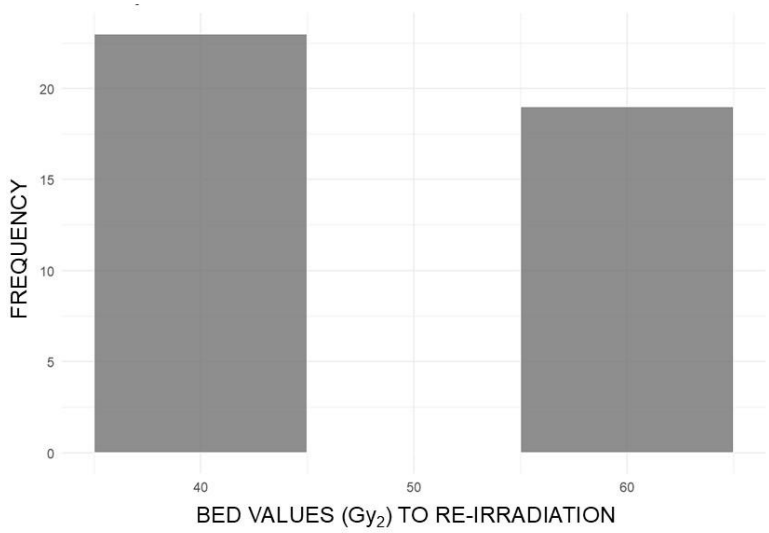

Figure 20 - Distribution of BED values in re-irradiation.

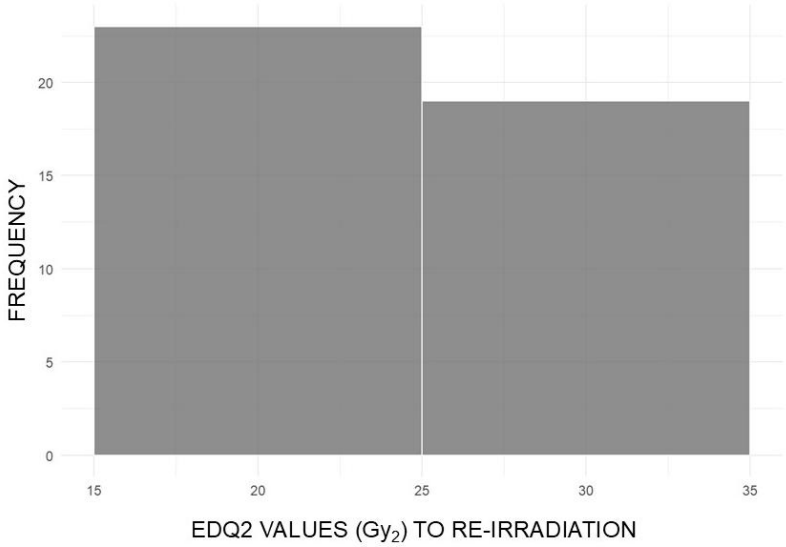

Figure 21 - Distribution of EDQ2 values in re-irradiation.

According to BED and EQD2 values obtained in the two irradiations, the respective cumulative BED and EQD2 values were calculated. The cumulative BED presents a median of 100 (80-160) Gy_2, while the cumulative EQD2 presents a median of 50 (40-80) Gy_2.

After analysing the cumulative BED and EQD2 values, another analysis was performed by two distinct groups (figure 22 and 23). Namely, values equal or lower than 120 Gy_2 and greater than 120 Gy_2 for BED and values equal or lower than 60 Gy_2 and values greater than 60 Gy_2 for EQD2. This latter analysis showed that the cumulative BED

values obtained were equal or less than 120 Gy_2 for a total of 38 (90%) patients and greater than this value for the remaining 4 (10%) patients. In the same follow-up, the cumulative EQD2 values were equal or less than 60 Gy_2 in 38 (90%) patients and greater than this value for the remaining 4 (10%) patients in the sample.

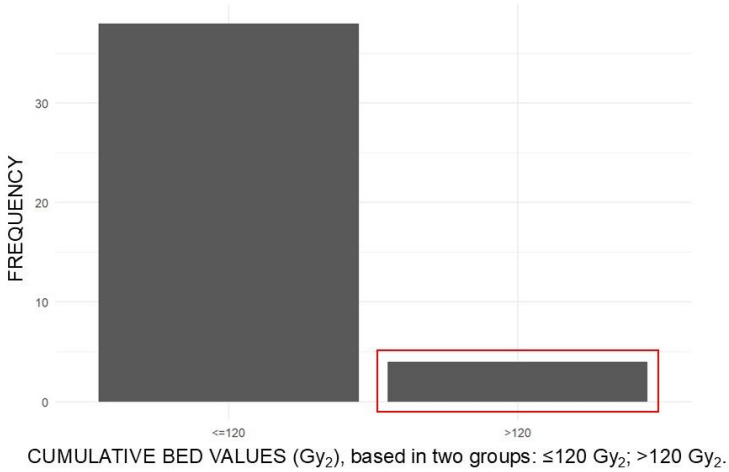

Figure 22 - Distribution of cumulative values of BED, based in two groups ≤120 Gy_2 and >120 Gy_2.

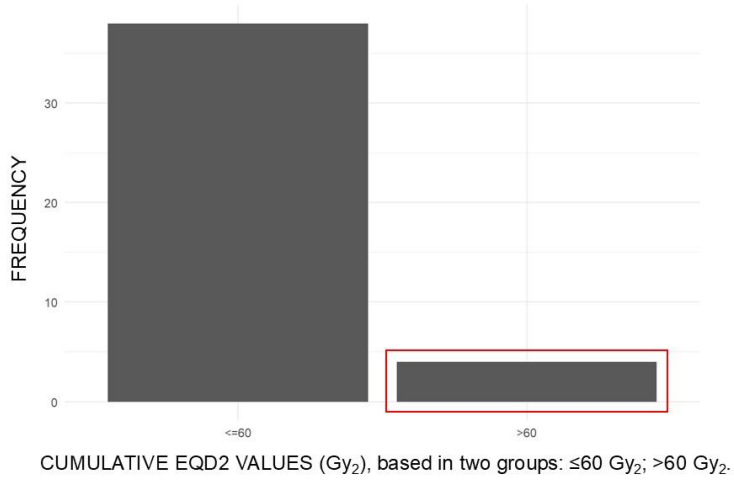

Figure 23 - Distribution of cumulative values of EQD2, based in two groups ≤60 Gy_2 and >60 Gy_2.

Once the values for the interval between treatments, the BED values for the first irradiation and re-irradiation, and the cumulative BED values had been collected, it was

possible to calculate the risk of myelopathy for each patient in the sample. This scoring is in accordance with the factors presented in Table 1 of Section 5.2 of the Introduction chapter:

- Time interval.
- BED/EQD2 for first or second course.
- Cumulative BED/EQD2.

Analysis of the risk of developing myelopathy according to the above parameters revealed that the highest percentage of patients had a low risk (0-3 points) (65%) and an intermediate risk (4-6 points) (26%) of developing myelopathy. The frequency distribution of this parameter is shown in Table 8 and Supplementary table 2 shows description date of these parameters for each patient.

Table 8 - Distribution of risk score for development of myelopathy (in green: low risk; in orange: intermediate risk; in red: high risk).

System scoring for risk of myelopathy	n (%)
0	27 (65%)
1	1 (2%)
2	2 (5%)
4,5	11 (26%)
8,5	1 (2%)
Total	42 (100%)

5. Overall Survival Data

Based on the sample of 40 patients, Kaplan-Meier survival curves were generated, considering the time from the end of the first irradiation and re-irradiation to the date of death.

Figure 24 shows the Kaplan-Meier survival curve for the **first RT treatment**, which demonstrates a rapid decline in patient survival during the first 12–18 months, indicating that most deaths occurred in this period. The curve shows a median overall survival of 15,4 (4-63) months, and after 60 months it approaches a survival probability of 0, indicating that only a very small number of patients survived beyond 5 years. It is also possible to observe a widening of the 95% confidence interval bands as follow-up time increases, reflecting the decreasing number of patients at risk and the corresponding reduction in data accuracy.

When overall survival was analysed at specific time points (6, 12, and 18 months), survival probability was highest at 6 months (95%) but showed a sharp decline by 12 months (67%). At 18 months, survival probability decreased further to 45% (Table 9).

In the **re-irradiation** setting, the Kaplan-Meier survival curve (figure 25) shows a marked decline within the first 6 months of follow-up, indicating a high mortality rate in this period. This is reflected by the median overall survival of 3,5 (0.4-17,9) months. As with the first treatment, the 95% confidence interval bands become increasingly wide over time, especially beyond 12 months, due to the progressively smaller number of patients in follow-up.

Analysis of survival at 6, 12, and 18 months revealed that only 43% of patients were alive at 6 months. However, this percentage dropped substantially by 12 months, with only 17% of patients alive. By 18 months, survival probability was just 5%, corresponding to approximately two patients from the total sample (Table 9).

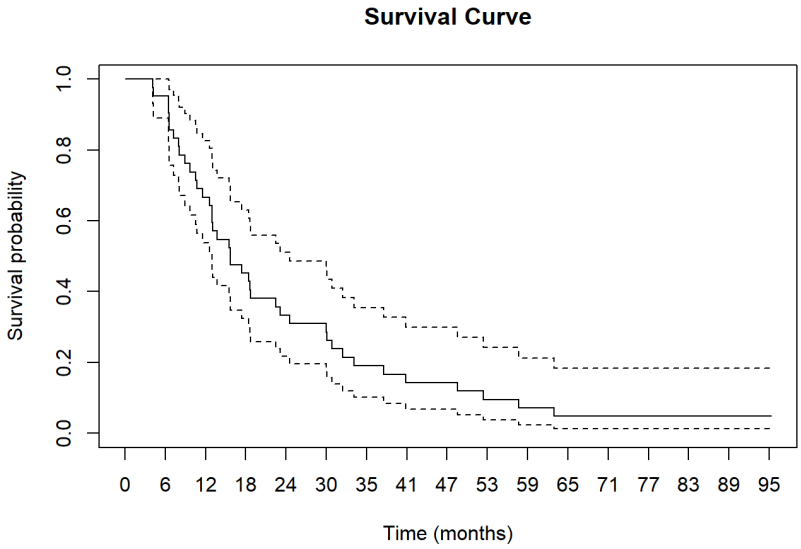

Figure 24 - Kaplan-Meier curve - First irradiation treatment.

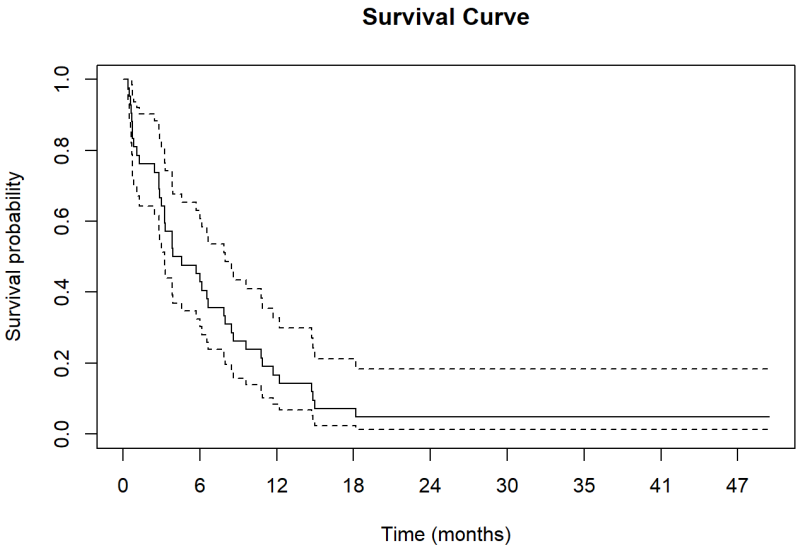

Figure 25 - Kaplan-Meier curve – Re-irradiation treatment.

Table 9 - Survival statistics at 6, 12, and 18 months for the first treatment and re-irradiation.

Time		%survival	Confidence interval (95%)
First Treatment			
-	6 months	95%	89-100
-	12 months	67%	54-83
-	18 months	45%	32-63
Re-irradiation			
-	6 months	43%	30-61
-	12 months	17%	8-32
-	18 months	5%	1-18

Until the final date for data collection, 40 patients (95%) had died with evidence of disease (DWD), while 2 patients (5%) were alive with evidence of disease (AWD).

We compared time till death between the previously defined groups (“In systemic treatment” and “Referred for palliative care”). Figure 26 shows the average time between the end of treatment and death. According to the *Wilcoxon rank-sum* test, the difference between groups was not statistically significant ($p = 0.13$; significance level $p < 0.05$). Patients in the systemic treatment group had a higher median survival, but this difference did not reach statistical significance, likely due to high variability within both groups and the presence of outliers, with some patients surviving much longer than the majority.

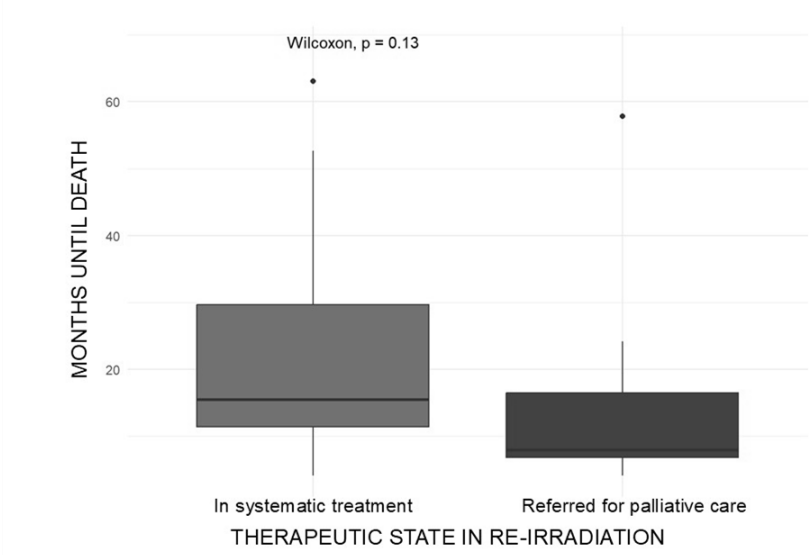

Figure 26 - Boxplot to the average time between the end of treatment and death in “Therapeutic state in re-irradiation”.

V. DISCUSSION

Metastatic cancer is associated with more than 90% of cancer-related deaths and leads to an impact on 5-year survival rates in patients. Bone is one of the most common regions affected by metastatic site, mainly by prostate, lung and breast cancers. The spine is the most common site for the development of bone metastasis (mainly thoracic spine), representing about 70% of all of them and originated from primary tumours of lung, breast and prostate (5, 6, 15, 17).

Our sample of 42 patients was selected based on specific inclusion and exclusion criteria, resulting in a group of individuals diagnosed with spinal metastases who had undergone type I re-irradiation during the defined period. Despite the application of these criteria, the sample remained heterogeneous, particularly with respect to the distribution of primary tumours. Our findings, in which primary tumours of the lung and bronchi (24%) were the most prevalent, followed by breast (14%) and prostate (12%) are consistent with previous reports from the literature.

The spinal cord is the main organ at risk in spinal metastases treatment and has gained high importance because 20% of patients with bone metastases require re-irradiation treatment to control disease or for symptom relief and to improve patients quality of life (60, 61).

Regarding the re-irradiated regions of the spine, two areas predominated in our study: the lumbar (33%) and thoracic (31%) regions, which align with what has been described in the literature (6, 15, 17). These data are to be expected given the high number of new cases of lung, breast, and prostate cancer, which therefore have a greater impact on a sample of this kind, since they are also the primary tumours that most commonly metastasize to the bone.

Van der Velden *et al.* (72) conducted a study involving 1,027 patients with the aim of developing and validating a risk scoring system to predict patient response to palliative radiotherapy in bone metastases. Among the variables analysed, the authors identified performance status (Karnofsky performance status index) and baseline pain score as significant predictors of pain response. Patients with a higher Karnofsky score were more likely to experience pain relief, whereas those with lower scores responded less favourably to radiotherapy.

In another study, Habberstad *et al.* (73) analysed data from 513 patients in a multicentre, multinational cohort to investigate predictive factors for analgesic response to radiotherapy in painful bone metastases. The authors concluded that, among other

variables, better performance status (Karnofsky index) was associated with improved treatment response.

Taken together, both studies highlight the importance of considering performance status as a key predictive factor, while also underscoring the need for broader evaluation of additional variables to achieve greater accuracy in predicting treatment outcomes.

In our study sample, and based on the clinical records available, the ECOG score proved to be the most consistent predictor of response, since it was documented in all medical histories.

The frequency with which ECOG values were collected was defined at two different time points for both the first course of treatment and for re-irradiation. According to the literature, a transient increase in pain may occur during the first five days after treatment, with effective pain relief typically reported between 4 and 6 weeks. In our study, ECOG values were collected at the consultation prior to the start of treatment and again between 2 and 5 weeks after the end of radiotherapy. This time window allowed us to capture values for patients with poorer prognoses and more limited survival, and according to available clinical records (74, 75).

However, two patients in our sample died within two weeks of re-irradiation. In these cases, the ECOG scores recorded were consistent with the clinical reports of hospitalization. It should be noted that the causes of death were related to comorbidities and the already debilitated condition of these patients.

In our sample, the most frequent ECOG score, both at the time of first treatment and at re-irradiation, was 1. Of the 42 patients included, 36 maintained their ECOG score after the first radiotherapy course. Three patients showed improvement, while another three experienced deteriorations in ECOG.

Regarding re-irradiation, some differences emerged, particularly the appearance of ECOG 4. At this stage, 24 patients maintained their baseline score after treatment, five improved their performance status, and 12 showed worsening ECOG scores.

Beyond this general analysis, outcomes were also evaluated according to two subgroups. The first consisted of patients who, at the time of re-irradiation, were still undergoing systemic treatment (35 patients), while the second included patients who had already been referred for palliative care (7 patients). ECOG scores before and after re-irradiation were assessed in both groups, showing differences.

A worsening of the patient performance status was noticed: “in referred for palliative care” patients group the only patient with ECOG 2 before treatment was ECOG 4 after RT. All other patients showed no change in ECOG.

In other group “In systemic treatment” an improvement in performance status was seen in one patient (change from ECOG 1 to 0), with 32 maintaining the same score and 2 patients with worsening (from ECOG 2 to 4).

Patients continuing systemic therapy had better scores at both time points, reflecting the eligibility requirements for such treatments. Conversely, patients in the palliative care group already had a worse prognosis and lower survival probability, which was reflected in their poorer ECOG scores.

In our study, ECOG values alone did not show any significant differences in patients’ quality of life after treatment, most likely because other relevant factors were not systematically considered, such as pre-existing comorbidities, toxicities from prior or concurrent therapies, and the absence of a standardized pain scale for a more objective assessment of each patient’s pain. Thus, while ECOG remains a useful and consistently recorded predictor, these findings underscore the need for multidimensional assessment in clinical practice and research.

In this regard, the radiotherapy techniques employed play a decisive role, as differences in planning and delivery directly affect treatment safety, efficacy, and the protection of critical structures such as the spinal cord.

The spinal cord is a critical dose-limiting organ in radiotherapy, particularly in the treatment of spinal metastases. As a serial organ, loss of function in even a small portion can compromise the entire structure, making the maximum point dose a key determinant of risk (33, 42). Given this, various radiotherapy techniques have been evaluated to optimize target coverage while protecting critical structures. Studies have consistently demonstrated the advantages of 3D-CRT over conventional 2D approaches in sparing organs at risk and achieving dose homogeneity (Soyfer *et al.*; Arnold *et al.*) (30, 76). More advanced techniques, such as IMRT and VMAT, offer benefits in hypofractionated schemes, including improved dose conformity (Lee *et al.*) (77), while SBRT has emerged for selected cases, showing potential for faster and more durable pain relief, as well as better local control in radioresistant tumours (Sprave *et al.*; Zhang *et al.*; Yang *et al.*) (29, 78, 79) .

In our study, both initial irradiation and re-irradiation achieved consistent dosimetric outcomes. Dmax values in the target and spinal cord were slightly above the prescribed dose, while coverage remained adequate. For 3D-CRT, the median V95% was

approximately 98%, and for IMRT/VMAT, D2% and D98% confirmed good homogeneity. Overall, 3D-CRT was the predominant technique, meeting dosimetric goals and allowing faster treatment planning, which is particularly important in patients requiring urgent palliative radiotherapy. These findings align with previous reports, confirming that this technique can achieve safe and effective dose delivery in spinal metastases.

According to Doi *et al.* (62), although various techniques allow for spinal cord sparing without compromising tumour control, there are cases of re-irradiation in which these constraints cannot always be achieved. In some instances, higher doses are required to offer the patient a therapeutic option. To address this, the authors proposed a method for estimating spinal cord tolerance in re-irradiation, if recovery depends on the interval between treatments, with 25% recovery after more than 6 months and 50% after 12 months.

In our sample the results showed a median interval of 10 months (range: 3–56 months) between the first irradiation and re-irradiation treatment. Based on these recovery values, the interval between irradiations in our sample was categorized into three groups: <6 months, ≥6 and <12 months, and ≥12 months. This allowed us to evaluate potential spinal cord recovery kinetics in our patient cohort.

Our results showed that 29% of patients were re-irradiated within less than 6 months, for whom recovery kinetics could not be assumed. The remaining patients were re-irradiated between 6 and 12 months (33%) or after 12 months or more (38%). Therefore, it can be inferred that 71% of the sample had the potential for partial spinal cord recovery, ranging from 25% to 50%.

In addition to the interval between treatments, the total dose delivered, and its fractionation are critical factors in re-irradiation planning. Assessing the biologically effective dose (BED) and equivalent dose in 2 Gy fractions (EQD2) allows for a more precise estimation of cumulative spinal cord exposure, integrating both the dose per fraction and the timing between courses. This approach provides a framework to balance treatment efficacy with safety, particularly in patients receiving multiple irradiation sessions.

The recommended dose scheme considered effective for cases of uncomplicated bone metastases is a single fraction of 8 Gy. Other authors have conducted studies evaluating the effectiveness of different fractionation in patients with bone metastases. Wegner *et al.* refers to the single fraction of 8 Gy as showing a steady increase in use, also referring to the 30 Gy in 10 fractions regimen as the most prevalent (22, 80).

In our study, in the first irradiation, four fractionation schemes were used, most frequently 20 Gy in 5 fractions (57%) and 8 Gy in a single fraction (34%). Less common

regimens included 30 Gy in 10 fractions (7%) and 36 Gy in 12 fractions (2%). In re-irradiation, only two schemes were adopted: 20 Gy in 5 fractions (45%) and 8 Gy in a single fraction (55%). All data are represented in **table 5 and 6 in results section**. In line with the literature, several patients in our sample received a single 8 Gy fraction, including at first treatment. This choice reflected clinical considerations such as tumour radioresistance and patient performance status.

To compare different treatment regimens, BED and EQD2 calculations were employed. These calculations also consider the α/β ratio of both tumours and adjacent organs at risk (OARs). Accordingly, late-responding tissues, such as the spinal cord, are typically assigned α/β values of 2 Gy (51, 69).

Nieder *et al.* (63) present a table in their study that summarises the parameters to be considered for assessing the risk of developing myelopathy. These parameters indicate that the risk of myelopathy is reduced to a minimum when the interval between treatments is higher than 6 months. It also states that the BED or EQD2 value should be equal or less than 102 Gy_2 or 51 Gy_2, respectively, for each treatment. In our study, in first irradiation as well in the re-irradiation, all treatments complied with these values. In first irradiation median BED was 60 (40-90) Gy_2 and median EQD2 was 30 (20-45) Gy_2. For re-irradiation median BED for was 40 (40-60) Gy_2 and the median EQD2 was 20 (20-30) Gy_2, as described **in section 4.1 of results.**

Considering the cumulative BED and EQD2 values: for minimal risk, these should be equal or less than 120 Gy_2 for BED or 60 Gy2 for EQD2. Our analysis showed that the cumulative BED values obtained were equal or less than 120 Gy_2 for a total of 38 (90%) patients and greater than this value for the remaining 4 (10%) patients. In the same follow-up, the cumulative EQD2 values were equal or less than 60 Gy_2in 38 (90%) patients and greater than this value for the remaining 4 (10%) patients in the sample.

These results on myelopathy risk underscore the importance of evaluating the cumulative biological dose when assessing spinal cord tolerance. In our sample, the highest percentage of patients (72%) fell into the low-risk category, 26% were at intermediate risk, and a single patient (2%) was classified as high risk. Notably, this high-risk patient was one of only two who underwent re-irradiation of the same spinal cord region more than once. The elevated risk resulted from a short interval between treatments (less than 6 months) and a cumulative BED of 160 Gy_2, derived from three fractionation schemes: 20 Gy in 4 fractions, 8 Gy in a single fraction, and 20 Gy in 4 fractions.

To assess the biological impact of these different fractionation regimens, including the single 8 Gy fraction, the linear-quadratic (LQ) model was applied. This model allows

calculation of the biologically effective dose (BED), considering both the dose per fraction and the total dose, providing a robust framework for evaluating cumulative spinal cord exposure and associated risks in re-irradiation scenarios.

Overall, the clinical validation of the linear-quadratic (LQ) model has been established mainly for fraction sizes between 1-5 Gy (Brown *et al.*) (81), with particular robustness in describing responses of late-reacting tissues (low α/β) compared to acutely responding tissues and tumours. A key assumption of the model is that complete reoxygenation occurs between fractions, which limits its explanatory power when applied to high single-dose treatments. According to the LQ framework, such regimens would be expected to cause relatively modest tumour cell kill for the same level of late normal tissue injury. Yet, clinical results from advanced techniques such as SBRT clearly contradict this expectation, demonstrating remarkable efficacy even with high-dose fractions, including in palliative settings (81).

Several hypotheses have been proposed to explain this discrepancy. One is that the LQ model may not accurately capture cell death dynamics at high doses, potentially overestimating late normal tissue toxicity while underestimating tumour control. This would imply that higher doses per fraction could be delivered with acceptable risks to serial organs such as the spinal cord. Other factors, not accounted for by classical radiobiology, may also play a role - such as radiation-induced vascular damage, enhanced antitumour immune responses, or the limited relevance of reoxygenation in non-hypoxic tumours (81).

Despite these reservations, experimental survival data suggest that the LQ model remains robust up to approximately 10 Gy per fraction, and even applicable in some contexts up to 15–20 Gy (Brenner) (82). In vitro and in vivo evidence in normal tissues supports its predictive validity across this range. Therefore, given that tumour control probability (TCP) increases monotonically with BED, it appears reasonable to apply the LQ model to the single-fraction doses used in our study and to compare them with alternative fractionation schemes (82).

This treatment choice reflects not only tumour biology and patient performance status but is also influenced by survival expectations. Indeed, prognosis often determines the suitability of hypofractionated regimens, making survival analysis an essential component of our results.

Studies reporting overall survival data for both initial irradiation and re-irradiation in patients with bone metastases are extremely scarce. Consequently, any comparison with our results will necessarily be indirect, relying on survival data from patients with bone metastases treated with radiotherapy. Thereafter, we will contrast our survival outcomes

after re-irradiation with literature specifically addressing re-irradiated patients with bone metastases.

In our study, the first treatment was associated with a median overall survival of 15.4 months (range 4-63), with most deaths occurring within the first 12-18 months. Survival probabilities were 95% at 6 months, 67% at 12 months, and 45% at 18 months. Survival outcomes in spinal metastases are generally poor and vary considerably according to the primary tumour, from only a few months in lung cancer to over two years in selected breast or prostate cancer cases. Overall, the aggressive nature of the disease is reflected in median survival times around six months, highlighting the deep impact on patients' quality of life, including pain, reduced mobility, and loss of independence (8, 15, 17).

In contrast, patients who underwent re-irradiation had a median overall survival of only 3,5 months (range 0,4–17,9). Survival dropped rapidly, with 43% alive at 6 months, 17% at 12 months, and just 5% at 18 months. In a study of Kawashiro *et al.* (66) with 23 patients the median overall survival for re-irradiated patients was 12 months with 2-year overall survival rates after re-irradiation were 20%. It is important to emphasise the need for caution when comparing survival times between the literature cited and our study. In the referenced article, only two patients had a primary lung tumour, whereas in our cohort lung tumours were the most common, with a total of 10 patients. As noted previously, survival varies according to the primary tumour, among other factors, which may explain the substantial difference in median survival between the published data and our results (12 months versus 3,5 months, respectively).

An analysis according to the two groups initially created ("In systemic treatment" and "Referred for palliative care") was performed with *Wilcoxon rank-sum* test. The results, however, showed that there is no statistical evidence, at a 95% significance level, that time to death differs significantly between patients undergoing systemic treatment and those referred for palliative care. While the systemic treatment group exhibited greater variability in time to death, the mean difference was not significant, underscoring the clinical challenges of managing this heterogeneous and vulnerable patient population.

Despite all these results, according to the risk scoring developed by Nieder *et al.* (63), none of the patients in the sample developed myelopathy during the follow-up or survival period.

Cheney *et al.* (64) indicate in their article that, although data are limited, the median time to development of myelopathy is approximately 11 (4-25) months after re-irradiation. As mentioned above, the median survival in our study was 15,4 months, but after re-irradiation, this dropped to 3,5 months. This may explain why, even among patients with an

intermediate to high risk of developing myelopathy, none presented clinical symptoms. It is important to note, however, that after analysing the results, patients had BED and EQD2 values considered safe for each individual course of treatment. Regarding cumulative BED and EQD2, only one patient exceeded 120 Gy2, as he underwent multiple re-irradiations. This patient also had a time interval of less than 6 months between the first irradiation and the first re-irradiation, contributing to the high-risk score obtained. The remaining patients with intermediate scores all had intervals of less than 6 months between irradiations, but met the other parameters defined by Nieder *et al.* (63).

For patients with a myelopathy risk score of 4,5, median survival after re-irradiation was 3,0 (0,59–17,9) months, which, based on the literature, could indicate a potential for clinical signs of myelopathy. Conversely, the patient with a score of 8,5 had a survival of only 2,1 months after the last re-irradiation. These short survival times may also explain why certain dosimetric parameters were not met. Radiotherapy in such cases is often one of the last therapeutic options for patients with poor prognosis and limited life expectancy. Nonetheless, following careful multidisciplinary decision-making and informed consent from both the patient and family, the treatment provides symptom relief and can improve quality of life, even for short durations.

Additionally, it is important to note that at the end of data collection on June 13, 2025, two patients in the sample were still alive with evidence of disease (22 and 49 months of follow-up). However, there was no sign of myelopathy development, consistent with their risk score of 0.

Finally, it is important to highlight some limitations of the study, which could be addressed in future research. The relatively small sample size (n=42) and the heterogeneity of the included patients, in terms of primary tumour and performance status, limit the applicability and comparability of the results, resulting in a study that is primarily descriptive.

As this is a retrospective study, the availability of data is limited. For instance, the assessment of treatment response using the ECOG scale proved insufficient, indicating that additional tools, such as standardized pain scales, would be necessary for a more accurate evaluation.

Furthermore, the short survival of the patients - largely due to the inclusion criteria (palliative intent and history of re-irradiation for metastases) - restricted the assessment of late effects. Consequently, it was not possible to directly validate the development of myelopathy, even in patients with higher scores indicating a greater risk of side effects.

VI. CONCLUSION AND FUTURE PERSPECTIVES

The results of this study demonstrate that spinal re-irradiation in patients with bone metastases can be safely performed within the currently recommended parameters, with no cases of myelopathy recorded in the analysed sample. The BED and EQD2 values obtained remained, in most cases, within the limits defined by Nieder et al., reinforcing the applicability of these criteria in clinical practice.

In summary, the safety parameters established at the beginning of the century remain valid, although more recent literature suggests the possibility of increasing treatment doses in selected clinical situations, provided that the risk-benefit balance is carefully assessed. It is important to emphasise, however, that definitive validation of these data requires adequate follow-up, which is often not achieved in studies involving palliative patients due to their limited survival.

Theoretically, this limitation also opens the possibility of considering therapeutic intensification in this patient group, since the primary goal is the improvement of quality of life. Thus, this work highlights not only the relevance of re-irradiation as a safe therapeutic option but also the need for future studies with larger samples and better performance status, to clarify the real tolerance limits of the spinal cord.

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VIII. APPENDIX

Supplementary table 1 - Description of Treatment Technique, Target (Dmax), Spinal Cord (Dmax), V95%, D2%, and D98% for first irradiation and re-irradiation.

	FIRST TREATMENT						RE-IRRADIATION					
	TECNIQUE	TARGET (Dmax) (Gy)	Spinal Cord (Dmax) (Gy)	V95% (%)	D2% (%)	D98% (%)	TECNIQUE	TARGET (Dmax) (GY)	Spinal cord (Dmax) (Gy)	V95%	D2% (%)	D98% (%)
1	3D-CRT	31,347	30,825	98,8	-	-	3D-CRT	20,65	20,254	98,6	-	-
2	3D-CRT	21,385	20,841	98	-	-	3D-CRT	21,437	20,415	98	-	-
3	3D-CRT	21,299	21,299	99,3	-	-	3D-CRT	8,215	8,215	99,9	-	-
4	3D-CRT	21,778	20,736	98	-	-	VMAT	21,727	20,178	-	104,9	95,9
5	3D-CRT	21,262	20,312	92,3	-	-	3D-CRT	8,366	8,108	95	-	-
6	3D-CRT	8,633	8,285	98	-	-	3D-CRT	8,606	8,286	98	-	-
7	3D-CRT	8,634	8,366	99,9	-	-	3D-CRT	21,451	20,264	98	-	-
8	3D-CRT	21,68	20,633	98	-	-	3D-CRT	8,604	8,235	99,5	-	-
9	3D-CRT	18,609	20,848	100	-	-	3D-CRT	8,169	8,058	99,4	-	-
10	3D-CRT	21,216	20,193	95,6	-	-	3D-CRT	21,192	20,429	98,5	-	-
11	3D-CRT	21,412	21,086	98,7	-	-	3D-CRT	8,579	8,451	99	-	-
2	3D-CRT	21,489	20,064	92,8	-	-	3D-CRT	21,43	19,962	90,2	-	-
13	3D-CRT	21,31	20,551	99	-	-	3D-CRT	21,277	20,097	98	-	-
14	3D-CRT	8,755	8,412	91,9	-	-	3D-CRT	21,045	20,74	99,9	-	-
15	3D-CRT	38,415	37,4	89,2	-	-	3D-CRT	8,447	8,138	97,5	-	-
16	3D-CRT	21,056	20,336	98	-	-	3D-CRT	8,338	8,054	99,4	-	-
17	3D-CRT	21,7	21,207	98	-	-	3D-CRT	8,575	8,395	96	-	-
18	3D-CRT	8,627	8,204	98	-	-	3D-CRT	8,429	8,219	98	-	-
19	3D-CRT	8,549	8,163	95,9	-	-	3D-CRT	8,532	8,187	93,7	-	-
20	3D-CRT	21,258	20,917	98,5	-	-	3D-CRT	21,422	20,879	99	-	-
21	3D-CRT	21,19	20,71	98	-	-	VMAT	22,264	20,022	-	108,3	95

22	IMRT	32,569	32,361	-	106,8	95	VMAT	8,515	8,445	-	104,8	99
23	3D-CRT	8,413	8,217	96	-	-	3D-CRT	21,414	21,06	99	-	-
24	3D-CRT	21,395	21,395	99	-	-	3D-CRT	8,504	8,504	99,5	-	-
25	3D-CRT	21,887	21,251	98	-	-	3D-CRT	21,454	21,292	99	-	-
26	3D-CRT	21,404	21,119	98	-	-	3D-CRT	21,495	20,604	99	-	-
27	3D-CRT	31,638	30,67	96,2	-	-	3D-CRT	8,497	8,17	99	-	-
28	3D-CRT	8,339	8,167	98,8	-	-	3D-CRT	8,542	8,293	98	-	-
29	3D-CRT	21,267	20,455	98	-	-	3D-CRT	21,575	21,13	98	-	-
30	3D-CRT	21,283	20,793	98	-	-	IMRT	22,008	21,22	-	106,5	96,7
31	3D-CRT	21,546	21,229	95,8	-	-	3D-CRT	20,978	20,619	98	-	-
32	3D-CRT	8,591	8,374	98	-	-	3D-CRT	21,71	21,391	95	-	-
33	3D-CRT	21,617	20,852	98,5	-	-	3D-CRT	21,399	20,46	99	-	-
34	3D-CRT	8,546	8,365	98,5	-	-	3D-CRT	8,591	8,181	92,5	-	-
35	3D-CRT	8,553	8,4	99	-	-	3D-CRT	8,618	8,317	96	-	-
36	3D-CRT	21,364	20,679	99,9	-	-	3D-CRT	8,558	8,306	99,3	-	-
37	3D-CRT	8,551	8,23	98,5	-	-	3D-CRT	8,546	8,252	98	-	-
38	3D-CRT	21,374	20,78	99,8	-	-	VMAT	8,513	8,407	-	104	96,3
39	VMAT	8,761	8,564	-	106,4	98	IMRT	8,51	8,419	-	105,3	95
40	3D-CRT	21,383	21,11	99	-	-	VMAT	20,787	20,462	-	101,7	95
41	3D-CRT	8,555	8,174	99,5	-	-	3D-CRT	8,601	8,386	99,6	-	-
42	3D-CRT	8,486	8,285	99,8	-	-	3D-CRT	8,598	8,467	99,9	-	-

Supplementary table 2 – Description of parameters for calculation of score risk for myelopathy. (* patients with more than one re-irradiation)

	First Irradiation				Time interval (months)	Re-irradiation						
	Total Dose (Gy)	Dose per fraction (Gy)	BED (Gy)	EQD2 (Gy)		Total Dose (Gy)	Dose per fraction (Gy)	BED (Gy)	EQD2 (Gy)	Cumulative BED (Gy)	Cumulative EQD2 (Gy)	Score risk for myelopathy
1	30	3	75	37,5	48,6	20	4	60	30	135	67,5	2
2	20	4	60	30	11,7	20	4	60	30	120	60	0
3	20	4	60	30	23,3	8	8	40	20	100	50	0
4	20	4	60	30	8,8	20	4	60	30	120	60	0
5	20	4	60	30	12,4	8	8	40	20	100	50	0
6	8	8	40	20	9,7	8	8	40	20	80	40	0
7	8	8	40	20	8,4	20	4	60	30	100	50	0
8	20	4	60	30	32,1	8	8	40	20	100	50	0
9	20	4	60	30	23,7	8	8	40	20	100	50	0
10	20	4	60	30	56,1	20	4	60	30	120	60	0
11	20	4	60	30	5,7	8	8	40	20	100	50	4,5
2	20	4	60	30	45,7	20	4	60	30	120	60	0
13	20	4	60	30	22,0	20	4	60	30	120	60	0
14	8	8	40	20	37,3	20	4	60	30	100	50	0
15	36	3	90	45	11,9	8	8	40	20	130	65	1
16	20	4	60	30	28,4	8	8	40	20	100	50	0
17	20	4	60	30	3,9	8	8	40	20	100	50	4,5
18	8	8	40	20	4,6	8	8	40	20	80	40	4,5
19	8	8	40	20	3,5	8	8	40	20	80	40	4,5
20	20	4	60	30	12,7	20	4	60	30	120	60	0
21	20	4	60	30	11,5	20	4	60	30	120	60	0

22	30	3	75	37,5	50,1	8	8	40	20	115	57,5	0
23*	8	8	40	20	38,6	20	4	60	30	140	70	2
24*	20	4	60	30	4,7	8	8	40	20	160	80	8,5
25	20	4	60	30	10,7	20	4	60	30	120	60	0
26	20	4	60	30	21,8	20	4	60	30	120	60	0
27	30	3	75	37,5	7,4	8	8	40	20	115	57,5	0
28	8	8	40	20	7,3	8	8	40	20	80	40	0
29	20	4	60	30	4,2	20	4	60	30	120	60	4,5
30	20	4	60	30	31,2	20	4	60	30	120	60	0
31	20	4	60	30	5,9	20	4	60	30	120	60	4,5
32	8	8	40	20	20,2	20	4	60	30	100	50	0
33	20	4	60	30	11,8	20	4	60	30	120	60	0
34	8	8	40	20	5,9	8	8	40	20	80	40	4,5
35	8	8	40	20	6,1	8	8	40	20	80	40	0
36	20	4	60	30	6,3	8	8	40	20	100	50	0
37	8	8	40	20	5,3	8	8	40	20	80	40	4,5
38	20	4	60	30	4,5	8	8	40	20	100	50	4,5
39	8	8	40	20	7	8	8	40	20	80	40	0
40	20	4	60	30	9.6	20	4	60	30	120	60	0
41	8	8	40	20	5,8	8	8	40	20	80	40	4,5
42	8	8	40	20	3,3	8	8	40	20	80	40	4,5