



MESTRADO EM ONCOLOGIA
ESPECIALIZAÇÃO EM ONCOLOGIA CLÍNICA

RIBRAIM - Re-Irradiation of recurrent Brain Metastases

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Dissertação de Candidatura ao grau de **Mestre em Oncologia – Especialização em Oncologia Clínica** submetida ao Instituto de Ciências Biomédicas de Abel Salazar da Universidade do Porto.

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“A persistência é o caminho para o sucesso”

Charlie Chaplin

“Tenho a impressão de ter sido uma criança brincando à beira-mar, divertindo-me em descobrir uma pedrinha mais lisa ou uma concha mais bonita que as outras, enquanto o imenso oceano da verdade continua misterioso diante dos meus olhos”

Isaac Newton

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Resumo

Introdução: As metástases cerebrais são os tumores secundários do sistema nervoso central mais frequentes em adultos entre as patologias intracranianas. A Radioterapia é um dos pilares do tratamento das metástases cerebrais. O aumento da sobrevivência destes doentes tem sido acompanhado por um maior risco de recidiva ou progressão intracraniana. A Re-irradiação é uma decisão complexa que exige uma avaliação individualizada.

Objetivo: Analisar o impacto da Re-irradiação em doentes com recidiva de metástases cerebrais.

Materiais e Métodos: Este estudo retrospectivo incluiu 34 doentes com recidiva ou progressão local de metástases cerebrais, tratados no Departamento de Radioterapia do IPO do Porto, entre janeiro de 2019 e dezembro de 2022. Os doentes foram divididos em quatro grupos de acordo com a combinação das técnicas de tratamento: Grupo 1 (WBRT+WBRT); Grupo 2 (SRT+WBRT); Grupo 3 (SRT+SRT); Grupo 4 (WBRT+SRT). A sobrevivência global foi estimada pelo método de Kaplan-Meier. Para comparação entre os grupos aplicou-se o teste de Log-rank, considerando-se diferenças estatisticamente significativas para $p < 0,05$.

Resultados: A sobrevivência global mediana após a Re-irradiação foi de 11,7 meses. Ao fim de 1 ano, 100% dos doentes do Grupo 3 (SRT+SRT) estavam vivos. Os doentes que apresentaram a sobrevivência mediana mais curta (4,1 meses) foram do Grupo 1 (WBRT+WBRT). As diferenças descritas não foram estatisticamente significativas ($p = 0,140$). As principais toxicidades foram as alterações neurocognitivas, a radionecrose e as cefaleias.

Conclusão: A Re-irradiação poderá prolongar a sobrevivência dos doentes com recidiva ou progressão local de metástases cerebrais. Os resultados sugerem que a SRT poderá ser a técnica de Radioterapia preferencial sempre que clinicamente viável. Apesar do maior risco de radionecrose associado à SRT, este foi considerado clinicamente aceitável, tendo em conta a deterioração neurocognitiva a longo prazo associada à WBRT. Estes achados reforçam a necessidade de uma decisão terapêutica individualizada e multidisciplinar.

Abstract

Introduction: Brain metastases are the most common secondary tumours of the central nervous system in adults among intracranial pathologies. Radiotherapy is one of the main pillars in their management. The increased survival of these patients has been accompanied by a higher risk of disease recurrence or progression. Re-irradiation represents a complex therapeutic decision that requires individualized assessment.

Objective: To evaluate the impact of re-irradiation in patients with recurrent brain metastases.

Materials and Methods: This retrospective study included 34 patients with local recurrence or progression of brain metastases, treated at the Department of Radiation Oncology, IPO Porto, between January 2019 and December 2022. Patients were divided into four treatment groups according to the combination of radiotherapy techniques: Group 1 (WBRT+WBRT); Group 2 (SRT+WBRT); Group 3 (SRT+SRT); Group 4 (WBRT+SRT). Overall survival was estimated using the Kaplan–Meier method. Group comparisons were performed with the Log-rank test, considering $p < 0.05$ as statistically significant.

Results: The median overall survival after re-irradiation was 11.7 months. At 1 year, 100% of patients in Group 3 (SRT+SRT) were alive, whereas Group 1 (WBRT+WBRT) showed the shortest median survival (4.1 months). These differences did not reach statistical significance ($p = 0.140$). The main toxicities observed were neurocognitive impairment, radionecrosis, and headaches.

Conclusion: Re-irradiation may prolong survival in patients with recurrent or progressive brain metastases. The results suggest that SRT could be the preferred technique whenever clinically feasible. Although SRT is associated with a higher risk of radionecrosis, this was considered clinically acceptable, particularly when weighed against the long-term neurocognitive deterioration commonly observed after WBRT. These findings highlight the importance of individualized and multidisciplinary decision-making.

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List of Common Abbreviations

3

3D-CRT - Three-Dimensional Conformal Radiation Therapy

A

ASCO – American Society of Clinical Oncology

ASTRO - American Society for Radiation Oncology

B

BBB - Blood-Brain Barrier

BED - Biologically Effective Dose

BMs – Brain Metastases

BTB - Blood-Tumour Barrier

C

CBCT - Cone Beam Computed Tomography

CCA - Contrast Clearance Analysis

CI - Confidence Interval / Conformity Index

CNS - Central Nervous System

CPA - Cranial Positioning Array

CSF - Cerebrospinal Fluid

CT - Computed Tomography

CTCs - Circulating Tumour Cells

CTV - Clinical Target Volume

D

DS-GPA - Diagnosis-Specific Graded Prognostic Assessment

DVH - Dose–Volume Histogram

DW-MRI - Diffusion-Weighted MRI

E

EANO - European Association of Neuro-Oncology

ECOG - Eastern Cooperative Oncology Group

EMR - Electronic Medical Records

EMT - Epithelial-to-Mesenchymal Transition

EORTC - European Organisation for Research and Treatment of Cancer

EQD2 - Equivalent Dose in 2 Gy Fractions

ESMO - European Society for Medical Oncology

ESTRO - European Society for Radiotherapy and Oncology

F

FRIS - Frameless Radiosurgery Imaging Support

G

GABA - Gamma-Aminobutyric Acid

GI - Gradient Index

GK - Gamma Knife

GTV - Gross Tumour Volume

H

HA-WBRT - Hippocampal Avoidance WBRT

HF-SRT - Hypofractionated Stereotactic Radiotherapy

HR - Hazard Ratio

HRQoL - Health-Related Quality of Life

HS - Hippocampal Sparing

HyTEC - Hypofractionated Treatment Effects in the Clinic

I

ICRU - International Commission on Radiation Units and Measurements

IGRT - Image-Guided Radiotherapy

IMRT - Intensity-Modulated Radiation Therapy

K

KPS - Karnofsky Performance Status

L

LC - Local Control

LQ - Linear-Quadratic

LTP - Long-Term Potentiation

M

MMPs - Matrix Metalloproteinases

MRI - Magnetic Resonance Imaging

MRS - Magnetic Resonance Spectroscopy

N

NCI - National Cancer Institute

NCCN - National Comprehensive Cancer Network

NHS - National Health Service

NMDA - N-methyl-D-aspartate

NSCLC - Non-Small Cell Lung Cancer

NTCP - Normal Tissue Complication Probability

O

OAR - Organs At Risk

OS - Overall Survival

P

PCI - Prophylactic Cranial Irradiation

PET - Positron Emission Tomography

PFS - Progression-Free Survival

PTV - Planning Target Volume

Q

QoL - Quality of Life

QUANTEC - Quantitative Analyses of Normal Tissue Effects in the Clinic

QUARTZ - Quality of Life After Treatment for Brain Metastases

R

RCR – Royal College of Radiologists

RCT – Randomized Controlled Trial

RPA - Recursive Partitioning Analysis

RT - Radiotherapy

RTOG - Radiation Therapy Oncology Group

S

sBMs - synchronous Brain Metastases

SCLC - Small Cell Lung Cancer

SD - Systemic Disease

SE - Status Epilepticus

SEER - Surveillance, Epidemiology, and End Results

SF-SRT - Single-Fraction Stereotactic Radiotherapy

SRS - Stereotactic Radiosurgery

ST - Systemic Treatment

SWI - Susceptibility-Weighted Imaging

T

TME – Tumour Microenvironment

V

VEGF - Vascular Endothelial Growth Factor

VMAT - Volumetric Modulated Arc Therapy

W

WBRT - Whole-Brain Radiotherapy

1 INTRODUCTION

1.1 Brain Metastases

Brain metastases (BMs) are secondary tumours of the central nervous system (CNS) that originate from tumour cells disseminated through the bloodstream from an extracranial primary tumour or, less commonly, from pre-existing extracranial metastases. [1, 2] The majority of brain metastases develops within the brain parenchyma due to its rich vascularization. However, metastases can also occur in other CNS-associated structures, that included the leptomeninges (pia and arachnoid mater), dura mater, and skull. [2]

The pathogenesis of BMs is a complex, multi-step process in which several theories in the literature try to explain how tumour cells overcome natural barriers, adapt and establish a new cancer niche within brain tissue, creating a favourable microenvironment for tumour cells to proliferate. [1-3]

Tumour cells can disseminate from an extracranial site by epigenetic and proliferative changes that confer invasive properties on these cells and promote angiogenesis, which is the formation of new blood vessels, or the expansion of existing vessels, as well as an epithelial-to-mesenchymal transition (EMT), that collectively create pathways that allow tumour cells to enter the bloodstream and spread throughout the body. [3]

Once inside the bloodstream, circulating tumour cells (CTCs) that reach the brain, face the central nervous system functional barriers. Those barriers include the blood-brain barrier (BBB) and the blood–cerebrospinal fluid (CSF), which maintain the neuronal signalling and homeostasis of CNS.[1] Tumour cells may use different molecular strategies to increase the permeability of the BBB potentially by upregulating proteins that are essential to this process. Among them, VEGF increases angiogenesis while matrix metalloproteinases (MMPs) weaken the BBB's structural integrity by breaking down extracellular matrix components. Proteolysis and extravasation are facilitated by this degradation, which allows tumour cells to adhere to brain endothelial cells. [3]

Following the cross of the BBB, tumour cells interact with brain endothelial cells, which can enable their adhesion to the brain parenchyma. In addition, tumour cells interact intricately with astrocytes and other brain-resident cells. Direct communication between these cells is made possible by the development of tumour-astrocyte gap junctions, which causes the release of inflammatory chemokines. These chemokines promote the growth and development of metastatic colonies within the brain tissue by improving tumour cell motility, invasion, and survival. As a metastasis forms, the integrity of the BBB becomes partially disrupted, giving rise to what is known as the blood-tumour barrier (BTB). [1, 3]

Apart from these molecular interactions, there is a strong correlation between cerebral blood flow and the distribution of brain metastases within the central nervous system. [2] Since they receive the most blood perfusion, the cerebral hemispheres account for about 80% of brain metastases, with the cerebellum coming in at 15% and the basal ganglia at 3%. [2]

1.1.1 Epidemiology

In clinical practice, BMs are a common diagnosis among adult patients with advanced solid tumours, emphasizing the need for a better comprehension of their epidemiological trends. [2, 4]

The true epidemiology of BMs is still unknown and an unresolved issue. [5] The incidence of intracranial malignancies, including BMs and leptomeningeal disease, has been increased due to improved screening methods and longer patient survival with more effective systemic treatments. However, the CNS is a "sanctuary" for metastasis due to therapeutic agents' restricted capacity to cross the BBB. [6]

In adults, BMs are up to ten times more common than primary brain cancers, making them the most prevalent type of intracranial malignancies. [6-8] Indeed, estimations indicate that between 10% and 40% of adult cancer patients experience the development of BMs. [6, 8-10]

Despite their high incidence/prevalence and substantial impact on morbidity and mortality, these metastases are not systematically recorded in any registry, specifically for secondary brain cancers. [10]

The National Cancer Institute (NCI) manages the Surveillance, Epidemiology, and End Results (SEER) Program in the United States, which acts as a population-based cancer registry that methodically collects data on all primary tumours diagnosed across the country. [10] It also records both synchronous metastases at other sites and synchronous brain metastases (sBM), which are those that were present at the time of primary cancer detection. [10, 11]

The most recent data from the SEER program available in the literature report a total number of 1,872,057 cancer diagnoses between 2015 and 2019, including 35,986 cases (1,92%) of synchronous brain metastases (sBM). [11] The incidence rate of sBM was 7.1 per 100,000 individuals, remaining relatively stable over the study period. [10]

Lung cancer consistently exhibited the highest incidence of sBM, accounting for 76.7% of all cases, with rates ranging from 5.18 to 5.64 per 100,000 individuals. Following these were

melanoma (0.30 to 0.34 per 100,000) and breast cancer (0.24 to 0.30 per 100,000). Among patients with primary lung cancer, those diagnosed with small-cell lung cancer had a significantly higher incidence of sBMs compared to those with non-small-cell lung cancer (0.84 vs. 0.29 per 100,000). [10]

Patients with sBMs had a poor prognosis, as evidenced by their 5-month median survival (95% CI: 4.9–5.1) and 29.3% overall survival (OS) rate at first year across all primary tumour sites. [10]

Although these data provide an important snapshot of the incidence of BMs, their epidemiology remains underestimated due to the fact that BMs can develop throughout a patient's disease course. Therefore, many cases are not captured in this program, leading to an incomplete epidemiological assessment. [11]

Jiang et al. evaluated the incidence and prognosis of synchronous and metachronous BMs over ten years (2013–2023) using data from the TriNetX Diamond Network, a large, nationwide, multi-institutional claims-based platform. [12] Among 11,497,663 patients with 15 primary cancer types, 300,863 (2.6%) developed BMs. Lung cancer had the highest BMs rate (11.0%) and accounted for the majority of BMs cases (50.1%). The oesophagus (3.1%), melanoma (2.6%), kidney, and renal pelvis (2.6%) were other primary cancers with important BMs rates. However, the lowest BMs rates were observed in bladder (0.9%), thyroid cancer (0.6%), and prostate cancer (0.6%). [12] Of all BMs, 187,036 (62.2%) developed metachronously, and 113,827 (37.2%) were diagnosed synchronously, corresponding to 1.6% and 1.0% of the total sample, respectively. With the exception of lung cancer, where 51% of BMs were synchronous, metachronous BMs were more prevalent in all primary cancers. The average time to BMs diagnosis for metachronous cases was 1.8 years, with a range of 1.3 to 2.5 years. [12]

1.1.2 Clinical Presentation

Brain metastases typically developed slowly, and patients wait for symptoms to manifest before seeking medical attention. [6] Growing tumour size or oedema can cause brain compression, increased intracranial pressure, and, in some cases, obstruction of CSF flow, all of which can contribute to the onset of symptoms. [6, 8]

Neurological symptoms are present in 60% to 75% of patients, which can include headaches, seizures, focal neurological deficits, motor impairment, hemisensory loss, altered mental status, cognitive dysfunction, gait abnormalities/ataxia, speech and visual changes, nausea/vomiting, and somnolence. [1, 4, 8, 13] Among these, headaches are the

most commonly reported symptom, affecting approximately half of the patients, and 15–25% of cases are accompanied by papilledema. [6] Headaches are more commonly linked to multiple metastases and/or lesions in the posterior fossa. [1] Focal neurologic deficits are another common symptom and can appear as the initial symptom in as many as 40% of patients. [6] Furthermore, seizures are a major cause of morbidity, occurring in 15–25% of BMs patients. [6].

In some patients, intra-tumour haemorrhage can result in acute stroke-like symptoms, particularly in melanoma or renal cell carcinoma metastases. [5, 6] In addition, cerebellar metastases can also result in obstructive hydrocephalus, which can rapidly worsen neurological conditions. [13]

A severe complication of BMs is status epilepticus (SE), a potentially fatal medical emergency with a high death rate—roughly 31.6% of patients pass away within 30 days of onset. SE may result from intracranial haemorrhage, infection, metabolic abnormalities, tumour progression with increasing metastasis size, or proximity of metastases to the cortex. [6]

The type and severity of symptoms are greatly influenced by the size, quantity, and location of the BMs. [8, 13]

Any patient with systemic cancer who presents with new neurological symptoms should be suspected of having brain metastases. In order to guarantee rapid access to suitable treatment and possibly improve results, prompt neurological evaluation is crucial. [1, 6, 8]

1.1.3 Diagnosis

Imaging is crucial to the diagnosis and clinical management of BMs, as biopsies are generally not recommended due to their invasive nature.[3]

Most BMs patients present with symptoms, as was previously mentioned. Computed tomography (CT) is frequently the initial imaging modality used in acute settings because it offers a quick evaluation of intracerebral complications and possible neurosurgical emergencies. It is particularly useful for detecting bleeding, calcifications, and osseous abnormalities. [14] Magnetic resonance imaging (MRI) with contrast is still the gold standard for detecting and evaluating BMs. It provides high-resolution imaging and superior soft-tissue contrast, enabling accurate evaluation of the size, quantity, and distribution of lesions within the central nervous system (CNS). [5, 6, 14]

On contrast-enhanced imaging, brain metastases typically appear as well-circumscribed, enhancing masses with cystic or mixed (cystic and solid) components, surrounded by vasogenic oedema. They are frequently located at the grey-white matter junction. However, these imaging characteristics are not specific to BMs but can also be observed in primary brain tumours, space-occupying infectious processes, or even vascular insults emphasising the necessity of careful differential diagnosis. [6]

In order to distinguish BMs from other intracranial pathologies, a number of sophisticated imaging modalities can offer extra information for their identification and assessment.

- **Diffusion-weighted MRI (DW-MRI):** Focuses on tumour cellularity. In BMs, signal intensity is reduced due to increased cellularity. [6, 14]
- **Susceptibility-weighted imaging (SWI):** Helps validate the diagnosis of BMs from melanoma. These lesions frequently contain paramagnetic melanin and blood products, which cause susceptibility artefacts on SWI. [14]
- **Perfusion-weighted MRI:** Evaluates the vascularity and haemodynamics of the tumour to help differentiate BMs from primary brain tumours and from normal brain tissue. [6, 14] Additionally, it has a proven role in monitoring BMs after treatment, especially by analysing relative cerebral blood volume. [15]
- **Magnetic resonance spectroscopy (MRS):** Provides metabolic information for tumour characterization. BMs typically have lower choline/creatinine ratios than high-grade gliomas. Additionally, MRS may help differentiate BMs from non-small cell lung cancer (NSCLC), breast cancer, and melanoma. [6, 14]
- **Combining positron emission tomography (PET) with CT or MRI:** Integrates metabolic and anatomical information to improve tumour evaluation. However, it can be challenging to differentiate BMs from high-grade gliomas due to the brain's high glucose uptake. [6, 14]
 - **¹⁸F-FDG PET:** The most widely used radiotracer in oncological practice is 2-[¹⁸F] fluoro-2-deoxy-D-glucose (¹⁸F-FDG), due to its high uptake in tumour cells. However, its diagnostic accuracy for the detection of BMs is limited, as normal cerebral tissue also exhibits physiologically elevated ¹⁸F-FDG uptake. [13, 14]
 - **Amino acids PET:** Radiolabelled amino acids have been used in brain lesion imaging due to their low physiological uptake in healthy brain tissue. The following amino acid tracers are suggested for BMs detection:
 - [¹¹C]-methyl-L-methionine(¹¹C-MET);
 - 3,4-dihydroxy-6-[¹⁸F]-fluoro-L-phenylalanine (¹⁸F-FDOPA);
 - O-(2-[¹⁸F]-fluoroethyl)-L-tyrosine (¹⁸F-FET). [13, 14]

A characteristic of BMs is the overexpression of the L-type amino acid transporter (LAT), which is indicated by these amino acids' high uptake values. [13, 14]

For patients who are unable to undergo an MRI due to factors such as implanted medical devices or allergies to contrast agents, CT is still a helpful imaging method despite its limitations. In such cases, brain CT is a viable alternative. [3, 8]

While imaging plays a crucial role in BMs detection, additional analysis is often required to make a definitive diagnosis. Histopathological analysis of tissue obtained by surgical resection remains the gold standard for confirming the diagnosis of BMs. [1]

In selected cases, minimally invasive surgical methods can be used to remove accessible lesions. According to the literature, patients with well-controlled systemic cancer or an unknown primary tumour benefit from it, especially if the cancer diagnosis was made more than five years before the brain lesion occurred. [1]

There is currently no consensus on screening for asymptomatic BMs, even for cancer types that are at high risk of developing BMs. [14]

The European Society for Medical Oncology (ESMO) recommends BMs screening for all patients with non-small cell lung cancer (NSCLC). In contrast, the National Comprehensive Cancer Network (NCCN) provides more selective recommendations, advising MRI screening for:

- Small cell lung cancer (SCLC) at any stage;
- Stage II-IV NSCLC (excludes routine screening for stage I NSCLC patients without BMs-related symptoms);
- Stage IIIC-IV melanoma, due to its high propensity for brain metastases. [2, 14]

On the other hand, intracranial imaging is usually saved for patients who exhibit neurological symptoms for the majority of other cancers. [3]

One argument against screening is that because BMs may develop later in the course of the disease, early screening may not detect them at a clinically relevant time point. [14]

One argument in favour of screening is the ability to identify asymptomatic BMs, which allows physicians to make better decisions regarding systemic and local treatment options. [14]

In general, BMs screening is taken into consideration when an advanced disease stage is present. If the detection of BMs would change the course of treatment for patients with extracranial metastatic disease, screening should be done. [14]

1.1.4 Treatment of Brain Metastases

Following a diagnosis of brain metastases, the estimated overall survival is only one to two months if treatment is not received. [16] Therefore, to improve clinical outcomes, timely and appropriate intervention is required. [9]

The group of patients with BMs is highly heterogeneous, with differences in the extracranial disease burden, tumour histology, and available systemic therapies. [17]

The main objectives of treatment are typically to prevent or delay neurological deterioration and improve survival while preserving a satisfactory quality of life. However, long-term survival and possibly even a cure may be possible in carefully chosen cases, especially those with small and limited lesions. [13]

The patient's BMs treatment decision is individualized and performed by a multidisciplinary group. It is worth noticing that the decision is always patient-centered. [17, 18] This group is responsible to evaluate multiple parameters both from the tumour and the patient, such as:

- Tumour histology;
- Tumour burden (size, volume, location, and number of metastases);
- Brain metastasis velocity (the number of distant brain relapses divided by the years or fraction of a year);
- Molecular and genetic profile;
- Extracranial disease status;
- Systemic treatment options;
- Performance status and prognosis;
- Baseline neurocognitive function;
- Access to MRI surveillance. [9, 18]

Some criteria are important to take into consideration to properly do the management of patients with BMs:

- A prognosis of at least 6 months;
- Controlled or treatable extracranial disease;
- Karnofsky Performance Status (KPS) of at least 70;

- Availability of systemic therapy options. [17, 19]

These criteria are crucial for assessing the patient's viability of high-dose treatments, so they can receive the most benefit from therapy for intracranial metastatic disease. Naturally, patients with a better performance status (Karnofsky Performance Status - KPS – greater or equal to 70 or Eastern Cooperative Oncology Group - ECOG – between 0-2) are more likely to respond favourably, as they can better tolerate higher-dose radiation. [17] On the other hand, patients with lower functional status (ECOG 3-4), have reduced capacity to tolerate aggressive treatments and frequently results in little to no clinical benefit. [9, 17]

Age is not a limitation, and older patients may still benefit from aggressive treatment. [17]

The treatment of patients with BMs is based on four main pillars: surgical resection, radiotherapy, systemic therapy (chemotherapy, targeted therapy, and/or immunotherapy), and best supportive care. [18]

Treatment decisions should prioritise the patient's quality of life while aiming for optimal tumour control. [18]

1.2 Radiotherapy

For BMs, radiotherapy is recognised as a fundamental therapeutic approach that stabilises the course of intracranial disease and provides palliative relief. [1]

The various radiotherapy techniques available for the treatment of BMs are described in major clinical guidelines, such as the American Society for Radiation Oncology (ASTRO), the European Association of Neuro-Oncology (EANO), the European Society for Medical Oncology (ESMO), the National Comprehensive Cancer Network (NCCN), and the American Society of Clinical Oncology (ASCO). The radiotherapy technique is specified in each of these guidelines according to various factors, including the size of the tumour, its performance status, the number of metastases, the neurosurgical evaluation, and the systemic disease status. [9, 13, 19, 20]

The main techniques used in external beam radiation therapy for the treatment of BMs are Whole-Brain Radiotherapy (WBRT), with or without hippocampal avoidance, and Stereotactic Radiotherapy (SRT). [3, 9, 13, 21]

WBRT was considered the gold standard for treating BMs for several years. [18, 22] However, there are considerable concerns about this technique's cognitive toxicity, which can often be observed after treatment and can significantly affect patients' quality of life. [18]

The biological processes that might be responsible for the neurocognitive deterioration seen following WBRT are described in the following section.

1.2.1 Mechanisms of Neurological Damage

The literature identifies two primary mechanisms of neurological damage associated with WBRT, both contributing significantly to neurocognitive decline in treated patients. [18]

The first mechanism that has been identified is the remodelling of N-methyl-D-aspartate (NMDA) receptors. These receptors are essential for memory and learning, along with glutamate. Excessive activation is known to cause neuronal death. [18]

WBRT induces changes in synaptic receptors that lead to a decrease in NMDA receptor density and an increase in inhibitory gamma-aminobutyric acid (GABA) receptor density. These changes impair long-term potentiation (LTP), an essential mechanism underlying neuroplasticity and functional memory. [18]

Memantine, an NMDA receptor antagonist used to treat Alzheimer's disease, has shown promise in maintaining cognitive function in WBRT patients. [3, 18] In the Radiation Therapy Oncology Group (RTOG) 0614 trial, patients were randomly allocated to receive memantine or placebo for 24 weeks during WBRT. According to the study, memantine helped preserve memory at 24 weeks and significantly delayed overall cognitive decline. These findings suggest that memantine may be a helpful additional therapy for decreasing the cognitive toxicity caused on by WBRT. [3]

The second mechanism that has been identified is radiation-induced selective damage to proliferating neuronal progenitor cells, which results in a severe and extended decrease in neurogenesis within the hippocampus's sub-granular zone. [3, 18, 22] The neurogenesis process is necessary for the formation of new memories. [18, 22]

Hippocampal avoidance WBRT (HA-WBRT) is a treatment technique that was developed to reduce the severity of neurocognitive deficits by changing the target volume to spare the hippocampus. [22] On the other hand, SRT can successfully protect the majority of normal brain tissue, including the hippocampus. [18]

As long as the hippocampus is excluded from the treatment volume, both techniques can be used to reduce neurocognitive deficits.

1.2.2 External Beam Radiation Therapy

This section presents the RT techniques employed on the treatment of BMs. For each of them some aspects are going to be presented some aspects such as clinical indications, main dosimetric characteristics, advantages, and inherent limitations.

Whole Brain Radiotherapy

For many years, WBRT has been the recognised standard of care for patients with leptomeningeal and multifocal brain metastases, and it remains the primary treatment technique for these patients, especially patients with poor performance status who are not good candidates for surgery or SRT. [3, 21, 23]

Apart from treating multiple metastases, WBRT has also been applied to intact and resected metastases, among other clinical situations. A few decades ago, it was also used as prophylactic cranial irradiation (PCI) to reduce the risk of brain metastases in patients with small cell lung cancer (SCLC). [22]

This treatment technique delivers ionizing radiation to the entire brain, including the cerebrum, cerebellum, brainstem, and typically the leptomeninges, with the intent of treating both macroscopic and microscopic BMs, as illustrated on Figure 1. [5, 18] WBRT fractionation regimens vary widely. [24] The fractionation regimens for WBRT have been evaluated in a number of randomised clinical trials, comparing once-daily and twice-daily schedules over a range of time periods, typically one to four weeks. As a result of these studies' guidance of clinical practice, many institutions have made a 2-week regimen consisting of 10 fractions of 3Gy (total dose of 30Gy) their standard method. [22]

Depending on the patient's characteristics, alternative regimens can be chosen. These include longer schedules, like 15 fractions of 2.5Gy, and shorter ones, like 5 fractions of 4Gy (total dose of 20Gy). [22] Shorter fractionation schedules are commonly selected for patients with low performance status and a poor prognosis, with an emphasis on treatment completion and symptom relief. [24]

WBRT offers a number of clinical benefits, such as quick treatment initiation, broad accessibility, and efficient symptom relief. [1]

Despite its benefits, WBRT presents significant challenges due to its short- and long-term toxicity profile, which can significantly affect quality of life. Short-term side effects include fatigue, anorexia, xerostomia, nausea, and alopecia. Long-term effects include leukoencephalopathy, cerebral atrophy and associated cognitive dysfunction, radionecrosis, balance problems, hearing loss, and neuroendocrine abnormalities. [3, 23]

As a curiosity, this technique is usually used in combination with supportive measures and oral steroids to treat peritumoral oedema. The importance of this combined treatment approach is demonstrated by the fact that symptoms frequently improve as a result of oedema reduction rather than tumour reduction. [22]

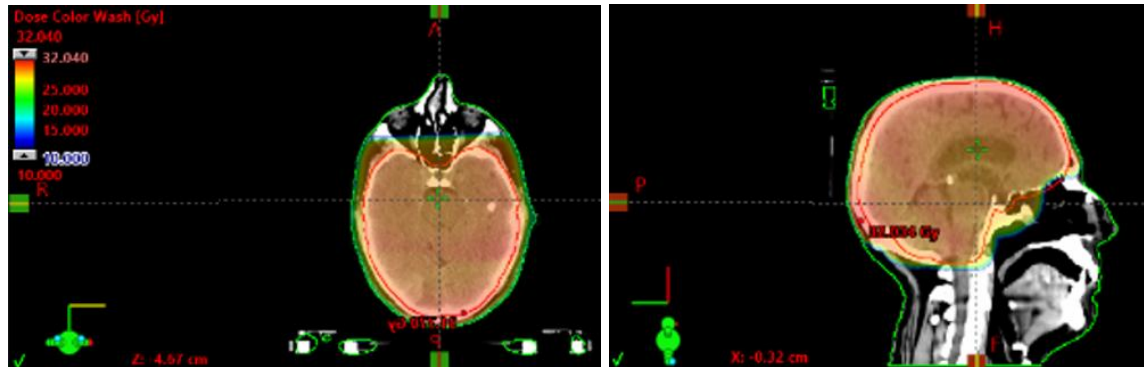


Figure 1 - Radiotherapy Technique: WBRT

1.2.2.1 Hippocampal Avoidance Whole Brain Radiotherapy

The hippocampus's crucial role in memory formation and learning makes it a vulnerable structure. [3, 18, 22]

In light of this, HA-WBRT was developed to sparing the hippocampal dentate gyrus while delivering therapeutic radiation doses to the remaining whole-brain parenchyma (Figure 2). As noted earlier, this modified technique reduces the risk of cognitive decline without compromising the efficiency of treatment. [3, 18, 22] It is important to keep in mind that patients with visible metastases near the hippocampus should not undergo this treatment. [22]

In the NCT02360215 trial study, 518 patients with brain metastases were randomised to receive WBRT (30Gy in 10 fractions) plus memantine, either with or without hippocampus avoidance. [22, 25] This study demonstrated that memantine and HA-WBRT together produced notable cognitive benefits without affecting overall or progression-free survival. Compared to those receiving standard WBRT, patients in this group reported fewer symptoms, such as less fatigue, memory problems, speech problems, and interference of neurological symptoms with everyday activities, and they also had a longer time to cognitive decline (hazard ratio: 0.74; $P = 0.02$). [22, 25]

A key concern with HA-WBRT is whether sparing the hippocampus might increase the risk of tumour recurrence near this region. To address this, the study also evaluated relapse rates near the hippocampus to compare the safety of HA-WBRT with conventional WBRT. The findings showed similar recurrence rates between the HA-WBRT and standard WBRT

groups, with 11 and 16 recurrences, respectively. These results confirm that hippocampal avoidance does not significantly increase the risk of peri-hippocampal tumour recurrence. [3] Based on clinical trials, HA-WBRT combined with memantine has become the standard treatment for most patients without brain metastases located within or near the hippocampus (≤ 5 mm) or with leptomeningeal disease. [3, 18]

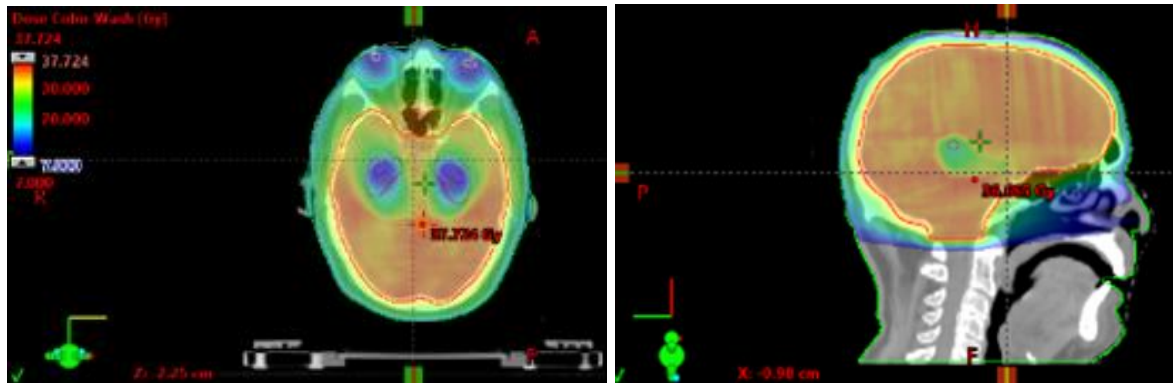


Figure 2 - Radiotherapy Technique: HA-WBRT

1.2.2.2 Stereotactic Radiotherapy

The cognitive adverse effects of WBRT, including fatigue, somnolence, learning and memory impairments, have gained greater recognition during the last two decades. Stereotactic Radiotherapy (SRT) is currently a standard of care for certain patients diagnosed with brain metastases. [1, 13]

SRT is a very accurate and precise treatment technique that delivers high ablative doses with submillimeter precision. With the use of targeted and conformal treatment fields to target volume, this technique reduces the toxicity to healthy brain tissue, as illustrated on Figure 3. [13, 18] The nomenclature for this technique can vary according to the fractionation scheme used. When a single fraction is used, it can be referred to as Single-Fraction Stereotactic Radiotherapy (SF-SRT) or Stereotactic Radiosurgery (SRS). Once the number of fractions is more than one (typically 3-5) it is known as Hypofractionated Stereotactic Radiotherapy (HF-SRT). [26] Single-fraction doses typically range from 15 to 24Gy, while hypofractionated regimens include 24–27Gy in 3 fractions, or 25–40Gy in 5 fractions. [3, 13]

Curiously, HF-SRT reduces toxicity in normal tissues allowing their recover in between fractions. When treating larger lesions or those close to critical structures such as the brainstem or optic pathways this regimen is especially beneficial, where a single-fraction could raise the risk of complications. [18]

To ensure precision, planning target volume (PTV) margins are typically kept between 0 and 2 mm to account for setup uncertainties. [3]

Patient immobilization in SRT can be achieved using either a frame-based or frameless mask-based approach. The frame-based approach provides superior cranial fixation, making it particularly advantageous for single-fraction treatments. However, the frameless mask-based is preferred because of its non-invasiveness and increased patient comfort. [13, 18]

One significant drawback of this technique is the elevated risk of subsequent BMs as result of untreated micrometastases, which may cause distant brain relapses. Regular MRI monitoring is therefore essential for the early detection of distant relapses, allowing for rapid salvage treatment prior to the beginning of symptoms. [18]

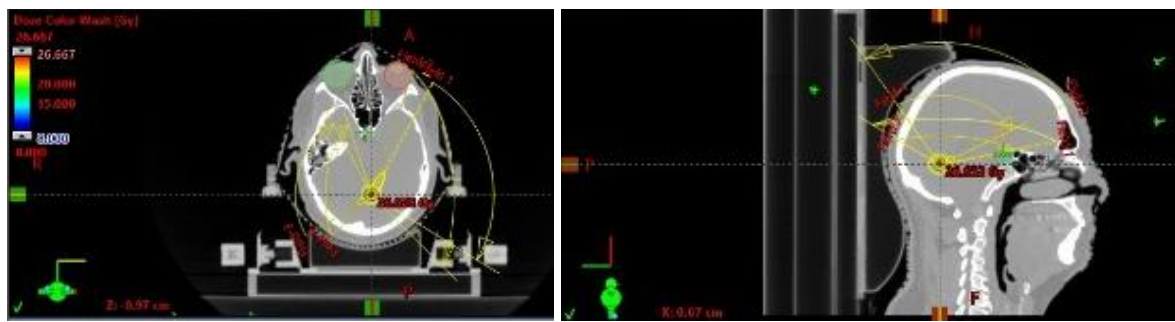


Figure 3 - Radiotherapy Technique: SRT

1.2.3 Clinical Guidelines

1.2.3.1 Single Brain Metastasis

The treatment of a single, intact brain metastasis requires an individualised approach that goes beyond the mere identification of the lesion. Therapeutic decisions should be guided by a comprehensive evaluation of clinical parameters, as previously outlined in the chapter *Treatment of Brain Metastases*. Key factors to consider include the patient's functional status (ECOG), the status of systemic disease (stable vs. active), and the availability of systemic therapeutic options. [9, 19] Only after this assessment can the most appropriate radiotherapy technique and dose be determined.

For patients with 1-3 brain metastases and ECOG 0-2, a prospective randomized study by El Gantery, Abd El Baky [27], involving 60 patients, compared SRS alone, WBRT alone, and the combination WBRT + SRS. Although OS was not significantly different across the arms, subgroup analysis revealed that patients with controlled primary tumours derived the

most benefit from WBRT + SRS, achieving a median OS of 12 months, compared to 8 months with SRS alone and 5.5 months with WBRT alone ($p = 0.027$). The same patient group (WBRT + SRS) also demonstrated superior local control of brain metastases. At 12 months, the rate of local brain control was 42.9% in the WBRT + SRS group, compared to 22.2% with SRS alone and 19% with WBRT alone ($p = 0.04$). However, this greater efficacy came at the cost of increased neurocognitive toxicity: 14% in the WBRT + SRS group, versus 11% in the SRS group and 9% in the WBRT group. [27]

Another RCT, **NCT00548756 study** [28], involving 58 patients, compared SRS alone to SRS + WBRT. Survival outcomes favoured SRS, with median OS of 15.2 months (63% at 12 months), versus 5.7 months (21% at 12 months) in the combined group. Nonetheless, intracranial control was markedly better with SRS + WBRT—achieving 100% local control at 12 months versus 67% with SRS alone ($p = 0.012$), and superior distant brain tumour control (73% vs. 45%, $p = 0.02$). This improved control, however, came at the cost of significantly greater neurocognitive decline at four months, particularly affecting learning and memory. [28]

The RCT **NCT00377156 study** [29], which included 213 patients, also compared SRS with SRS + WBRT. Overall survival was similar between groups (10.4 vs. 7.4 months, $p = 0.92$), but local control again favoured the combined group (89.5% vs. 20%, $p < 0.001$). Neurocognitive deterioration at three months was more frequent with WBRT + SRS (91.7%) than with SRS alone (63.5%) ($p < 0.001$). Overall, the reviewed studies suggest that combining treatment techniques may offer improved control of brain disease. However, this strategy must be carefully considered against the increased risk of long-term adverse effects. On the other hand, **SRS** has been shown to provide comparable, and in some cases superior, overall survival compared to combined treatment technique, with the added benefit of reduced neurotoxicity by sparing healthy brain tissue. [29]

Radiotherapy has progressively evolved - from WBRT, to SRS combined with adjuvant WBRT, and more recently, to SRT alone. [17]

In this context, for small, single intact metastases, **SRT** is considered the **gold-standard** treatment modality, offering high precision and favourable survival outcomes with lower risk of neurocognitive decline. [9, 17] However, when SRT is delivered without adjuvant WBRT, close radiographic surveillance is essential—typically involving brain MRI every 2–3 months for the first 1–2 years, then every 4–6 months indefinitely. [9, 18]

The Radiation Therapy Oncology Group (RTOG) phase I dose-escalation study RTOG 90-05 established the standard SRS dose recommendations for intact brain metastases measuring ≤ 4 cm in diameter. The maximum tolerated doses were determined to be 24Gy

for lesions with ≤ 2 cm, 18Gy for lesions between 2.1 and 3 cm, and 15Gy for those between 3.1 and 4 cm. [30]

It is well documented that **metastases not greater than 2 cm** are suitable for SRS with doses ranging between 20–24Gy, with studies demonstrating excellent local control. [9] However, if the metastasis fails to meet established dosimetric parameters—such as a V12Gy exceeding 10 cm³ or proximity to a critical organ at risk—HF-SRT should be considered as an alternative strategy. According to the Hypofractionated Treatment Effects in the Clinic (HyTEC) report, SRS is associated with increasing rates of radionecrosis when the volume of normal brain tissue (excluding the gross tumour volume) receiving 12Gy (V12Gy) exceeds certain thresholds. Specifically, radionecrosis rates are approximately 10% when V12Gy is 5 cm³, 15% at 10 cm³, and 20% when it exceeds 15 cm³. [17]

For metastases **larger than 2 cm** in diameter, the RCT by Minniti, Scaringi [31], involving 289 patients, compared local control and the risk of radionecrosis between SRS and HF-SRT. The study found that HF-SRT provided better local control at 12 months and lower rates of radionecrosis. For metastases between 2 and 3 cm, local control was 91% with HF-SRT and 77% with SRS ($p = 0.01$). For lesions over 3 cm, rates were 73% for HF-SRT and 54% for SRS ($p = 0.03$). Radionecrosis was also lower with HF-SRT: 8% vs. 20% for metastases < 3 cm ($p = 0.004$), and 14% vs. 33% for those > 3 cm ($p = 0.01$). These findings indicate that HF-SRT could represent a more effective and safer treatment option compared to SRS. [31]

A meta-analysis by **Lehrer, Peterson [32]**, including 1672 patients, compared SRS and HF-SRT in two patient groups: Group A included metastases measuring 2–3 cm, and Group B included metastases larger than 3 cm. In both groups, local control at 12 months was higher with HF-SRT compared to SRS—92.9% vs. 77.1% in Group A, and 81.8% vs. 70.0% in Group B—but the differences were not statistically significant ($p = 0.18$ and $p = 0.76$, respectively). Regarding radionecrosis, HF-SRT was associated with lower toxicity in both groups. In Group A, the difference was statistically significant, with rates of 7.3% for HF-SRT and 23.1% for SRS ($p = 0.003$). In Group B, a similar trend was observed—6.5% with HF-SRT versus 11.7% with SRS—although the difference was not statistically significant ($p = 0.29$). [32]

Based on current evidence, either **SRS or HF-SRT is conditionally** recommended for brain metastases measuring **2.0 to 2.9 cm** in diameter. For lesions measuring **≥ 3 to 4 cm**, **HF-SRT** is the **conditionally** preferred approach. [9]

The most commonly used HF-SRT fractionation schedules include:

- 27Gy in 3 daily fractions
- 30Gy in 5 daily fractions
- 35Gy in 5 daily fractions (occasionally applied in clinical practice). [17]

Metastases exceeding 4 cm in diameter are generally unsuitable for SRS, as the radiation dose delivered to normal brain tissue becomes unacceptable, increasing the risk of radionecrosis. However, the latest American Society for Radiation Oncology (ASTRO) guidelines suggest a maximum lesion diameter of up to 6 cm as a threshold for treatment consideration. [9, 17]

In this context, treatment options become limited to WBRT, with or without hippocampal avoidance. HA-WBRT is a strategy to reduce the risk of neurocognitive decline associated with WBRT, provided there are no lesions near the hippocampus or evidence of leptomeningeal disease. [9, 17]

The most commonly used WBRT fractionation schedules include:

- 30Gy in 10 daily fractions
- 20Gy in 5 daily fractions. [17]

For patients with a favourable prognosis (ECOG 0-2), the recommended schedule is 30Gy in 10 fractions. In contrast, for patients with a poor prognosis (ECOG 3-4), shorter courses such as 20Gy in 5 fractions are generally preferred. [9]

Regardless of lesion size, any brain metastasis causing significant mass effect should be evaluated in a multidisciplinary discussion with neurosurgery to assess the feasibility of surgical resection. [9]

The following flowchart (Figure 4) outlines the recommended decision-making process, based on the latest evidence and recommendations from ASTRO, RCR and NCCN. [9, 17, 19]

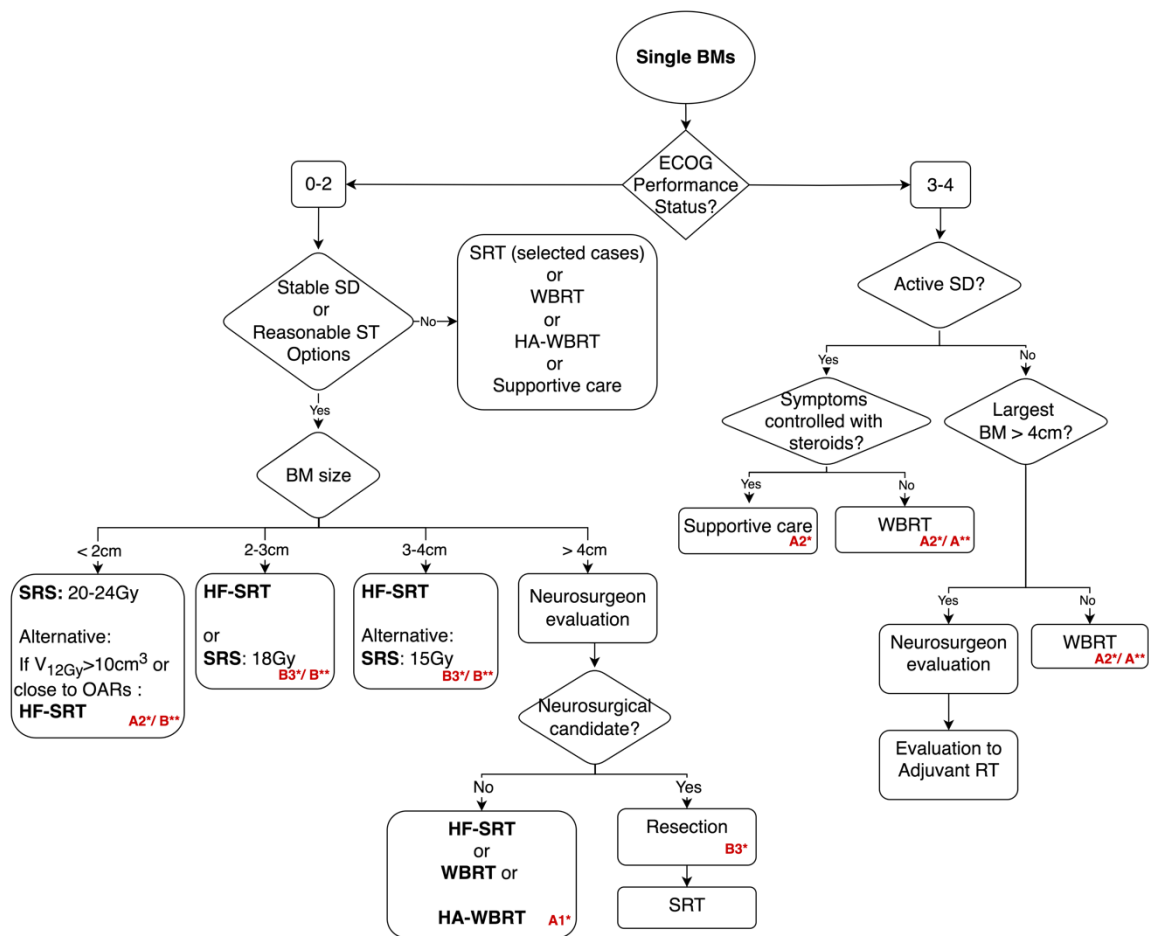


Figure 4 - Single Brain metastasis clinical guidelines schema. (Adapted from Gondi, Bauman [9]) **Legend:** A1* - Strongly Recommended with high-quality evidence; A2* - Strongly Recommended with moderate-quality evidence; B3* - Conditionally Recommended with low-quality evidence; A** Grade A – RCR; B** Grade B – RCR. **Abbreviations:** SD – Systemic Disease; ST – Systemic Therapy.

1.2.3.2 Multiple Brain Metastases

The treatment of multiple brain metastases requires an individualized approach. The clinical parameters used to do the management of multiple BMs are similar to the ones already described in Single Brain Metastasis, namely: patient's functional status, the status of systemic disease, and the availability of systemic therapeutic options remain fundamental. In this context, however, additional factors such as the number of metastases and the total intracranial tumour volume, become particularly relevant in treatment decisions. [9]

In patients with more than one brain metastasis that have good functional status (ECOG 0–2), stable systemic disease, and access to systemic treatment options, it is essential to assess the size of the largest intracranial metastasis. If no metastasis exceeds 4cm in diameter, the total number of brain metastases should then be considered to guide treatment strategy. [9]

For patients with **up to four brain metastases**, **SRT is strongly recommended**, as supported by high-quality evidence. [9, 13, 17] This recommendation is consistent with the evidence presented in the previous section (Single Brain Metastasis), where most of the included studies focused on patients with up to three metastases, showing survival outcomes being equal or better than combined techniques or WBRT alone, while offering the added benefit of reduced neurotoxicity. [9]

For patients with **five to ten brain metastases**, optimal treatment remains controversial. [9]

The RCT **JLGK0901 study** [33], which included 1194 patients, evaluated the use of SRS in patients with multiple brain metastases comparing outcomes across three groups: patients with a single metastasis, those with 2–4 metastases, and those with 5–10 metastases. One of the main findings was that OS in patients with 5–10 metastases was comparable to that of patients with 2–4 metastases, provided that the total tumour volume was below 15 cm³ and no individual lesion exceeded 3 cm in diameter. The median OS in both groups was 10.8 months ($p = 0.78$). There were also no statistically significant differences in local recurrence rates between the groups. At 12 months, neurological function was preserved in 92% of patients with a single metastasis, 91% with 2–4 metastases, and 88% with 5–10 metastases ($p = 0.60$). [33]

So far, **SRT is conditionally recommended** for patients with **five to ten BMs**, due to the absence of prospective randomized trials that support its use. [9, 13, 17] However, the clinical debate becomes more pronounced in patients presenting with more than ten BMs. [9]

Several clinical trials are currently ongoing to compare OS in patients—including those with more than ten lesions—treated with SRS versus HA-WBRT. Results from these studies are eagerly awaited (trial identifiers: NCT03550391, NCT01592968, NCT03075072, and NCT03775330). [17]

Instead of setting a maximum number of brain metastases, the National Health Service (NHS) clinical commissioning criteria and EANO guidelines base the indication for SRT on total intracranial disease volume. The NHS defines an upper limit of 20 cm³, whereas the EANO recommends a more conservative threshold of 15 cm³. [17]

Furthermore, it is essential to consider additional factors, such as brain metastasis velocity (defined as the number of distant brain relapses over time), access to regular MRI surveillance, and the feasibility of subsequent SRS treatments. [9]

The following flowchart (Figure 5) outlines the recommended decision-making process, based on the latest evidence and recommendations from ASTRO, RCR, EANO, ESMO, NHS Clinical Commissioning Criteria and NCCN. [9, 13, 17, 19]

The current recommendations are intended for patients with good functional status (ECOG 0–2). For those with ECOG 3–4, treatment typically follows the same guidelines used for single brain metastases.

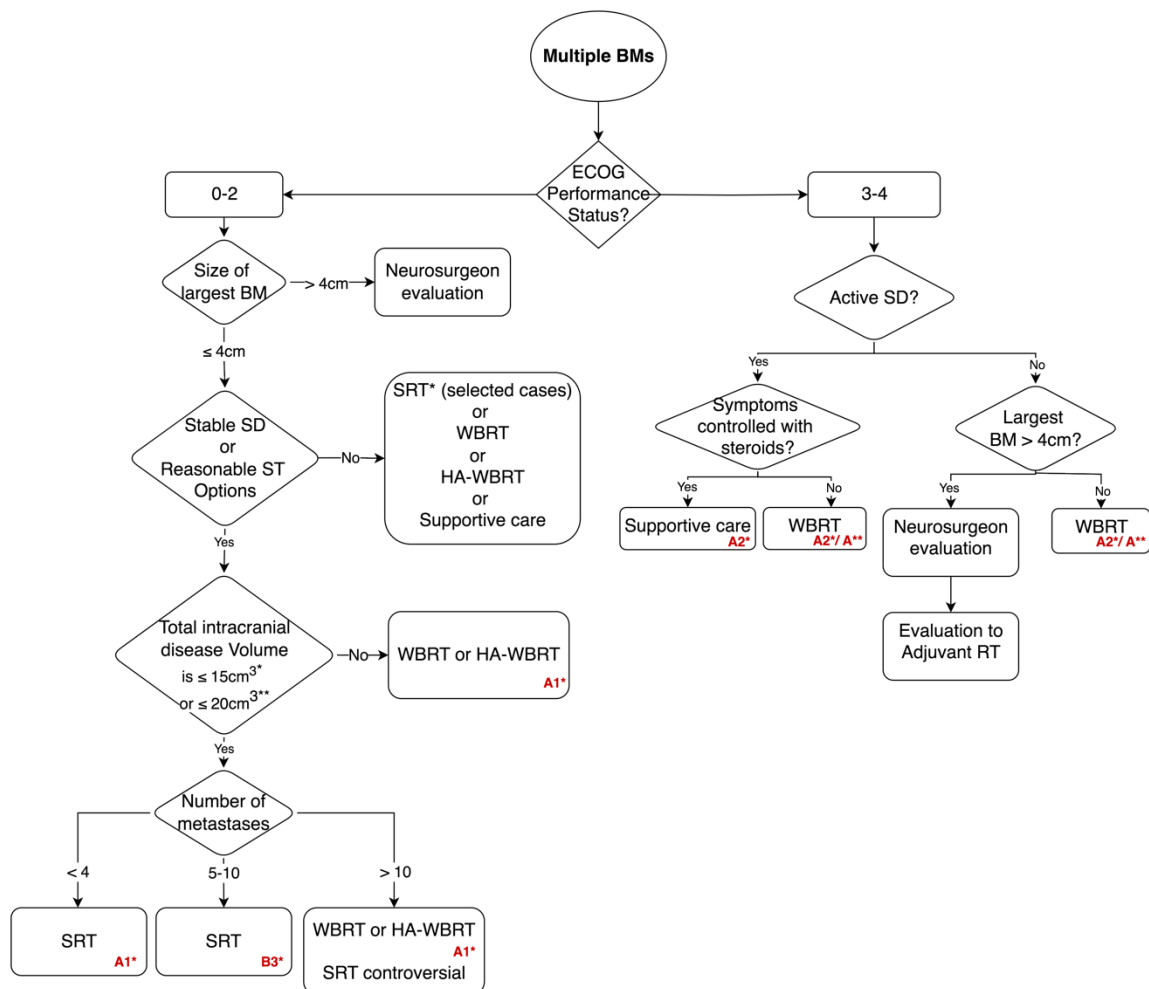


Figure 5 - Multiple brain metastases clinical guidelines schema. (Adapted from Gondi, Bauman [9]) **Legend:** A1* - Strongly Recommended with high-quality evidence; A2* - Strongly Recommended with moderate-quality evidence; B3* - Conditionally Recommended with low-quality evidence; A** Grade A – RCR. **Abbreviations:** SD – Systemic Disease; ST – Systemic Therapy.

1.2.3.3 Postoperative Radiotherapy

Randomised clinical trials have indicated that adjuvant WBRT after surgical resection significantly reduces the risk of local recurrence, distant intracranial failure, and neurological death compared to surgery alone. Also, patients treated with surgical resection alone had presented twice the risk of recurrence in the resection cavity. [9]

The RCT conducted by **Patchell, Tibbs [34]**, with 95 patients, has compared surgical resection followed by **adjuvant WBRT** versus **observation** in patients with a single brain metastasis. The results at 12 months, indicate that there was no statistically significant difference in OS between the two groups (49 vs. 48 weeks; $p = 0.39$). However, the rate of brain recurrence was significantly lower in the WBRT group (18% vs. 70%; $p < 0.001$). In addition, the risk of death due to neurological causes was also significantly reduced with WBRT (14% vs. 44%; $p = 0.003$). On the other hand, this adjuvant strategy is associated with a risk of neurocognitive decline. [34]

Therefore, whenever possible, a more targeted therapeutic technique is preferred, such as **adjuvant SRT**. [9]

The RCT **NCT00950001 study** [35], which included 128 patients, compared surgical resection followed by adjuvant SRS versus observation alone. The study found no statistically significant difference in median OS between the two groups (17 vs. 18 months; $p = 0.24$). However, adjuvant SRS significantly improved local control at 12 months, with rates of 72% in the SRS group compared to 43% in the observation group ($p = 0.015$). [35]

Another RCT NCCTG N107C/CEC.3 study [36], which included 194 patients, compared the effects of **postoperative SRS and WBRT** on survival and cognitive outcomes in patients with resected brain metastases. In terms of median overall survival, no statistically significant difference was observed between the two groups (12.2 months with SRS vs. 11.6 months with WBRT; $p = 0.70$). At 6 months, local control was significantly better in the WBRT group compared to SRS (87.1% vs. 80.4%; $p = 0.00068$). However, neurocognitive preservation was markedly superior with SRS, with 48% of patients maintaining cognitive function versus only 15% in the WBRT group ($p = 0.00031$). [36]

In the **postoperative context**, **SRT is strongly recommended over WBRT**, particularly for patients with a limited number of additional lesions, and this recommendation is supported by moderate-quality evidence. Moreover, this targeted strategy not only better preserves neurocognitive function but also maintains patient-reported quality of life (QoL), while achieving overall survival outcomes comparable to those of adjuvant WBRT. [9, 17] The SRT dose prescription for the resection cavity was determined based on cavity volume and its corresponding equivalent sphere diameter. As the cavity size increases, the recommended SRT dose decreases to minimize the risk of adverse effects such as radiation necrosis. In cases where the cavity exceeds a certain threshold, HF-SRT may be considered as an alternative to SRS treatment. [9, 17]

The following flowchart (Figure 6) outlines the recommended decision-making process based on the equivalent sphere diameter.

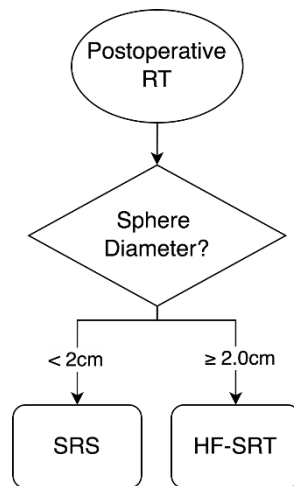


Figure 6 - Postoperative RT clinical guidelines schema.

1.3 Local Recurrence or Progression of Brain Metastases

Developments in systemic and local therapies, led to an improvement of progression-free survival (PFS) and OS in patients with BMs, however, this increased survival has been followed by a higher cumulative risk of CNS failure over the patient's lifetime. [37-39]

As previously mentioned, patients undergoing SRT are monitored through serial MRI. The literature recommends follow-up intervals of every two to three months with the main objective of detection of new intracranial metastases and local recurrent or progression of BMs. The last one, most of the times, is hard to distinguish from radiation-induced effects, namely pseudoprogression and radiation necrosis, because both can manifest with similar symptoms and have similar MRI characteristics. [40, 41]

Pseudoprogression is a process that may occur within a time frame ranging from 6 weeks to approximately 15 months after radiotherapy and is characterized by the appearance of a new area of contrast enhancement or by the enlargement of a pre-existing lesion within the irradiated region, without evidence of true tumour growth. Typically, this process tends to regress or stabilize on follow-up imaging, without requiring any change in therapy. [41]

Radionecrosis is a late toxicity induced by radiotherapy, typically occurring between 6 and 24 months after the completion of treatment and is influenced by the prescribed dose and the volume of brain tissue irradiated. Radiologically, it is characterized by a necrotic lesion within the irradiated area, showing surrounding vasogenic edema and a contrast

enhancement that is described in the literature as resembling “Swiss cheese,” “soap bubbles,” or “cut green pepper”. [41]

In clinical practice, it is difficult to make a proper evaluation of contrast-enhancing lesions as they are often a combination of tumour recurrence and post-treatment effects. [41]

After initial treatment, the CNS failure may be presented as local recurrence (regrowth within the previously treated volume), distant brain failure (emergence of new lesions within the brain parenchyma outside the initially irradiated area), or leptomeningeal dissemination, the latter being associated with the poorest prognosis. [37, 42, 43]

These failures or even the post-radiation treatment effects should be carefully re-evaluated within a multidisciplinary team setting to guide an appropriate therapeutic strategy. [37, 41] In case of post-radiation treatment effects, the condition is handled with observation, steroid therapy, or vascular endothelial growth factor inhibitors such as bevacizumab. [41] When on tumour progression, the evaluation aims to determine whether additional treatment is likely to prolong survival and improve the patient’s quality of life, or whether intracranial progression reflects a terminal phase of systemic disease, in which case, active management of brain metastases may no longer offer meaningful clinical benefit. [42]

When salvage therapy is warranted, the available treatment modalities comprise surgical resection, systemic therapy, re-irradiation, and best supportive care. [41, 44, 45]

There are currently no established guidelines to support decision-making on the optimal therapeutic strategy, mainly due to the lack of evidence. Nonetheless, all clinical decisions are guided by a patient-centred approach. [46]

Evidence suggests that surgical resection and re-irradiation, often used sequentially or in combination, remain the preferred therapeutic strategies for symptomatic patients.[39] Surgical resection not only provides immediate relief of mass effect but also allows histopathological differentiation between tumour recurrence and radionecrosis. [47, 48] If tumour recurrence is confirmed, adjuvant treatment is recommended, as surgery alone does not achieve sufficiently high local control rates. [47, 48]

1.3.1 Diagnosis: Distinguishing Between Recurrence or Progression of BMs and Post-Treatment Radiation Effects

The distinction between post-radiotherapy effects and local recurrence or progression of BMs is complex in neuroimaging, because there is an overlap in their radiological characteristics. To improve the diagnostic accuracy, a range of advanced imaging techniques is progressively employed. [41, 49] For each technique, the main radiological characteristics associated with radionecrosis and local progression of BMs will be outlined:

- **Post-Contrast T1-Weighted Sequences:** In both cases, they usually present peripheral enhancement and central necrosis. The main difference resides in the fact that, in case of radionecrosis, the enhancement is characteristically thin and irregular, without any well-defined solid component while, in local progression, it is usually associated with thicker or more solid enhancement. [49]
- **MRI-based contrast clearance analysis (CCA):** This technique consists on subtracting two T1-weighted MRI images. One acquired 5 minutes after the administration of a gadolinium-based contrast agent and other acquired 60 to 105 minutes post-contrast. The result of this subtraction provides additional information about the temporal dynamics of contrast retention. [50] In theory, progression of BMs displays blue on CCA, as tumour tissue is highly vascularized while, radionecrosis appears red due to contrast agent leakage, caused by radiation-induced vascular damage. [50, 51]
- **DW-MRI:** Central diffusion restriction is a typical finding in radionecrosis and can be used as a useful imaging feature in its identification. [49]
- **SWI:** In cases of radionecrosis, often shows several small spots of magnetic susceptibility. These can appear around the enhancing edge of the lesion, the necrotic core, or in the nearby brain tissue. This finding isn't unique to radionecrosis because local recurrence or progression of BMs (especially when there's bleeding inside) have characteristics very similar. Still, if no susceptibility spots are seen at all, it might be a sign that is recurrence or progression of BMs. [49]
- **Perfusion-weighted MRI:** Dynamic susceptibility contrast perfusion is the most commonly used technique in the evaluation of brain lesions. In the context of BMs, local recurrence or progression is typically associated with higher relative cerebral blood volume compared to radionecrosis, although absolute values and diagnostic thresholds vary across studies. [49]

- **Amino Acid Positron-Emission Tomography:** The amino acid radiotracers recommended for the detection of BMs are the same as those used to differentiate between recurrence or progression of BMs and radionecrosis. [41] These include:
 - [^{11}C]-methyl-L-methionine(^{11}C -MET);
 - 3,4-dihydroxy-6- ^{18}F -fluoro-L-phenylalanine (^{18}F -FDOPA);
 - O-(2- ^{18}F -fluoroethyl)-L-tyrosine (^{18}F -FET). [41]

Radionecrosis typically demonstrates a progressively increasing tracer uptake over time, whereas recurrence or progression of BMs is characterized by an early peak in amino acid uptake followed by either a plateau or a rapid decline. [41, 49]

A probable diagnosis can often be established through the combined use of various imaging techniques and their specific diagnostic criteria. However, a definitive diagnosis is not always possible, as lesions may represent a mixture of tumour recurrence and post-treatment effects. In such cases, close imaging follow-up may be appropriate until a more confident diagnosis can be made. [41]

1.4 Re-Irradiation

A standardized definition and classification of re-irradiation was established by The European Society for Radiotherapy and Oncology (ESTRO) and the European Organisation for Research and Treatment of Cancer (EORTC), which define re-irradiation as: *“a new course of radiotherapy, either to a previously irradiated volume (irrespective of concerns of toxicity) or where the cumulative dose raises concerns of toxicity”*. In addition, re-irradiation was also distinguished re-irradiation from other forms of radiotherapy retreatment. [52]

Re-irradiation can be categorized into two distinct types:

- Type 1 involves geometric overlap between the initial and current targets, when a new course of radiotherapy is delivered to a previously irradiated volume. [46, 52]
- Type 2 involves no direct geometric overlap with the previous treatment. Despite this gap, there are still concerns regarding the cumulative radiation dose, as surrounding organs and tissues may have also been exposed during the first treatment. [46, 52]

In cases where there is an absence of both overlap and cumulative dose toxicity, an additional distinction can be made based on the location of target volumes. In case of the target volumes of the current and previous radiotherapy courses are within the same organ but in a different region, the term “repeated organ irradiation” is used. If the target volumes are in different organs, the term “repeated irradiation” is used. [46, 52]

The ESTRO-EORTC consensus of 2022 on re-irradiation defined a set of recommendations which should be taken into consideration in the process of decision making for re-irradiation, despite the lack of evidence level in some scenarios. [52]

Clinical practice should be guided by the following considerations and recommendations: [52]

- Interdisciplinary management and shared decision making;
- Factors specific to patients and tumours;
- Radiobiological aspects;
- Factors specific to re-irradiation.

Re-irradiation must be recommended only in clinical cases where the patients do not have other viable treatment alternatives or, when the main goal is the symptomatic relief. [46] It is important to notice that, whenever other viable treatments exist with comparable results or lower toxicity, this should be preferred rather than re-irradiation when in the decision-making process. If the re-irradiation still is the treatment to be used then, the treatment goal must be clearly defined and properly communicated to the patient (either it is curative, palliative, or locally ablative). [46, 53]

Anytime high-dose re-irradiation is considered, it is recommended that patients have a stable performance status, corresponding to an ECOG score ≤ 2 , and an estimated survival greater than six months. When patients have a limited life expectancy, this treatment should only be considered if it can provide symptom relief without worrying about irreversible toxicity. [46, 52]

Radiobiological parameters must also be considered, including the intrinsic radiosensitivity or radioresistance of the tumour and its response to previous irradiation. Cumulative dose assessment (which take in consideration data of the previous treatment) should be based on robust radiobiological models, particularly through the application of the linear-quadratic (LQ) equation, using appropriate α/β values for both tumour tissues and organs at risk (OARs). [46]

Following re-irradiation, it is important to establish a rigorous clinical follow-up to monitor treatment outcomes and detect potential toxicities at an early stage. This monitoring includes appropriate imaging modalities and structured clinical assessments, allowing timely and effective intervention whenever necessary. [46]

1.4.1 Re-Irradiation - Local Recurrence or Progression

Re-irradiation strategies used for the management of local recurrence or progression of brain metastases are varied and should be carefully individualized according to the clinical scenario. The available treatment techniques include (HA-)WBRT and SRT and, based on prior treatments, several clinical scenarios may arise:

- WBRT, with or without hippocampal avoidance, following a previous course of SRT;
 - Repeated courses of WBRT, with or without hippocampal avoidance;
 - Repeated courses involving SRS and/or HF-SRT, which may be delivered in alternating sequence;
 - SRT delivered after a prior course of WBRT, with or without hippocampal avoidance.
- [43, 54]

Selection of an appropriate re-irradiation technique for recurrent brain metastases should also take in consideration patient-related, tumour-specific, and treatment-related factors. [54]

Starting with patient-related aspects, key variables include: age, performance status, neurological status, presence of comorbidities, and the overall life expectancy. These parameters are essential for estimating the patient's capacity to tolerate additional treatment. [54]

Tumour-specific factors include number, location, size and cumulative volume of recurrent brain metastases, temporal rate at which these lesions have developed, as well as the tumour histology and the extent of extracranial disease. [43, 54]

Regarding treatment-related factors, several parameters must be meticulously reviewed. These include the total dose and fractionation scheme administered during the initial course of radiotherapy, the interval between the previous treatment and the proposed re-irradiation scheme, the total volume to be re-irradiated, and the cumulative dose received by organs at risk (OARs). [54]

A minimum interval of 6 to 12 months following prior radiotherapy is commonly adopted in clinical practice as a threshold for re-irradiation eligibility, as reported in the literature. [55]

In the context of re-irradiation, there is growing evidence that WBRT is associated with a rapid and frequent decline in cognitive function. [48, 56]

As a therapeutic alternative, SRT has emerged as the predominant strategy for managing locally recurrent brain metastases, largely owing to the limited availability of other viable treatment options for this clinical scenario. [57]

1.5 Radiobiology

Radiobiology can be described as the science that study the effects of the ionizing radiation to biological systems. [58, 59]

The Hallmarks of radiobiology are currently known as the *7Rs* (the number of *Rs* have been evolving since the initial four by Withers in 1975, last 7th *R* being introduced in 2024). These biological features help the definition of the result of RT in the clinical practice, being a balance between the tumour control and side effects on normal tissues rate. [58, 59]

Currently the 7 *Rs* can be described as: [58, 59]

- Repair of sublethal damage
- Reoxygenation
- Redistribution of cells through the cell cycle
- Repopulation
- Radiosensitivity
- Reactivation of antitumor immune response
- Reinforcement by tumour microenvironment

The **Repair of sublethal damage**, refers to the capacity of the cells to repair from damage on DNA produced by radiation. Normal cells tend to repair DNA damage in a more efficient way than the tumoral ones. [58, 59]

The **Reoxygenation** principle is based on the fact that hypoxic cells (with low oxygen, like tumoral cells) are more radioresistant. Reoxygenation is the process where the hypoxic cells become more oxygenated which results in an increased radiosensitivity between radiation fractions. [58, 59]

The sensibility of cells to radiation varies according to the cell cycle stage where it is in a certain point in time. Cells on synthesis phase are reported as more radioresistant than other phases, while cells in mitosis are more radiosensitive. The radiation can induce a **Redistribution of cells through the cell cycle** to more sensitive phases. [58, 59]

After irradiation, the cells that survive usually have a higher resistance to radiation, which means that they are able to maintain their clonogenic capacity (ability to replicate indefinitely). This capacity allows them to repopulate the tumour, which reflects in a decrease of treatment efficacy. In case of normal tissues, the **Repopulation**, helps to regenerate the damaged tissue, reducing the early toxicity. So, one of the most important

aspects of radiobiology is the actual reproductive death of cells (mainly the tumour cells). [58, 59]

The **Reactivation of antitumour immune response**, refers to the possibility of activation of the immune system after irradiation, inducing a rare systemic antitumoral response (known as abscopal effect), which can attack distant and not irradiated tumoral cells. [58, 59]

The **Reinforcement by tumour microenvironment**, explains how tumour cells can receive support from cellular and non-cellular components - such as cancer-associated fibroblasts, myeloid-derived suppressor cells, tumour-associated macrophages, etc - to block immune system cell recruitment and activation, creating a protective tumour microenvironment (TME). [59]

In the context of this study, the recommendation for SRT in the treatment of BMs is quite clear, however, it is subject to compliance with various established criteria. The RT fractionation paradigm is shifting from conventional multifractionated radiation to extremely hypofractionated radiation. Therefore, the radiobiological mechanisms underlying the understanding of the benefits of this ablative radiotherapy technique that allows the delivery of a higher dose per fraction (>5Gy) and fewer fractions (1–5 fractions), geometrically sparing healthy tissue compared to conventional radiotherapy techniques, have not yet been fully elucidated to date. [60-62]

From the hallmarks described above, it is known that the use of high doses in treatment (without reference to absolute values) can lead to the induction of necroptosis (rather than apoptosis) of tumour cells, which result on most tumour cells suffering lethal damage during this process. In single doses above 20Gy, there is no redistribution of tumour cells, regardless of their cell cycle phase and regarding reoxygenation, it is not relevant for this process, as there is widespread vascular destruction. However, in hypofractionated regimens, vascular damage may be negligible, and in this case, surviving hypoxic cells may be favoured. Repopulation of surviving cells usually occurs 3 to 4 weeks after the start of treatment, and therefore, in hypofractionated or single-fraction regimens, this mechanism may not even occur. [61, 62]

Interestingly, the time taken to administer the treatment dose may be associated with the loss of biological efficacy because, when treatment lasts longer than 30 minutes, there is a 10% loss in efficacy. [61]

Clinical studies confirm that the stereotactic ablative radiotherapy beside the direct ablation of tumoral cells, may also induce indirect effects, including vascular endothelial lesion and immunological activation.

When the doses administrated are higher than 8Gy, the acid sphingomyelinase pathway can be activated or translocated. The activation of this pathway can trigger the apoptosis of tumour endothelial cells, which regulates the angiogenesis-dependent tumour growth and so, increase tumour cell death. The translocation, on the other side, will create pro-apoptotic ceramide which will activate the mitochondrial-mediated apoptotic response. [62, 63] In response to SRT treatment, the immune system also plays an important role in tumour surveillance and suppression. This treatment is believed to trigger the release of tumour-specific antigens and cytokines that enhance the innate antitumor immune response. [63]

1.5.1 Biologically Effective Dose and Equivalent Dose in 2Gy Fractions

The Biologically Effective Dose (BED) is a radiobiological metric that allows the comparison of doses from different fractionation schedules in RT which will result in different biological effects. [58, 64]

To calculate the BED, it can be used the following formula (from Fowler [65]), where n describes the number of fractions, d the dose per fraction and α/β representing the sensitivity of the tissue or tumour. [58, 64]

$$BED = n * d * [1 + \frac{d}{\alpha/\beta}]$$

The equivalent dose in 2Gy fractions (EQD2) is also a radiobiological metric derived from the BED concept, that expresses any radiotherapy treatment schedule in terms of the total equivalent dose that would be required if delivered with the conventional 2Gy fractionation. [58, 66]

This metric has been recommended as it helps clinicians to better understand the likely effectiveness of relatively new treatment regimens. EQD2 is also valuable for normalizing diverse fractionated treatment schedules. [58, 66]

To calculate the EQD2, the following formula (from Fowler [65]) can be used:

$$EQD_2 = n * d * \frac{d + \alpha/\beta}{2 + \alpha/\beta} = \frac{BED}{1 + \frac{2}{\alpha/\beta}}$$

2 OBJECTIVES

The primary objective of this retrospective cohort study was to analyse the impact of Re-irradiation on BMs recurrence or progression.

Accordingly, the specific objectives of this work were:

- To describe the demographic, clinicopathological and treatment characteristics (first radiotherapy treatment and re-irradiation) of patients re-irradiated after recurrence or progression of BMs;
- To describe the radiotherapy-related characteristics of target volumes (first radiotherapy treatment and re-irradiation) in patients re-irradiated after recurrence or progression of BMs;
- To calculate the time to re-irradiation;
- To evaluate the long-term toxicity and follow-up outcomes, namely local progression and distant intracranial progression, after re-irradiation;
- To analyse overall and median survival of patients with BMs after first RT treatment;
- To analyse overall and median survival of patients with recurrence or progression of BMs after re-irradiation;
- To calculate the cumulative biological effective dose and equivalent Dose in 2Gy fractions of both treatments in the brain;
- To compare outcomes across different sequences of WBRT and SRT used for first radiotherapy treatment and re-irradiation.

3 MATERIALS AND METHODS

3.1 Setting and population

IPO-Porto is a highly differentiated institute, belonging to the National Health Service of Portugal, which provides specialized cancer care. It is a comprehensive cancer centre, admitting around eight thousand new patients annually and providing healthcare to over 45 thousand patients *per year* covering the entire cancer continuum, from diagnosis to treatment and follow-up.

3.2 Patient Selection Criteria

This retrospective cohort study included adult patients diagnosed with brain metastases progression or recurrence and who underwent re-irradiation. Patients were treated at the Radiation Oncology Department of the Portuguese Oncology Institute of Porto, between January 2019 and December 2022.

Patients were considered eligible for inclusion if they satisfied all of the following criteria: (i) adult patients (those who were at least 18 years old) (ii) presence of brain metastases with radiologically verified local recurrence or progression, as assessed by follow-up magnetic resonance imaging (MRI) or computed tomography (CT); and (iii) completion of two distinct courses of cranial radiotherapy, with the second course clearly intended as re-irradiation type 1, as defined by the ESTRO/EORTC classification, targeting the recurrent lesion(s).

Patients were excluded if they met any of the following criteria (Table 1): (i) presence of brainstem metastases with radiologically confirmed recurrence or progression, because of their distinct clinical behaviour and associated unfavourable prognosis; (ii) Type 2 re-irradiation (without geometrical overlap between irradiation volumes); (iii) the absence of follow-up data, particularly in patients referred from external institutions; (iv) treatment that involved a third course of cranial radiotherapy; (v) incomplete treatment; or (vi) cases in which radiotherapy was administered for prophylactic purposes or leptomeningeal dissemination.

The application of these criteria led to the removal of 61 cases from the initial sample of 85, resulting in a final study sample of 34 patients.

Table 1 - Exclusion Criteria Summary

Exclusion Criteria	Number of patients
Duplicate patient entries	10
Brainstem metastases	1
Lack of follow-up data	21
Third course of cranial Radiotherapy	7
Type 2 Re-irradiation	6
Incomplete treatment	2
Prophylactic treatment or extracranial irradiation	4
Total	61

3.3 Radiotherapy Planning and Treatment Procedures

All procedures were performed according to institutional clinical protocols in place at the Department of Radiation Oncology, Portuguese Oncology Institute of Porto, between 2019 and 2022.

3.3.1 Immobilization and Planning CT

3.3.1.1 WBRT with or without hippocampal avoidance

Patients undergoing WBRT or HA-WBRT were positioned supine on the treatment couch, with their arms placed alongside the body. Head immobilization was performed using a Timo headrest placed on a standard Uni-frame® supine baseplate, to which a UON® thermoplastic head mask was securely fixed. For lower body stabilization and to improve setup reproducibility, the MacroMedics® Lower Extremity Positioning System (LEPS™) was also used.

Planning computed tomography scans were acquired in helical mode with slice thicknesses of 2.5mm, encompassing the region from the vertex of the skull to the mentum, including the soft tissues of the face and cranial base.

3.3.1.2 SRT

Patients undergoing SRT were positioned supine on the treatment couch, with their arms placed alongside the body, using the Frameless Radiosurgery Imaging Support System

(FRIS). This system accommodates a rigid thermoplastic mask composed of three parts: posterior, intermediate, and anterior layers. For optimal anatomical conformity, nasal support spheres are positioned between the intermediate and anterior layers of the mask. Between the posterior and intermediate layers, 2 mm spacers are inserted to ensure precise fit and spacing. All components—including the spacers and fixation clips—are integrated into the mask system. Finally, the Cranial Positioning Array (CPA) is attached to the FRIS, allowing submillimetric positioning accuracy through pre-treatment image guidance and intra-fractional motion verification.

Planning computed tomography scans were acquired in helical mode with slice thicknesses of 1.25mm, encompassing the region from the top of the immobilization system to the mentum, including the entire head support setup, facial soft tissues, and cranial base.

3.3.2 Radiotherapy Planning

All treatment plans were developed using the appropriate planning system, according to the radiotherapy technique employed. For patients undergoing WBRT or HA-WBRT, treatment plans were developed using the Eclipse® treatment planning system (Varian Medical Systems). In cases where SRT was indicated, planning was conducted using either the iPlan® system (Brainlab®) or the Cone planning system (Varian Medical Systems).

In all patients, the brain was the only organ at risk (OAR) analyzed in this study. The assessment of normal tissue adverse effects following radiotherapy depends on the prescribed dose and fractionation scheme. For conventional fractionation, the QUANTEC (Quantitative Analyses of Normal Tissue Effects in the Clinic) recommendations are applied, whereas for hypofractionated regimens with higher doses per fraction, the HyTEC guidelines are followed. [67, 68]

3.3.2.1 WBRT

Patients undergoing WBRT were planned to use either three-dimensional conformal radiotherapy (3D-CRT) or volumetric modulated arc therapy (VMAT) techniques.

Planning with 3D-CRT followed the recommendations of the International Commission on Radiation Units and Measurements (ICRU) Reports 50 and 62. [69, 70] The clinical target volume (CTV) include the whole brain and, the planning target volume (PTV) include the CTV with a uniform isotropic margin of 3–5 mm. Plan evaluation was based on dose–volume histogram (DVH) analysis, with the objective of ensuring that 100% of the PTV volume received at least 95% of the prescribed dose.

Planning with VMAT was conducted according to ICRU Report 83, which provides recommendations specific to intensity-modulated radiotherapy (IMRT) techniques. [71] The CTV and PTV volumes were identical to those used in the 3D-CRT plans. Plan evaluation was based on DVH analysis, with the objective of ensuring that 98% of PTV volume received at least 95% of the prescribed dose, while 2% of the PTV volume must not receive doses higher than 107% of the prescribed dose.

Total doses of 20–30Gy delivered in 5 or 10 fractions were prescribed to the patients.

3.3.2.2 HA-WBRT

Patients undergoing HA-WBRT were planned in accordance with the RTOG 0933 protocol, which provides specific clinical and dosimetric guidelines for hippocampal avoidance. [72] In this setting, the CTV include the whole brain, excluding the hippocampal structures delineated on fused T1-weighted contrast-enhanced MRI and planning CT images. The PTV include the CTV with a 3-5 mm uniform isotropic margin, excluding a 5 mm margin from hippocampal structures.

Plans were evaluated based on DVH analysis, and the following PTV dose constraints from RTOG 0933 were applied: $D2\% < 37.5\text{Gy}$, to limit high-dose regions, and $D98\% > 25\text{Gy}$, to ensure sufficient dose coverage. [72]

Regarding fractionation schemes, only one was prescribed: a total dose of 30Gy delivered in 10 daily fractions of 3Gy each.

3.3.2.3 SRT

SRT was planned in accordance with the recommendations of ICRU Report 91, which provides specific guidelines for stereotactic treatments with small photon beams. [73] Gross tumour volume (GTV) was delineated on fused planning CT and gadolinium-enhanced T1-weighted MRI sequences. A uniform margin of 1 mm was added to the GTV to create the PTV.

Plan evaluation was based on DVH analysis, with the objective of ensuring that at least 95% of the PTV volume received 100% of the prescribed dose. Additionally, the maximum dose was constrained not to exceed 130–140% of the prescribed dose.

Regarding the prescription dose, for SRS, total doses between 21 to 24Gy were prescribed. When HF-SRT was used, the most common regimens were 27Gy in 3 fractions and 30Gy in 5 fractions. In selected cases, 35Gy in 5 fractions was also administered.

3.3.3 Dosimetric Criteria

All treatment plans were analysed within the planning system, considering both direct dose metrics and DVHs.

3.3.3.1 WBRT

For all 3D-CRT plans, the evaluation of the PTV was based on the **V95%** parameter, which represents the percentage of the PTV receiving at least 95% of the prescribed dose. The value of this parameter will be close to 100%. It is important to note that plan assessment was performed visually, slice by slice, using isodose distributions, however, V95% was selected as the representative dosimetric parameter.

For all VMAT plans, the evaluation of the PTV was based on the **D98%** and **D2%** parameters. D98% was used as a representative parameter of the minimum dose within the PTV, corresponding to the dose received by 98% of the volume, and its value should be at least 95% of the prescribed dose. On the other hand, D2% was used as a representative parameter of the maximum dose within the PTV, corresponding to the dose received by 2% of the volume, and this value should not exceed 107% of the prescribed dose.

The brain was evaluated using two parameters: the mean and maximum doses. The mean dose (**Dmean**) should be equal to or close to the prescribed dose. The maximum dose (**Dmax**) should be not exceeded 107% of the prescribed dose.

3.3.3.2 HA-WBRT

The PTV evaluation was based on **D98% > 25Gy** and **D2% < 37.5Gy**, in accordance with RTOG 0933. [72] These constraints ensure that at least 98% of the PTV volume receives a minimum therapeutic dose of 25Gy, while 2% of the PTV volume must not be exposed to doses higher than 37.5Gy.

As in WBRT, the brain was evaluated using both the **Dmean** and **Dmax** parameters.

3.3.3.3 SRT

The PTV evaluation was based on the **D95% parameter** to verify whether at least 95% of the volume received 100% of the prescribed dose. Additionally, **D98% parameter** was also assessed. In cases where the D95% criterion was not met, the **D90% parameter** was analysed. The value of all the mentioned parameters should correspond to 100% of the prescribed dose. Other dosimetric parameters were also recorded, including D100%, the median dose to the PTV, and the median dose to the GTV.

Finally, the **maximum dose** within the PTV was evaluated to ensure it did not exceed 130–140% of the prescribed dose.

Plan quality was assessed using the **conformity index (CI)**, defined as the ratio between the treated volume and the PTV volume. This value was obtained directly from the treatment planning system. CI values should range between 1 and 2, with values closer to 1 indicating better conformity of the prescribed dose to the target volume.

Additionally, the **gradient index (GI)** was recorded, calculated as the ratio between the volume encompassed by the 50% isodose line and the volume encompassed by the prescription isodose. This metric quantifies dose fall-off outside the target volume. The GI was documented for future analysis purposes only, as there is currently no consensus in the literature regarding its ideal values. [74, 75]

For brain dose evaluation in stereotactic treatments, the percentage of healthy brain volume irradiated was assessed. The specific dose–volume metrics analysed varied according to the fractionation scheme: **V10Gy** and **V12Gy** for single-fraction treatments; **V18Gy** and **V20Gy** for three-fraction regimens; and **V24Gy** and **V30Gy** for five-fraction regimens.

The dose-volume criteria analysed are represented in the Table 2.

Table 2 - Dose-volume criteria and risk of radiation-induced brain necrosis

Fractionation scheme	Dose-volume Metric	Radionecrosis Risk
1	V10Gy $\leq$ 10cm ³	0% ⁽¹⁾
	V10Gy > 10cm ³	24% ⁽¹⁾
	V12Gy $\leq$ 5cm ³	10% symptomatic ⁽²⁾
	V12Gy $\leq$ 10cm ³	15% symptomatic ⁽²⁾
	V12Gy $\leq$ 15cm ³	20% symptomatic ⁽²⁾
3	V18Gy < 30.2cm ³	5% ^(3,4)
	V18Gy > 30.2cm ³	14% ^(3,4)
	V18Gy > 41.2cm ³	24% ^(3,4)
	V20Gy $\leq$ 20cm ³	10% ⁽²⁾
	V20Gy $\leq$ 30cm ³	20% ⁽²⁾
5	V24Gy $\leq$ 20 cm ³	10% ⁽²⁾
	V24Gy $\leq$ 30 cm ³	20% ⁽²⁾
	V30Gy < 10.5cm ³	13% ⁽³⁾
	V30Gy $\geq$ 10.5cm ³	61% ⁽³⁾

Sources: ⁽¹⁾ Milano, Usuki [76] ; ⁽²⁾ Grimm, Marks [67] ; ⁽³⁾ Milano, Grimm [77] ; ⁽⁴⁾ Minniti, Scaringi [31]

3.4 Radiotherapy Treatment

All patients with an indication for WBRT using 3D-CRT, treatment was delivered using one of the following linear accelerators: Trilogy®, DHX®, Novalis®, or TrueBeam®.

Patients indicated for WBRT using VMAT, as well as those indicated for HA-WBRT, were treated on the Trilogy®, Novalis®, or TrueBeam® linear accelerators.

Finally, for patients indicated for SRT, treatment was exclusively delivered using the Novalis® or TrueBeam® linear accelerators.

3.5 Data collection

Demographic, clinical, treatment-related, and follow-up data were retrospectively obtained from the electronic medical records (EMRs) and Varian's ARIA® patient information system.

Demographic variables included age and gender. Considering the context of this study, patient's age was reported at the time of Re-irradiation.

Before both first Radiotherapy and Re-irradiation, the following clinical variables were collected: primary tumour type; location of brain metastases (cerebrum, cerebellum, or both); status of the primary and locoregional disease (classified as active or stable); presence of extracranial metastases and corresponding disease status (active or stable disease); prior intracranial surgery; systemic therapy; and patient functional status (assessed using the ECOG performance status).

Treatment-related variables were collected for both the first treatment and re-irradiation. These included: planning target volume (PTV); gross tumour volume (GTV); treatment technique (WBRT, HA-WBRT, SRS, or HF-SRT); planning technique (3DCRT or VMAT); prescribed dose; fractionation schedule; interval between treatments; dosimetric parameters for evaluation of PTV coverage and healthy brain tissue; and plan quality parameters.

Dosimetric parameters for PTV coverage and for the evaluation of healthy brain tissue varied according to the treatment technique. Dosimetric parameters for PTV coverage included: D98%, D95%, D90%, D2%, V95%, as well as median and maximum doses. In SRT, additional parameters were recorded, including D100% and the median GTV dose. For the evaluation of healthy brain tissue included the analysis of V10Gy, V12Gy, V18Gy, V20Gy, V24Gy, V30Gy, as well as maximum and mean brain doses.

Plan quality parameters included CI while the GI was recorded for reference.

Follow-up data collected after re-irradiation included the presence of local recurrence or distant intracranial progression, treatment-related toxicities (including radiation-induced brain necrosis), the patient's vital status at the last follow-up or time of death. Among treatment-related toxicities, particular attention was given to the development of radionecrosis.

3.6 Grouping

In order to perform a more detailed analysis of the effect of the different treatment combinations in the outcome, the patients were divided into four different groups according to the radiotherapy technique combinations for their first treatment and re-irradiation.

All patients who had their whole brain treated, regardless of whether the hippocampus was spared, were grouped together in the WBRT group, with the aim of a better sample distribution. The patients that performed the SRS or HF-SRT (regardless of the fractions number) were grouped into the SRT classification.

The following classification emerged from this stratification process:

- Group 1 – WBRT and WBRT
- Group 2 – SRT and WBRT
- Group 3 – SRT and SRT
- Group 4 – WBRT and SRT

3.7 Statistical Analysis

Descriptive statistics were used to describe demographic, clinical, treatment-related characteristics of the patients and follow-up data. Age was reported as the median and interquartile range (IQR). Other continuous variables were presented as the median, minimum and maximum (min-max). Categorical variables are presented as counts and proportions.

Time to re-irradiation was defined as the time between the end of first radiotherapy treatment and the start of re-irradiation.

Local progression was defined as the time between the end of re-irradiation and the radiologic evidence of recurrence or local progression. This event considers the recurrence or progression of BMs within the re-irradiated area.

Distant intracranial progression was defined as the time between the end of re-irradiation and the radiologic evidence of new BMs. This event describes the formation of new BMs in areas of the brain that were not previously affected.

Overall survival was computed from two distinct time points: (i) the initiation of first treatment and (ii) the initiation of re-irradiation. OS was defined as the time from each respective starting point to the date of death or any censoring event (date of study end or date of loss to follow-up), whichever occurred first. The date of loss of follow-up was defined as the date of last information available in the patient's medical record. The end of follow-up was considered on September 18, 2024, allowing at least 20 months of follow-up.

For a graphical interpretation, the previously described intervals, are described on the Figure 7.

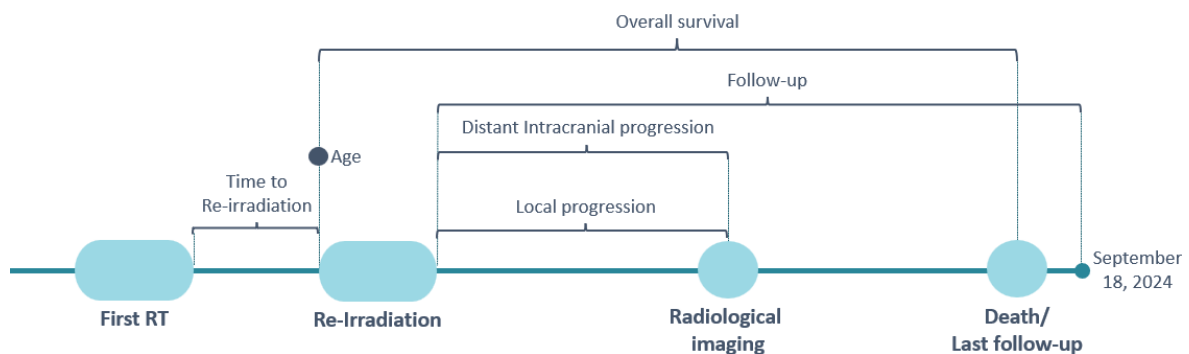


Figure 7 Graphical representation of the time to re-irradiation, outcomes, follow-up and overall survival.

Survival curves were plotted using the Kaplan-Meier estimator and were compared using the log-rank test.

All analyses were performed using R version 4.1.2 (R Core Team, Vienna, Austria). Results were considered statistically significant for p-values less than 0.05.

3.8 Ethics

This study was approved by the Ethics Committee of the IPO-Porto (ref. CES 055/024). The data comprised no unique personal identifiers and were extracted from EMRs and Varian's ARIA® patient information system. Thus, patient informed consent was not required.

4 RESULTS

4.1 Baseline Characteristics

At the time of reirradiation treatment, the median age of patients was 62 years (interquartile range: 53–65). Although there was a balanced distribution of genders in the sample, there was a slight predominance of male patients (52.9%).

The most frequent primary tumour, according to the analysis, was lung cancer (44.1%), which was followed by breast cancer (20.6%) and melanoma (14.7%). Other pathologies encountered, including colon, kidney, cervix, larynx, and ovary, were less frequent, each represented less than 6.0% of cases.

4.2 First Radiotherapy Treatment

4.2.1 Clinical Data

A summary of all the clinical data gathering the state of the patients at the time of the first radiotherapy treatment is present at Table 3.

The majority of patients had favourable performance status before they started the first treatment, with 91.2% of them having an ECOG score between 0 and 1.

70.0% had one to four brain metastases, with the cerebrum accounting for the majority of BMs (64.7%).

More than half of the patients (55.9%) had extracranial metastases in addition to BMs. Of those, 68.4% had active extracranial metastases, representing 38.2% of the total sample. Furthermore, locoregional disease was active at the primary tumour site in 38.2% of cases.

Half of the patients underwent surgical resection of BMs before radiotherapy. Regarding systemic therapy, the majority (58.8%) had not received any treatment. Chemotherapy alone accounted for 64.3% of treated cases among those who had received at least one option of systemic therapy, with targeted therapy coming in second at 14.3%.

4.2.2 Treatment Characteristics

Among the 34 patients included in the study, 15 underwent WBRT with or without hippocampal avoidance, while 19 were treated with SRT during the initial course of radiotherapy.

Table 3 - Clinical data of first RT treatment

First Radiotherapy		Overall N=34
		n (%)
ECOG		
	0	11 (32.4)
	1	20 (58.8)
	2	2 (5.9)
	3	1 (2.9)
Location of BMs		
	Cerebrum	22 (64.7)
	Cerebellum	4 (11.8)
	Cerebrum + Cerebellum	8 (23.5)
Number of BMs		
	1	13 (38.2)
	2-4	11 (32.4)
	5-10	3 (8.8)
	>10	7 (20.6)
Active Primary Tumour Locoregional Disease		
	No	21 (61.8)
	Yes	13 (38.2)
Extracranial Metastases		
	No	15 (44.1)
	Yes	19 (55.9)
Active Extracranial Metastases		
	No	21 (61.8)
	Yes	13 (38.2)
Prior Surgery		
	No	17 (50.0)
	Yes	17 (50.0)
Systemic Therapy Type		
	No	20 (58.8)
	Chemotherapy	9 (26.5)
	Targeted Therapy	2 (5.9)
	Immunotherapy	1 (2.9)
	Chemotherapy + Immunotherapy	1 (2.9)
	Targeted Therapy + Hormone Therapy	1 (2.9)

4.2.2.1 WBRT with or without Hippocampal Avoidance

All the data presented on this section is summarized on Table 4. Within this subgroup of 15 patients, nearly half (46.7%) presented more than ten brain metastases. The next most frequent group included patients with two to four metastases (33.3%).

Between both techniques, WBRT was more widely used, with 93.3% of cases, while HA-WBRT was used in a single patient (6.7%).

Table 4 - Characteristics and dosimetric parameters on First RT treatment with (HA-)WBRT

		First treatment - WBRT (N=15)
Metastases number, n (%)		
	1	1 (6.7)
	2-4	5 (33.3)
	5-10	2 (13.3)
	>10	7 (46.7)
Treatment technique, n (%)		
	WBRT	14 (93.3)
	HA-WBRT	1 (6.7)
Dose prescription, median (min-max)		
	Total dose (Gy)	30.0 (30.0-30.0)
	Fractions, n	10.0 (10.0-10.0)
	Dose per fraction (Gy)	3.0 (3.0-3.0)
PTV, median (min-max)		
WBRT		
	Volume (cm ³)	1636.9 (1219.9-2039.8)
	3D-CRT: V95% (%)	99.5 (96.3-99.8)
HA-WBRT		
	Volume (cm ³)	1605.1 (1605.1-1605.1)
	D98% (Gy)	22.9 (22.9-22.9)
	D2% (Gy)	36.2 (36.2-36.2)
Brain, median (min-max)		
	Dmean (Gy)	30.0 (30.0-31.6)
	Dmax (Gy)	31.9 (31.4-38.6)

All patients received a total dose of 30Gy, delivered in 10 fractions of 3Gy.

All patients undergoing WBRT were planned to use 3DCRT. The median PTV volume was 1636.9 cm³. Accordingly, PTV evaluation was based on the V95% parameter, with median

value of 99.5%, which is considered satisfactory, despite being slightly below the ideal threshold of 100.0%.

The single patient treated with HA-WBRT had a PTV evaluation that was based on the D98% and D2% parameters. The D98% was 22.9Gy, falling below the optimal threshold of 25.0Gy but, despite being below this reference value, it can be considered an acceptable variation according to the RTOG 0933 protocol. [72] In contrast, the D2% was 36.2Gy, remaining within the acceptable upper limit (<37.5Gy), indicating an appropriate control of the maximum dose.

In the brain dose evaluation, the median Dmean was equal to the median prescribed dose (30.0Gy), suggesting a uniform dose distribution across the sample. The median Dmax was 31.9Gy, corresponding to approximately 106.3% of the prescribed dose, and remaining below the tolerance threshold of 107.0%.

4.2.2.2 SRT

In this subgroup, as it is possible to analyse on Table 5, all but one patient presented one to four brain metastases. At diagnosis, a total of 36 metastases were identified in the 19 patients, however, only 32 metastases were included in the present study (Table 6), as these corresponded to the metastases that were subsequently re-irradiated.

Table 5 - Characteristics on first RT treatment with SRT

	First treatment - SRT (N=19)
Metastases number at diagnosis, n (%)	
1	12 (63.2)
2-4	6 (31.6)
5-10	1 (5.3)
PTV, median (min-max)	
Cumulative volume patient (cm ³)	19.6 (1.4-55.0)

Overall Analysis

A metastases-based analysis (Table 6) was conducted on the 32 metastases treated with SRT which was delivered using one of three fractionation regimens: single-fraction, three-fractions, or five-fractions.

Considering the overall perspective (irrespective of the fractionation scheme applied), the median total dose was 27.0Gy, delivered in 3 fractions.

Regarding target volumes, the median GTV and PTV volumes were relatively small, at 2.9cm³ and 4.7cm³, respectively. The PTV coverage can be considered very good with only one metastasis failing to achieve the D95% criterion but still meeting the D90%. When evaluating the relative maximum dose within the target volume, all metastases met the criterion of remaining below 130.0–140.0% of the prescription dose.

In terms of quality of the plan, the median conformity index was 1.3, indicating good conformity (with ideal values between 1 and 2, and values closer to 1 being preferable).

Single Fraction

The second column “1 Fraction” of Table 6 shows that SRS treated 12 out of 32 analysed metastases with a median prescription dose of 24.0Gy.

The target volume analysis shows that the GTV measured 0.2 cm³ while the PTV measured 0.6 cm³ which matches the standard use of this treatment for small-volume targets. The GTV received 27.0Gy and the PTV received 26.6Gy as median doses which were higher than the prescription dose.

All metastases achieved perfect PTV coverage because 100% of targets received 100% of the prescribed dose with a median dose of 25.4Gy. The D98% criterion was satisfied in 91.7% of metastases and the median absolute dose reached 25.1Gy. The median maximum dose inside the PTV reached 121.2%.

Quality of the plan parameter showed a median CI of 1.6 which falls within the recommended range of 1 to 2.

The brain dose evaluation included an examination of V10Gy and V12Gy parameters. The V10Gy values of 81.8% of metastases were below 10 cm³ which does not typically indicate a high risk of radionecrosis. The remaining 18.2% of metastases showed V10Gy values that exceeded 10 cm³ which corresponds to a predicted 24% risk of radionecrosis.

The V12Gy values of 81.8% of metastases fell below 5 cm³ which is a threshold associated with a 10% risk of radionecrosis. The remaining 18.2% of metastases showed V12Gy values between 5 cm³ and 10 cm³ which correspond to a 15% risk of symptomatic radionecrosis.

Three-Fractions

HF-SRT delivered in three fractions (column “3 Fractions” of Table 6) was used in the treatment of 12 out of the 32 analysed metastases, mirroring the number treated with SRS.

The prescribed dose was uniformly 27.0Gy, delivered in three fractions of 9.0Gy each.

Regarding target volumes, the median GTV and PTV were intermediate volumes, at 7.8cm³ and 11.7cm³, respectively. The median doses to the GTV and PTV were 29.3Gy and 29.0Gy, respectively, both slightly higher than the prescribed dose.

The PTV coverage was excellent, with 100% of the metastases meeting the D95% criterion and the median absolute dose was 27.6Gy. Additionally, the D98% criterion was met in 75.0% of the metastases, with a median absolute dose of 27.3Gy. In the remaining 25.0%, the values were very close to the prescription dose, which was still considered satisfactory. The relative maximum dose of the PTV reached a median of 115.7%.

Quality of the plan was excellent across all metastases, as all conformity index values fell within the recommended range. Furthermore, the median conformity index was 1.2, which is very close to 1 and reflects a high level of dose conformity.

Regarding brain dose assessment, V18Gy and V20Gy were selected parameters. For V18Gy, all metastases had values below 30.2cm³, which are associated with an estimated 5% risk of radionecrosis.

For V20Gy, all metastases had values below 20 cm³, a threshold generally associated with a 10% risk of radionecrosis.

Five-Fractions

HF-SRT delivered in five fractions (column "5 Fractions" of Table 6) was used in the treatment of 8 out of the 32 analysed metastases.

The median prescribed dose in this group was 30.0Gy, resulting in a lower dose per fraction but a higher total dose.

The GTV and PTV volumes were large in this group with a median of 22.4cm³ and 31.0cm³, respectively. The median doses to the GTV and PTV were slightly higher than the prescribed dose.

The PTV coverage was very good, with 87.5% of the metastases meeting the D95% criterion with a median absolute dose corresponding to 30.8Gy. Only one metastasis failed to meet this criterion (with a D95% of 29.4Gy); however, it still had fulfilled the D90% criterion. Additionally, the D98% criterion was met in 62.5% of the metastases, with a median absolute dose of 30.2Gy. The relative maximum dose within the PTV reached a median of 120.5%.

Quality of the plan was favourable, with 87.5% of conformity index values falling within the range of 1 to 2, that is recommended. The median conformity index was 1.2, which reflects a high level of dose conformity since is close 1.

The assessment of brain dose included the analysis of the V24Gy and V30Gy parameters. For V24Gy, 62.5% of the metastases had values below 20cm³, which are associated with an estimated 10% risk of radionecrosis. The remaining 37.5% presented values above 20cm³ but below 30cm³, a range associated with an estimated 20% risk of radionecrosis.

Table 6 - Dosimetric parameters for first RT treatment with SRT

Parameters SRT1	Overall N =32 median (min-max)	1 Fraction N=12 median (min-max)	3 Fractions N=12 median (min-max)	5 Fractions N=8 median (min-max)
Dose prescription				
Total dose (Gy)	27.0 (20.0-35.0)	24.0 (20.0-24.0)	27.0 (27.0-27.0)	30.0 (30.0-35.0)
Fractions, n	3.0 (1.0-5.0)	1.0 (1.0-1.0)	3.0 (3.0-3.0)	5.0 (5.0-5.0)
Dose per fraction (Gy)	9.0 (6.0-24.0)	24.0 (20.0-24.0)	9.0 (9.0-9.0)	6.0 (6.0-7.0)
GTV				
Volume (cm3)	2.9 (0.0-43.0)	0.2 (0.0-2.4)	7.8 (1.7-30.1)	22.4 (1.0-43.0)
Dmedian (Gy)	29.4 (24.7-37.7)	27.0 (24.7-31.4)	29.3 (28.6-32.9)	33.2 (31.8-37.7)
PTV				
Volume (cm3)	4.7 (0.1-55.0)	0.6 (0.1-3.6)	11.7 (3.2-40.1)	31.0 (1.9-55.0)
Dmedian (Gy)	29.0 (24.5-37.5)	26.6 (24.5-30.5)	29.0 (28.5-32.3)	33.1 (31.5-37.5)
D100% (Gy)	25.2 (17.1-32.6)	22.9 (17.1-24.2)	25.6 (24.2-27.0)	27.7 (20.7-32.6)
D98% (Gy)	27.2 (22.0-35.0)	25.1 (22.0-26.4)	27.3 (26.5-29.2)	30.2 (28.5-35.0)
D95% (Gy)	27.6 (22.6-35.5)	25.4 (22.6-27.2)	27.6 (27.0-30.0)	30.8 (29.4-35.5)
D90% (Gy)	27.9 (23.1-36.0)	25.8 (23.1-28.0)	27.9 (27.3-30.5)	31.4 (30.2-36.0)
Dmax (%)	118.5 (107.2-133.3)	121.2 (111.0-133.3)	115.7 (107.2-124.6)	120.5 (112.6 - 131.4)
Plan quality				
Conformity Index, n	1.3 (0.9-3.0)	1.6 (1.1-3.0)	1.2 (1.1-1.7)	1.2 (0.9-1.3)
Gradient Index, n	3.8 (2.5-6.9)	3.3 (2.5-5.7)	4.2 (3.3-6.9)	4.0 (3.0-5.0)
Brain				
V10Gy (cm3)	-	3 (1.3-10.6)	-	-
V12Gy (cm3)	-	2.3 (1.0-7.9)	-	-
V18Gy (cm3)	-	-	15.6 (6.0-25.4)	-
V20Gy (cm3)	-	-	12.2 (5.0-19.8)	-
V24Gy (cm3)	-	-	-	13.3 (2.1-27.9)
V30Gy (cm3)	-	-	-	6.6 (0.6-13.1)

For V30Gy, 87.5% of the metastases had values below 10.5cm³, a threshold generally associated with a 13% risk of radionecrosis. Only one metastasis had values above 10.5 cm³ (V30Gy = 13.1cm³), a threshold generally associated with a 61% risk of radionecrosis.

4.3 Re-Irradiation

4.3.1 Clinical data

The data in Table 7 showed that two thirds of patients had favourable performance status with ECOG scores ranging from 0 to 1 before re-irradiation.

The brain metastases were mainly located in the cerebrum (58.8%).

The distribution of patients across the subgroups of single metastasis (26.5%), two to four (29.4%), and five to ten metastases (29.4%) was relatively balanced.

The majority of patients (61.8%) had brain and extracranial metastases and among these 71.4% had active extracranial disease which represented 44.1% of the total sample. However, regarding locoregional disease at the primary tumour, the greater part of patients did not exhibit active disease.

Surgical resection prior to re-irradiation was uncommon (reported in only 11.8% of the sample) and systemic treatment was received by 61.8% of patients. Chemotherapy alone was the most common treatment option (29.4%), followed by targeted therapies (14.7%). Notably, 38.2% of patients were not receiving any systemic therapy option before re-irradiation.

4.3.2 Treatment Characteristics

Among the 34 patients, 21 underwent a second course of WBRT with or without hippocampal avoidance, and 13 received SRT during the re-irradiation.

4.3.2.1 WBRT with or without Hippocampal Avoidance

In this subgroup of 21 patients (with treatment characteristics data represented on Table 8), there was a marked predominance of patients presenting with multiple brain metastases, accounting for 85.7% of cases. Among those, the distribution was relatively balanced:

28.6% had between two and four lesions, 33.3% had between five and ten, and 23.8% presented with more than ten brain metastases.

Table 7 - Clinical data of re-irradiation treatment

Re-Irradiation		Overall N=34
		n (%)
ECOG		
	0	6 (17.7%)
	1	17 (50.0%)
	2	6 (17.7%)
	3	5 (14.7%)
Location of BMs		
	Cerebrum	20 (58.8%)
	Cerebellum	4 (11.8%)
	Cerebrum + Cerebellum	10 (29.4%)
Number of BMs		
	1	9 (26.5%)
	2-4	10 (29.4%)
	5-10	10 (29.4%)
	>10	5 (14.7%)
Active Primary Tumour Locoregional Disease		
	No	27 (79.4%)
	Yes	7 (20.6%)
Extracranial Metastases		
	No	13 (38.2%)
	Yes	21 (61.8%)
Active Extracranial Metastases		
	No	19 (55.9%)
	Yes	15 (44.1%)
Prior Surgery		
	No	30 (88.2%)
	Yes	4 (11.8%)
Systemic Therapy Type		
	No	13 (38.2%)
	Chemotherapy	10 (29.4%)
	Targeted Therapy	5 (14.7%)
	Immunotherapy	2 (5.9%)
	Chemotherapy + Targeted Therapy	2 (5.9%)
	Hormone Therapy	1 (2.9%)
	Hormone Therapy + Targeted Therapy	1 (2.9%)

Table 8 - Characteristics and dosimetric parameters on Re-irradiation treatment with (HA-)WBRT

Re-Irradiation - WBRT N=21	
Metastases number, n (%)	
1	3 (14.3)
2-4	6 (28.6)
5-10	7 (33.3)
>10	5 (23.8)
Treatment technique, n (%)	
HA-WBRT	6 (28.6)
WBRT	15 (71.4)
Dose prescription, median (min-max)	
Total dose (Gy)	30.0 (20.0-30.0)
Fractions, n	10.0 (5.0-10.0)
Dose per fraction (Gy)	3.0 (2.0-4.0)
PTV, median (min-max)	
WBRT	
Volume (cm3)	1602.9 (1386.1-1761.0)
3D-CRT: V95% (%)	99.8 (99.0-100.0)
VMAT: D98% (Gy)	25.2. (21.9-28.5)
VMAT: D2% (Gy)	27.2 (23.3-31.1)
HA-WBRT	
Volume (cm3)	1533.2 (1360.6-1750.6)
D98% (Gy)	23.4 (21.5-25.6)
D2% (Gy)	34.8 (28.2-37.4)
Brain, median (min-max)	
Dmean (Gy)	29.9 (19.8-32.9)
Dmax (Gy)	31.5 (20.6-39.0)

Between both treatment techniques, WBRT remained the most frequently used technique, applied in 71.4% of patients.

Patients were treated with different fractionation schemes, and the median of total prescription dose of 30.0Gy delivered in 10 fractions.

All patients undergoing WBRT were planned to use either 3DCRT or VMAT techniques. Among these, the median PTV volume was 1602.9 cm³.

The greater part of patients treated with WBRT were planned with 3DCRT (86.7%), for which PTV evaluation was based on the V95% parameter. The median V95% was 99.8%, indicating excellent target coverage, closely approaching the ideal value of 100.0%.

Only two patients were treated with WBRT using VMAT, each with a different fractionation scheme. One patient was treated with a prescribed dose of 25.0Gy, the D98% was 21.9Gy, falling below the ideal threshold of 23.7Gy (corresponding to 95% of the prescribed dose). The D2% in this case was 23.3Gy. In the other patient, who received a prescribed dose of 30.0Gy, the D98% reached 28.5Gy, meeting the ideal coverage threshold (95% of the prescribed dose), while the D2% was 31.1Gy, corresponding to 103.7% of the prescribed dose, thus remaining below the 107.0% upper limit.

All patients treated with HA-WBRT, the median PTV volume was 1533.2 cm. PTV evaluation was based on D98% and D2%. The median D98% was 23.4Gy falling below the optimal threshold of 25.0Gy, however, it is considered an acceptable variation according to the RTOG 0933 protocol. In contrast, the median D2% was 34.8Gy, remaining within the acceptable upper limit (<37.5Gy), thereby reflecting appropriate control of the maximum dose.

In the brain dose evaluation, the median mean dose was equal to the median prescribed dose. The median maximum dose was 31.5Gy, corresponding to approximately 105.0% of the prescribed dose, remaining below the 107.0% tolerance threshold.

4.3.2.2 SRT

In this subgroup of 13 patients (

Table 9), 77.0% presented between one and four brain metastases. At diagnosis, a total of 37 metastases were identified, however, only 24 metastases were included in the present study, as these corresponded to the metastases that were re-irradiated.

Table 9 - Characteristics on re-irradiation treatment with SRT

Re-Irradiation - SRT (N=13)	
Metastases number at diagnosis, n (%)	
1	6 (46.2)
2-4	4 (30.8)
5-10	3 (23.0)
PTV, median (min-max)	
Cumulative volume per patient (cm ³)	11.8 (0.4 - 22.1)

Overall Analysis

A metastasis-based analysis (Table 10) was conducted on the 24 metastases treated with SRT which was delivered using one of three fractionation regimens: single-fraction, three-fraction, or five-fractions.

In the overall analysis (irrespective of the fractionation scheme applied), the median total dose and number of fractions were 27.0Gy delivered in 3 fractions.

Regarding target volumes, the median GTV and PTV volumes were relatively small, at 2.7cm³ and 4.0cm³, respectively. The PTV coverage was excellent, with 100.0% of the metastases meeting the D95% criterion.

When evaluating the relative maximum dose within the target volume, all metastases met the criterion of remaining below 130.0–140.0% of the prescription dose.

In terms quality of plan, the median conformity index was 1.2, indicating good conformity since the value it is close to 1.

Single Fraction

The second column “1 Fraction” of Table 10 shows that SRS was used in the treatment of 10 metastases out of the 24 analysed. The median prescribed dose was 23.0Gy delivered in a single fraction.

Regarding target volumes, the median GTV was 0.4cm³ and the corresponding median PTV was 0.9cm³, reflecting the typical indication of this treatment for notably small-volume targets. The median doses delivered to the GTV and PTV were 28.7Gy and 27.4Gy, respectively, both slightly higher than the median prescription dose.

The PTV coverage was also excellent, with 100.0% of the metastases meeting the D95% criterion and the median absolute dose was 25.4Gy. Additionally, the D98% criterion was also met in 100.0% of the metastases, with a median absolute dose of 24.4Gy.

Regarding the highest dose levels within the target volume, the median maximum dose within the PTV was 125.0%.

The quality of the plan parameter revealed a median conformity index of 2.1, which slightly exceeds the recommended range of 1 to 2 but remains close to the upper limit.

The brain dose evaluation included an examination of V10Gy and V12Gy parameters.

For V10Gy, 80.0% of the metastases presented values below 10cm³, which are not typically associated with a significant risk of radionecrosis. The remaining 20.0% had values slightly above 10cm³, a threshold associated with an estimated 24% risk of radionecrosis.

For V12Gy, 60.0% of the metastases presented values below 5cm³, a level generally associated with a 10% risk of radionecrosis. The remaining 40.0% showed V12Gy values above 5cm³ but below or equal to 10cm³, which are linked to a 15% risk of symptomatic radionecrosis. It is worth mentioning that one metastasis presented a value of 10.1cm³ but was still included in this group.

Three-Fractions

HF-SRT delivered in three fractions (column “3 Fractions” of Table 10) was used in the treatment of 7 out of the 24 analysed metastases and the prescription dose was 27.0Gy.

Regarding target volumes, the median GTV and PTV were intermediate volumes, at 6.5cm³ and 10.9cm³, respectively. The median doses to the GTV and PTV were 29.4Gy and 29.0Gy, respectively, both slightly higher than the prescription dose.

The PTV coverage results were excellent, with 100.0% of the metastases meeting the D95% criterion and the median absolute dose was 27.4Gy. Additionally, the D98% criterion was met in 85.7% of the metastases, with a median absolute dose of 27.0Gy. In the remaining 14.3%, values were very close to the prescription dose, which was still considered satisfactory.

Regarding the highest dose levels within the PTV, the median maximum dose reached a median of 116.7%.

Quality of the plan was excellent across all metastases, as all conformity index values fell within the recommended range. The median conformity index was 1.2, reflecting a high level of dose conformity.

The evaluation of brain dose considered the V18Gy and V20Gy parameters.

For V18Gy, 85.7% of the metastases had values below 30.2cm³, which are associated with an estimated 5% risk of radionecrosis. The remaining 14.3% had values between 30.2cm³ and 41.2cm³, corresponding to an estimated 14% risk of radionecrosis.

For V20Gy, 85.7% of the metastases had values below 20cm³, a threshold generally associated with a 10% risk of radionecrosis. The remaining 14.3% had values between 20cm³ and 30cm³, corresponding to an estimated 20% risk of radionecrosis.

Five-Fractions

HF-SRT delivered in five fractions (column “5 Fractions” of Table 10) was used to treat 7 out of the 24 analysed metastases.

The prescription dose in this group was 30.0Gy. So, this fractionation regimen results in a lower dose per fraction but a higher total dose.

The median GTV and PTV were intermediate volumes, at 6.5cm³ and 9.0cm³, respectively. The median doses to the GTV and PTV were 32.0Gy and 31.8Gy, respectively, with both slightly higher than the prescribed dose.

The PTV coverage results were excellent, with 100.0% of the metastases meeting the D95% criterion, with a median absolute dose of 30.5Gy. Additionally, the D98% criterion was met in 57.1% of the metastases, with a median absolute dose of 30.0Gy. The remaining 42.9%, values were very close to the prescription dose, and can still be considered satisfactory.

Regarding the highest dose levels within the PTV, the median maximum dose was 116.4%.

Plan quality was excellent across all metastases, as the median CI value was 1.1.

Brain dose evaluation have considered the V24Gy and V30Gy parameters.

For V24Gy, 85.7% of the metastases had values below 20.0cm³, that are associated with an estimated 10% risk of radionecrosis. The remaining 14.3% presented values between 20.0cm³ and 30.0cm³, a range associated with an estimated 20% risk of radionecrosis.

For V30Gy, 100.0% of the metastases had values below 10.5cm³, a threshold generally associated with a 13% risk of radionecrosis.

4.3.3 Grouping

Patient distribution (Table 11) revealed that WBRT was the most frequent treatment technique for re-irradiation, regardless of the initial treatment. Patients who started with WBRT were almost evenly divided between receiving WBRT again (Group 1, n=7) or switching to SRS (Group 4, n=8). In contrast, most patients who began with SRS were later treated with WBRT (Group 2, n=14), while only a few received SRS again (Group 3, n=5).

Table 10 - Dosimetric parameters for re-irradiation treatment for SRT

Parameters SRT2	Overall N =24	1 Fraction N=10	3 Fractions N=7	5 Fractions N=7
	median (min-max)	median (min-max)	median (min-max)	median (min-max)
Dose prescription				
Total dose (Gy)	27.0 (21.0-30.0)	23.0 (21.0-24.0)	27.0 (27.0-27.0)	30.0 (30.0-30.0)
Fractions, n	3.0 (1.0-5.0)	1.0 (1.0-1.0)	3.0 (3.0-3.0)	5.0 (5.0-5.0)
Dose per fraction (Gy)	9.0 (6.0-24.0)	23.0 (21.0-24.0)	9.0 (9.0-9.0)	6.0 (6.0-6.0)
GTV				
Volume (cm3)	2.7 (0.1-17.3)	0.4 (0.1-0.6)	6.5 (2.3-17.3)	6.5 (1.6-16.3)
Dmedian (Gy)	29.4 (23.0-32.5)	28.7 (23.0-30.5)	29.4 (28.9-31.2)	32.0 (31.7-32.5)
PTV				
Volume (cm3)	4.0 (0.2-24.3)	0.9 (0.2-1.6)	10.9 (3.4-24.3)	9.0 (2.9-22.1)
Dmedian (Gy)	29.1 (22.6-32.7)	27.4 (22.6-29.8)	29.0 (28.6-30.9)	31.8 (31.4-32.7)
D100% (Gy)	25.1 (19.4-28.7)	22.0 (19.4-24.9)	25.6 (22.4-26.3)	27.5 (25.2-28.7)
D98% (Gy)	27.0 (21.0-30.2)	24.4 (21.0-26.8)	27.0 (26.8-27.2)	30.0 (29.5-30.2)
D95% (Gy)	27.4 (21.3-30.6)	25.4 (21.3-27.2)	27.4 (27.2-27.7)	30.5 (30.0-30.6)
Dmax (%)	119.5 (111.7-138.9)	125.0 (120.1-138.9)	116.7 (111.7-126.1)	116.4 (112.4-117.7)
Plan quality				
Conformity Index, n	1.2 (1.0-3.5)	2.1 (1.4-3.5)	1.1 (1.1-1.3)	1.1 (1.0-1.4)
Gradient Index, n	4.2 (2.4-9.8)	3.0 (2.4-9.8)	4.6 (3.0-5.2)	4.8 (3.3-8.8)
Brain				
V10Gy (cm3)	-	5.1 (0.8-15.7)	-	-
V12Gy (cm3)	-	4.0 (0.6-10.1)	-	-
V18Gy (cm3)	-	-	14.0 (7.7-33.4)	-
V20Gy (cm3)	-	-	11.3 (6.0-25.6)	-
V24Gy (cm3)	-	-	-	10.3 (6.5-23.1)
V30Gy (cm3)	-	-	-	2.4 (0.5-7.4)

Table 11 - Patients distribution among the different groups

		Re-irradiation		
		WBRT	SRS	Total
First	WBRT	7	8	15
Treatment	SRS	14	5	19
	Total	21	13	

4.3.4 Time to re-irradiation

Table 12 presents the different time intervals between treatments for the total sample as well as for each treatment technique combination group.

The entire sample demonstrated an overall median time period of 13.1 months between the first RT treatment and re-irradiation. However, 17.6% of the patients presented an interval of less than 6 months and, based on the results of Table 12, it can be inferred that all of these patients belong to Group2.

The median time between treatments has the higher value on Group 1 (WBRT+WBRT) with 37.9 months while Group 2 (SRT+WBRT) had the shortest interval at 7.5 months.

Table 12 - Time between treatments

Time to Re-Irradiation	Overall N=34	Group1 N=7	Group2 N=14	Group3 N=5	Group4 N=8
Median Interval, (months)	13.1	37.9	7.5	20.5	17.0
Minimum Interval, (months)	2.9	8.9	2.9	16.4	8.5
Maximum Interval, (months)	65.5	58.8	16.7	35.6	65.5
<u>Legend:</u> Group 1 (WBRT+WBRT); Group 2 (SRT+WBRT); Group 3 (SRT+SRT) and Group 4 (WBRT+SRT).					

4.3.5 Radiobiology

The cumulative BED and EQD2 values in the normal brain tissue ($\alpha/\beta=2\text{Gy}$) for the overall sample and for each treatment group are presented on Table 13 and Table 14, respectively.

For the overall sample, the median cumulative BED and EQD2 were 223.5Gy and 111.8Gy, respectively, but with considerable variability across groups. The minimum and maximum values in the normal brain tissue highlight substantial heterogeneity, with cumulative BEDs ranging from 115.0Gy to more than 1300.0Gy and cumulative EQD2 ranging from 57.5Gy to more than 650.0Gy.

Patients in Group 1 (WBRT+WBRT) demonstrated the lowest median cumulative BED (131.3Gy) and the lowest median cumulative EQD2 (65.6Gy). In contrast, Group 3 (SRT+SRT) reached the highest median cumulative BED (340.0Gy) and the highest median cumulative EQD2 (170.0Gy).

All groups composed with patients who underwent at least one course of SRT (Groups 2, 3, and 4) exhibit higher cumulative BED and EQD2 values compared to Group 1.

Table 13 - Cumulative BED in the normal brain tissue with $\alpha/\beta=2\text{Gy}$

Cumulative BED	Overall N=34	Group1 N=7	Group2 N=14	Group3 N=5	Group4 N=8
Median (Gy)	223.5	131.3	281.3	340.0	297.8
Minimum (Gy)	115.0	115.0	195.0	268.5	195.0
Maximum (Gy)	1330.5	135.0	1144.5	631.5	1330.5
<u>Legend:</u> Group 1 (WBRT+WBRT); Group 2 (SRT+WBRT); Group 3 (SRT+SRT) and Group 4 (WBRT+SRT).					

Table 14 - Cumulative EQD2 in the normal brain tissue with $\alpha/\beta=2\text{Gy}$

Cumulative EQD2	Overall N=34	Group1 N=7	Group2 N=14	Group3 N=5	Group4 N=8
Median (Gy)	111.8	65.6	140.6	170.0	148.9
Minimum (Gy)	57.5	57.5	97.5	134.3	97.5
Maximum (Gy)	655.3	67.5	572.3	315.8	665.3
<u>Legend:</u> Group 1 (WBRT+WBRT); Group 2 (SRT+WBRT); Group 3 (SRT+SRT) and Group 4 (WBRT+SRT).					

4.3.6 Follow-up after Re-Irradiation

Follow-up time after the last re-irradiation treatment for the entire sample and for each treatment group is presented in Table 15.

The entire sample demonstrated an overall median time of 11.7 months with values ranging from 0.8 to 55.4 months, reflecting substantial heterogeneity in follow-up time.

Group 3 (SRT+SRT) showed the longest median follow-up interval (31.7 months), whereas Group 1 (WBRT+WBRT) had the shortest median follow-up (4.1 months).

Table 15 - Follow up after Re-irradiation.

Follow-up after Re-Irradiation	Overall N=34	Group1 N=7	Group2 N=14	Group3 N=5	Group4 N=8
Median Interval, (months)	11.7	4.1	10.7	31.7	10.3
Minimum Interval, (months)	0.8	1.3	0.8	15.0	2.5
Maximum Interval, (months)	55.4	55.4	32.0	40.9	50.6
<u>Legend:</u> Group 1 (WBRT+WBRT); Group 2 (SRT+WBRT); Group 3 (SRT+SRT) and Group 4 (WBRT+SRT).					

Follow-up of patients after re-irradiation treatment included assessment of the following outcomes:

- The definition of **local progression** includes both the recurrence of BMs and their growth inside the treated area.
- The term **distant intracranial progression** describes the formation of new BMs in areas of the brain that were not previously affected.
- The documentation of treatment-related **toxicities**.

All follow-up parameters will be presented both overall and by the previously defined groups, which reflect the different combinations of radiotherapy techniques used.

4.3.6.1 Local Progression after Re-Irradiation

The data on Table 16 gathers local progression information. Here, it is possible to see that, 35.3% of patients have experienced local progression following re-irradiation and, the same proportion, corresponded to patients who, at the time of the last follow-up or at the occurrence of the event (death), showed no signs of local progression. On a significant proportion of patients (29.4%), local progression status was considered unknown since there was no follow-up imaging.

The median time to local progression was 6.9 months, ranging from 1.7 to 12.4 months.

To complement these results, a stratified evaluation by treatment group was conducted in order to identify potential differences between us.

Group-Based Evaluation

The stratified analysis by treatment group revealed that Group 3 (SRT+SRT) demonstrated no evidence of local progression.

Group 4 (WBRT+SRT) showed the highest rate of local progression at 62.5% while also having the second-longest median time to progression after re-irradiation at 7.3 months.

The main difference between Groups 2 and 4 results from the order of SRT and WBRT delivery which could explain some observed differences. The high number of patients without follow-up imaging in Group 2 (SRT+WBRT) resulted in limited robustness of its findings. Group 4 presented the lowest rate of missing imaging data at 12.5% because patients received more consistent post-treatment imaging follow-up.

Local progression rate in Group 1 (WBRT+WBRT) ranked as the second highest at 42.9% and patients experienced the shortest median time to progression at 3.5 months indicating that local recurrence happens quickly after re-irradiation in this group.

Considering that Groups 1 and 2 presented the highest proportion of patients with unknown status, both re-irradiated with WBRT, an analysis of the interval between the date of the last treatment and the date of death was performed. This interval was generally less than 5 months, except for one patient who survived approximately 10 months. This finding explains the absence of imaging follow-up in these patients and should be considered when interpreting the results.

Table 16 - Local progression status after re-irradiation on follow-up.

Local Progression Status after Re-Irradiation	Overall N=34	Group1 N=7	Group2 N=14	Group3 N=5	Group4 N=8
Progression Observed, n (%)	12 (35.3)	3 (42.9)	4 (28.6)	0 (0.0)	5 (62.5)
No Evidence of Progression, n (%)	12 (35.3)	1 (14.3)	4 (28.6)	5 (100.0)	2 (25.0)
Progression Status Unknown, n (%)	10 (29.4)	3 (42.9)	6 (42.9)	0 (0.0)	1 (12.5)
Median Time to Progression (months)	6.9	3.5	8.5	NA	7.3
Minimum Time to Progression (months)	1.7	1.7	3.6	NA	3.3
Maximum Time to Progression (months)	12.4	12.2	11.4	NA	12.4

Legend: Group 1 (WBRT+WBRT); Group 2 (SRT+WBRT); Group 3 (SRT+SRT) and Group 4 (WBRT+SRT).

Abbreviations: NA - Not Achievable

4.3.6.2 Distant Intracranial Progression after Re-Irradiation

Re-irradiation treatment led to distant intracranial progression in nearly one-quarter of patients, with a median time to progression of 7.3 months. At the time of the last follow-up or time of death revealed that 44.1% of patients had no signs of distant intracranial progression, as it can be observed in Table 17.

Group-Based Evaluation

The study detected different rates of distant intracranial progression across all treatment groups (Table 17).

The highest rate of distant intracranial progression was observed in Group 4 (WBRT+SRT) while Group 2 (SRT+WBRT) had the lowest rate (50.0% vs 14.3%, respectively). The regular follow-up imaging of SRT patients can lead to earlier detection of progression however, patients treated with WBRT, typically do not receive systematic post-treatment imaging.

The combination of treatment techniques in Group 2 resulted in the longest median time to progression at 10.9 months.

The two groups with the highest proportion of missing follow-up imaging data were Group 1 (WBRT+WBRT) and Group 2 (SRT+WBRT) at 42.9% each, as previously reported in the analysis of Local Progression after Re-Irradiation.

Table 17 - Distant intracranial progression status after re-irradiation on follow-up.

Distant Intracranial Progression Status after Re-Irradiation	Overall N=34	Group1 N=7	Group2 N=14	Group3 N=5	Group4 N=8
Progression Observed, n (%)	9 (26.5)	2 (28.6)	2 (14.3)	1 (20.0)	4 (50.0)
No Evidence of Progression, n (%)	15 (44.1)	2 (28.6)	6 (42.9)	4 (80.0)	3 (37.5)
Progression Status Unknown, n (%)	10 (29.4)	3 (42.9)	6 (42.9)	0 (0.0)	1 (12.5)
Median Time to Progression (months)	7.3	7.9	10.9	3.5	5.6
Minimum Time to Progression (months)	3.3	3.5	10.4	3.5	3.3
Maximum Time to Progression (months)	12.2	12.2	11.4	3.5	7.8

Legend: Group 1 (WBRT+WBRT); Group 2 (SRT+WBRT); Group 3 (SRT+SRT) and Group 4 (WBRT+SRT).

4.3.6.3 Toxicities

The three most frequently reported toxicities (Figure 8) were neurocognitive changes, radiation-induced brain necrosis, and headache.

Group 2 (SRT+WBRT) exhibited the widest variety of adverse events, with visual changes being the only event not observed in this group (

Table 18 and Figure 8).

Group 1 (WBRT+WBRT) recorded the highest proportion of neurocognitive changes with 57.1% of the patients reporting this adverse effect (

Table 18), which is consistent with the fact that both treatments involved whole-brain irradiation. Followed by Group 4 (WBRT+SRT), which also showed a notably high rate of neurocognitive changes (50.0%).

Interestingly, Group 3 (SRT+SRT) showed a relatively high incidence of radiation necrosis with 40.0% (

Table 18), although this finding should be interpreted with caution due to the small sample size in this group.

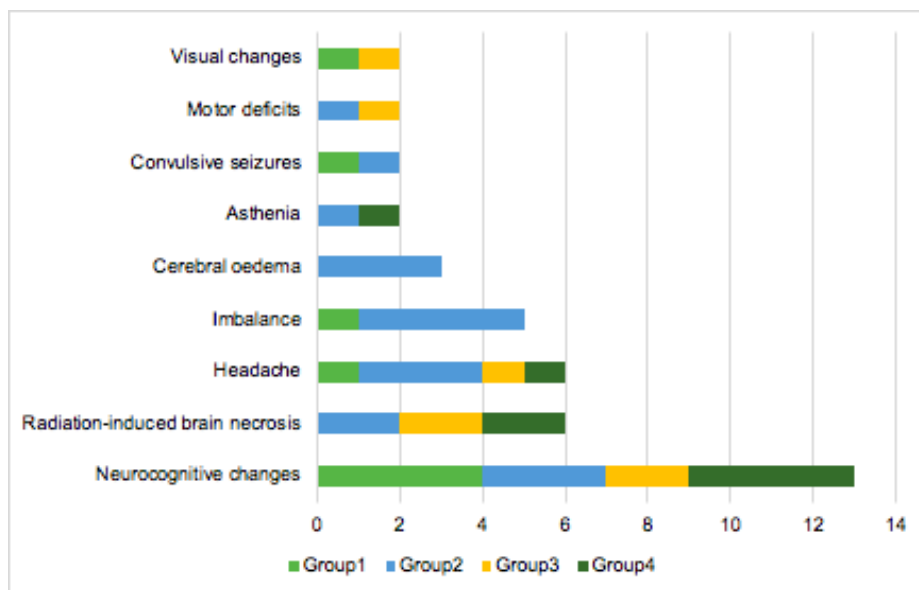


Figure 8 – Toxicities number of adverse effects by treatment group. Legend: Group 1 (WBRT+WBRT); Group 2 (SRT+WBRT); Group 3 (SRT+SRT) and Group 4 (WBRT+SRT).

Table 18 - Registration of toxicities by treatment group.

Type of adverse event	Group1 N=7	Group2 N=14	Group3 N=5	Group4 N=8
Neurocognitive changes	4 (57.1)	3 (21.4)	2 (40.0)	4 (50.0)
Radiation-induced brain necrosis	0 (0.0)	2 (14.3)	2 (40.0)	2 (25.0)
Headache	1 (14.3)	3 (21.4)	1 (20.0)	1 (12.5)
Imbalance	1 (14.3)	4 (28.6)	0 (0.0)	0 (0.0)
Cerebral oedema	0 (0.0)	3 (21.4)	0 (0.0)	0 (0.0)
Asthenia	0 (0.0)	1 (7.1)	0 (0.0)	1 (12.5)
Convulsive seizures	1 (14.3)	1 (7.1)	0 (0.0)	0 (0.0)
Motor deficits	0 (0.0)	1 (7.1)	1 (20.0)	0 (0.0)
Visual changes	1 (14.3)	0 (0.0)	1 (20.0)	0 (0.0)

Legend: Group 1 (WBRT+WBRT); Group 2 (SRT+WBRT); Group 3 (SRT+SRT) and Group 4 (WBRT+SRT).

Radiation-induced brain necrosis

The patients who developed radionecrosis after re-irradiation are presented in Table 19, together with a description of some relevant characteristics.

Overall, the volumes of BMs treated with SRT, both in the first RT and in the re-irradiation, were predominantly of intermediate size. Exceptions were observed in four lesions: two presented with considerably larger volumes (43.6 cm³ and 55.0 cm³), while the remaining two were notably small (0.7 cm³ and 0.9 cm³). Hypofractionation was the most commonly used scheme in SRT.

Table 19 - Treatment characteristics of patients who developed radionecrosis

ID	First RT					Re-Irradiation									
	Treatment	Total Dose (Gy)	Fractions	Volume (cm³)	BED* (Gy)	EQD2* (Gy)	Treatment interval (months)	Treatment	Total Dose (Gy)	Fractions	Volume (cm³)	BED* (Gy)	EQD2* (Gy)	Cumulative BED* (Gy)	Cumulative EQD2* (Gy)
4	HF-SRT	30.0	5	12.7	120.0	60.0	23.7	HF-SRT	27.0	3	5.7	148.5	74.3	268.5	134.3
10	WBRT	30.0	10	1609.8	75.0	37.5	8.5	HF-SRT	27.0	3	10.9	148.5	74.3	223.5	111.8
21	HF-SRT	30.0	5	43.6	120.0	60.0	8.2	WBRT	30.0	10	1468.1	75.0	37.5	195.0	97.5
25	HF-SRT	27.0	3	21.2	148.5	74.3	35.6	SRS	21.0	1	0.9	241.5	120.8	631.5	315.8
26	HF-SRT	30.0	5	55.0	120	60.0	16.7	SRS	21.0	1	0.7	241.5	120.8	195.0	97.5
34	WBRT	30.0	10	2039.8	75.0	37.5	55.1	HF-SRT	27.0	3	13.5	148.5	74.3	223.5	111.8

* - BED and EQD2 were calculated based on the normal brain tissue $\alpha/\beta=2\text{Gy}$

Among all patients who underwent WBRT, the prescribed fractionation regimen was 30.0Gy delivered in 10 fractions.

A heterogeneity was observed in the time intervals between the two radiotherapy treatments, which ranged from 8.2 to 55.1 months.

The cumulative BED and EQD2 values in the normal brain tissue ($\alpha/\beta = 2\text{Gy}$) were also heterogeneous, ranging from 195.0 to 631.5Gy (BED) and from 97.5 to 315.8Gy (EQD2), reflecting the variability in fractionation regimens.

4.4 Overall Survival

OS is commonly used in oncological research to measure the duration between a clinically relevant starting point and death from any cause. The OS assessment in this study began at two different time points: (i) the initiation of first radiotherapy treatment, with follow-up extending from February 18, 2016 to September 18, 2024, and (ii) the initiation of re-irradiation, with follow-up extending from March 18, 2019 to September 18, 2024.

A total of 29 death events were documented, while the remaining patients were censored at their last follow-up date.

4.4.1 From First Radiotherapy Treatment

The first survival analysis was based on the start date of the first radiotherapy treatment as a starting point to describe the temporal evolution of intracranial metastatic disease and to present survival estimates over time.

The Figure 9 shows the OS of patients with brain metastases through a graphical display which Table 20 supports by showing OS probability values at different time points.

The OS probability was high in the first year after radiotherapy treatment, reaching values of 91.2%. A sharp decline in survival was observed until the second year, reaching 55.9%. The survival curve showed a more gradual decline from the third to the fifth year (from 47.1% to 31.4%, respectively). Less than one tenth of the patients from the initial sample remained alive by the sixth year (6.7%), which emphasizes the severity of long-term outcomes.

The 95% confidence interval, represented by the shaded area around the curve of Figure 5, widens progressively over time.

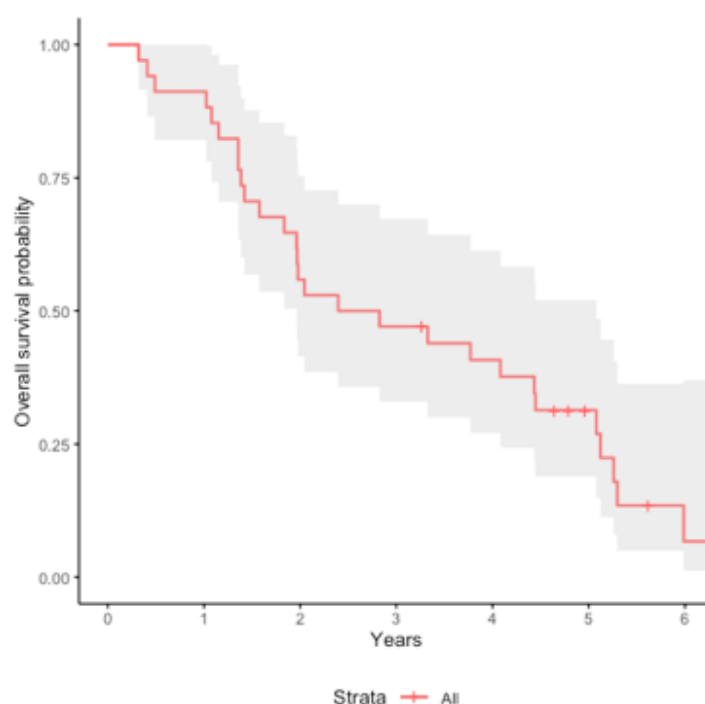


Figure 9 – Kaplan-Meier curve of patients with BMs

Table 20 - Overall survival probabilities and 95% confidence interval at different time points

	Overall Survival
1-year	91.2 (82.1-100.0)
2-year	55.9 (41.5-75.3)
3-year	47.1 (32.9-67.2)
4-year	40.8 (27.1-61.3)
5-year	31.4 (18.9-52.0)
6-year	6.7 (1.2-37.0)

The median overall survival was 31.3 months, indicating that half of the patients had died within approximately 2.6 years after the beginning of radiotherapy.

4.4.2 From Re-Irradiation

A second survival analysis was based on the start date of re-irradiation as starting point. This analysis is interesting to assess the impact of different combinations of radiotherapy techniques on patient survival.

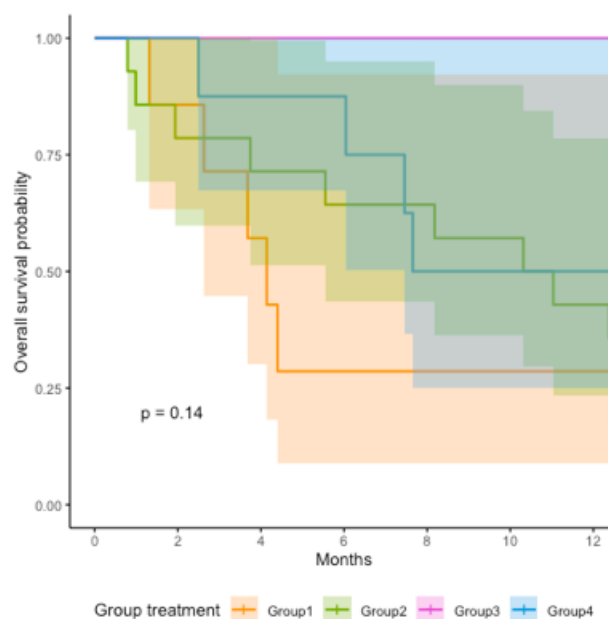


Figure 10 - Kaplan-Meier curve by treatment groups. Legend: Group 1 (WBRT+WBRT); Group 2 (SRT+WBRT); Group 3 (SRT+SRT) and Group 4 (WBRT+SRT).

Table 21 - Overall survival probabilities and 95% confidence interval at different time points by treatment groups.

	Group1 N=7	Group2 N=14	Group3 N=5	Group4 N=8
3-month	71.4 (44.7-100.0)	78.6 (59.8-100.0)	100.0 (100.0-100.0)	87.5 (67.3-100.0)
6-month	28.6 (8.9-92.2)	64.3 (43.5-95.0)	100.0 (100.0-100.0)	87.5 (67.3-100.0)
9-month	28.6 (8.9-92.2)	57.1 (36.3-89.9)	100.0 (100.0-100.0)	50.0 (25.0-100.0)
12-month	28.6 (8.9-92.2)	42.9 (23.4-78.5)	100.0 (100.0-100.0)	50.0 (25.0-100.0)
Median (months)	4.1	10.7	NA	10.3

Legend: Group 1 (WBRT+WBRT); Group 2 (SRT+WBRT); Group 3 (SRT+SRT) and Group 4 (WBRT+SRT).

Abbreviations: NA – Not Achievable

Median overall survival of re-irradiated patients was 11.7 months, indicating that half of the patients had died within approximately the first year after the start of re-irradiation.

Figure 10 displays the survival probabilities between the four treatment groups and the Table 21 contains the survival probabilities at different points in time to show different results for each group and respective median values within a 12-month observation period.

Survival probabilities for Group 3 remained at 100.0% because no patients died throughout the first year. This constant value during this follow-up interval did not allow for mathematical calculation of median survival.

Survival rates for Group 1 experienced the most significant deterioration throughout the follow-up period. The Kaplan-Meier curve demonstrates a significant decrease in survival rates around the first 4 months following re-irradiation, where was reached a survival rate of 28.6% that remained constant until the end of the period. Survival data reflects the quick deterioration on an early stage, resulting in a median survival time of 4.1 months following re-irradiation treatment.

Groups 2 and 4 present intermediate results which can be confirmed through the different points in time probability values and final median value, not being one meaningfully better than the other one.

Wide confidence intervals (represented both on the grey are of the Figure 10 and the intervals on Table 21) indicate substantial statistical uncertainty in the results.

To further investigate the differences in survival observed between the treatment groups, a Cox proportional hazards model was calculated (Table 22). This analysis allows for the comparison of the risk of death over time across the four groups by estimating the hazard ratio (HR) of each group relative to a reference group, with Group 1 serving as the reference in this case.

Table 22 - Cox Regression by treatment groups.

	Crude HRs	p-value (log-rank)
Group1	ref	
Group2	1.10 (0.40 - 3.03)	0.140
Group3	0.22 (0.04 - 1.12)	
Group4	0.74 (0.25 - 2.21)	

In the comparison between treatment groups, Group 3 demonstrated the most favourable outcome with a HR of 0.22, suggesting a 78% reduction in the risk of death compared to Group 1. On the other hand, Group 2 had an HR of 1.10, indicating a 10% increase in the risk of death.

Although some results suggest a potential trend toward clinical benefit for Group 3, no statistically significant differences were observed between treatment groups. This is supported by the p-value ($p = 0.140 > 0.05$) and the confidence intervals for the hazard ratios are quite wide and included the value 1.

5 DISCUSSION

This retrospective study reports re-irradiation data between 2019 and 2022.

The first RT treatment's descriptive analysis revealed a high conformity with the recent clinical guidelines that are used and described through the Introduction chapter. [9, 13, 19, 20] On the first RT treatment it was perceived that the WBRT technique was used mainly on patients with more than ten BMs, corresponding to 20.6% of the total sample. The number of metastases, as mentioned early, is not the only factor for the decision making for treatment with SRT. From the total sample, 14.7% of the patients had between two and four metastases and were treated with WBRT. The SRT technique was used in 52.9% of the patients which had between 1 and 4 BMs. These results, despite prior to the current guidelines, are in line with them (section 1.2.3). The indication for SRT treatment and postponing the use of WBRT treatment is preferred, whenever possible, for a better patient's quality of life and reduced cognitive toxicity.

The descriptive analysis of the re-irradiation treatment showed the clinical practice on a Tertiary Radiotherapy Department during 2019 and 2022. At the RT Department, when the patients were directed towards this treatment, the procedure was: current clinical evaluation of the patient, interval between both RT treatments, analysis of the first RT technique used and the one that is foreseen to be used on the new treatment and, finally, the evaluation of the cumulative dose to OARs. Treatment plan was defined only after the full analysis of all the parameters.

The NCCN (2024's guidelines) presented a set of general indications according to the previous treatment and the type of recurrence. [19] The focus of this study is local recurrence, however, if distant intracranial progression is observed at the same time as the local recurrence, then it will be also considered. Overall, the option of treatment techniques that provide an increased avoidance of organs risk, such as SRT are preferred. Then, the treatment technique that provided a better quality of live regarding the individual cognitive preservation of the patient was the HA-WBRT.

The time interval between both treatments was larger on Group 1 (WBRT+WBRT) with a median of 37.9 months. Group 1 was composed by a reduced number of patients (N=7) and the total median dose administered was 30.0Gy in 10 fractions for the first RT treatment and 25.0Gy in 10 fractions for the re-irradiation. Time interval between the two treatments was defined from the last day of the first treatment of RT and the first day of re-irradiation treatment.

Two retrospective studies with the use of WBRT were analyzed and compared with the current study. Guo, Balagamwala [78] analyzed 49 patients and reported a median interval between the initial diagnosis of initial BMs and the appearance of recurrence, of

11.5months, which is lower than the current study result. Median doses of first treatment and re-irradiation were 30.0Gy in 10 fractions and 20.0Gy in 10 fractions, respectively.

Ozgen [79] also reported a median interval lower between the two treatments, namely 9.5 months. The median dose of the first treatment was 30.0Gy in 10 fractions, while on re-irradiation it was 25.0Gy in 10 fractions.

The median overall survival of the current study regarding Group 1 is in agreement with the retrospective studies previously mentioned (current study – Group 1: 4.1months vs Guo, Balagamwala [78]: 3.0 months vs Ozgen [79]: 3.0 months).

Ozgen [79] has concluded on his multivariate analysis that longer intervals between the two treatments were associated with improved survival. However, the current study does not confirm this result, a higher interval between the two treatments actually does not reflect a better overall survival.

The minimum interval between the two treatments required in the literature is 6 to 12 months to consider re-irradiation. [55] Group 2 (SRT+WBRT) presented the shortest median time interval between the two treatments (7.5 months), although still within the recommended interval. Within this group, as previously mentioned, all patients had an interval shorter than the recommended threshold; however, none of the patients who developed radionecrosis belonged to this subset.

After re-irradiation, patients had a median follow-up of 11.7 months, which is shorter than the minimum follow-up time initially defined for this study (20.0 months). However, follow-up was highly heterogeneous, ranging from 0.8 months to 55.4 months at the study endpoint.

Regarding patient outcomes after reirradiation treatment, local progression was not observed in any patients of group 3 (SRT+SRT), during a 12-month follow-up period. During this period, there was no record of progression in the radiological imaging reports. Given that these patients are monitored periodically, this was a very positive result in descriptive terms, but without statistical significance due to the small number of patients in this group and in the others.

Various studies have shown efficacy and tolerance in these patients with SRS irradiation. The study by Touati, Bourbonne [57] included 32 patients and determined local control of reirradiation treatment and the occurrence of radionecrosis after a median follow-up of 12 months, obtaining rates of 68.0% and 12.0%, respectively. The study by Yan, Lee [80] included a larger number of patients (91 patients) and analysed the rates of local failure and radionecrosis, reaching values of 27.7% and 15.6%, respectively, at 12 months. These two

retrospective studies did not show results as favourable as those obtained in descriptive terms in the present study.

The group with the highest rate of local progression and distant progression was group 4 (WBRT + SRT), where almost two-thirds of the patients progressed locally (N=5) and half of the patients presented distant progression (N=4), in separate analyses. A retrospective study conducted by Maranzano, Trippa [81] consisted of 69 patients and analysed a treatment sequence similar to that of group 4. Regarding the results obtained, this study obtained local control rates of 74% (+/- 4%). However, the same author conducted a mono-institutional prospective phase II trial, published in 2019 including 59 patients. [82] The objective of the study was to obtain similar results and limited toxicity in a more restricted patient selection. Local progression was found in 12% of patients (N=7), distant intracranial progression was seen in 25% of patients (N=15) and, furthermore, 14% of patients (N=8) progressed both locally and remotely. That said, the local and distant progression rates obtained in group 4 of the present study were much higher compared to the rates obtained in the prospective study mentioned above.

Distant intracranial progression would be expected to be higher in group 3, given that treatment targeted only the brain lesion. However, this occurred in only one patient 3.5 months after reirradiation. Conversely, in groups 1 and 2, where patients received WBRT at reirradiation, lower distant progression rates and longer median times to progression were observed (Group 1: 28.6% and 7.9 months; Group 2: 14.3% and 10.9 months, respectively). This result is consistent with the advantages of WBRT, which allows treatment of not only macroscopic but also microscopic metastases, an effect that was confirmed in both groups. [5, 18]

The rates of unknown status in the analysis of local and distant progression were more pronounced in group 1 (WBRT+WBRT) and group 2 (SRT+WBRT), with rates of 42.9% in both groups and in both settings. In these groups, the reirradiation treatment technique used was WBRT. Additional analysis of these cases revealed that survival after re-irradiation was generally very short, usually less than 5 months (with only one patient surviving approximately 10 months). Therefore, the high rate of unknown status can be mainly attributed to the short survival of these patients after re-irradiation. Radiological imaging after WBRT was only recommended in the case of symptom development. Currently, the NCCN guidelines [19] recommend periodic brain MRI for all patients, regardless of the technique used, every 2 to 3 months for the first 2 years. Thereafter, the radiographic surveillance is recommended every 4 to 6 months indefinitely. [9, 19]

In the toxicity's analysis, group 2 (SRT+WBRT) presented the greatest variability in adverse effects, with the exception of visual changes. The difference between group 2 and group 4 is due to the order of treatment techniques. Therefore, it is postulated that when SRT is used in the first treatment, there is greater flexibility in complying with tolerance doses. However, when SRT is used in reirradiation (after WBRT), there is greater restriction, given the increased care required to comply with tolerance doses for organs at-risk.

To assess the biological impact of the different fractionation regimens used in our retrospective study, the linear quadratic model (LQ) was used. This model allows calculating the biological effective dose considering the dose per fraction and the total dose prescribed, providing a valuable system for the evaluation of cumulative dose to the brain as well as re-irradiation risks. In fact, SRT represents a major change from the standard radiotherapy practice when relatively large amounts of normal tissue received high doses and the objective was to maximize tumour control with an acceptable level of normal tissue injury.

When comparing the relative biological effectiveness of the large doses per fraction of SRT (i.e. 27Gy/3fx or 30Gy/5fx) with conventional fractionation or moderately hypofractionated regimens (i.e. 30Gy/10fx or 20Gy/10fx), the differences observed in cumulative EQD2 in reirradiation schemes may be one of the contributing factors for explaining the higher risk of brain necrosis after SRT when compared with conventional fractionated regimens.

Overall, the clinical validation of the LQ has been established mainly for fraction sizes between 1–5Gy (Brown, Carlson [83]), with particular validity 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 system, 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 SRT clearly contradict this expectation, demonstrating remarkable efficacy even with high-dose fractions, including in palliative settings. [84]

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. Other factors, not accounted for by classical radiobiology, may also play a role—such as radiation-induced vascular damage, enhanced anti-tumour immune responses, or the limited relevance of reoxygenation in non-hypoxic tumours.

Despite these reservations, experimental survival data suggest that the LQ model remains robust up to approximately 10Gy per fraction, and even applicable in some contexts up to 15–20Gy Brown, Carlson [83]. 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.

In our study, radionecrosis was one of the most prominent toxicities among the diverse adverse effects during follow-up, reported in 17.6% of the total sample. This toxicity was based solely on brain MRI, without the inclusion of any other radiological imaging technique to confirm radionecrosis or differentiate it from pseudoprogression and brain progression. Currently, the Department already has other imaging techniques available, namely perfusion-weighted MRI and MRI-based contrast clearance analysis, which help in distinguishing between these (although true confirmation is only achieved through histopathological analysis).

The only group where radionecrosis was not observed was group 1 (WBRT+WBRT). In the other groups, SRT technique was used, either in the first radiotherapy treatment (Group 2), in re-irradiation (Group 4) or in both treatments (Group 3). Radionecrosis rate was higher in group 3 (SRT+SRT), corresponding to 40% of this group, followed by group 4 (25%) and, lastly, group 2 (14.3%). It is important to emphasize that the composition of each group was distinct (Group 2: 14 patients; Group 3: 5 patients; Group 4: 8 patients). The literature indicates that radionecrosis is the major side effect after SRT. [57] Indeed, its rate varies according to studies in the literature between 4% and 25%. [57, 80, 85-88] “Radiation dose, fraction, and subsequent chemotherapy administration are known to be the main risk factors”. [57] Furthermore, “repeat single fraction SRS has been consistently observed as associated with a high risk of adverse events” which is also confirmed by our results. [80]

Radionecrosis rate reported by Touati, Bourbonne [57] and Yan, Lee [80], who used a sequence of treatment techniques comparable to group 3, was 12% and 19.2%, respectively. Touati, Bourbonne [57] reported that the radionecrosis rate was considered acceptable considering “the possible neurocognitive deterioration and decreased quality of life seen particularly in long-term WBRT survivors”.

In the present study, neurocognitive changes were also one of the most prominent toxicities during patient follow-up. As expected, group 1 (WBRT+WBRT) had the highest rate, corresponding to 57.1%. However, less expected was group 3, which had a relatively high rate of 40.0%.

In the survival analysis after reirradiation treatment, the results obtained by group 3 exceeded expectations, showing that all patients remained alive at the end of 12 months. Survival analysis was performed up to a maximum follow-up period of 12 months, as beyond this interval, the data became uninformative due to the small number of patients under observation. The literature presents survival probabilities at 1-year of around 60% for this sequence of treatment techniques (SRT+SRT). [48, 57, 80]. Only one study reported survival probabilities of 80%. [89]

In contrast, group 1 had the least favourable results, with a median survival of 4 months. Survival in this group of patients is generally short, with median times reported in the literature ranging from 2.9 to 4.1 months and our results also confirmed this. [90]

Groups 2 and 4 were intermediate groups, and the results were comparable between them. No studies to date have reported results from the treatment sequence of group 2 (SRS+WBRT). However, literature shows that the median survival after reirradiation, with a sequence comparable to group 4 (WBRT+SRT), ranges from approximately 8 months to 14 months, which agrees with the median survival of group 4 in our study, which corresponds to 10.3 months. [81, 82, 91]

Despite the differences described between the groups, in statistical terms, they are not significant ($p=0.140$).

This study is retrospective in nature and therefore may be subject to potential bias. Some possible bias detected were:

- Selection bias may have occurred, as only patients treated at IPO Porto and with available follow-up data were included, limiting the sample's representativeness in relation to the general population.
- Information bias is also possible, given that medical records were not always complete and radiographic surveillance were not performed uniformly for all patients after re-irradiation. Furthermore, at the time of the study, there were no other imaging techniques available that would allow the differentiation of radionecrosis, tumour progression, or pseudoprogression.
- The fact that this was not a randomized study, implies a risk of confounding variables, since relevant clinical characteristics (age, performance status, number of metastases, and previous treatments) were not evenly distributed between the groups, which may have influenced the results.

The limitations found on this study were:

- Although the initial sample was promising (N=85), the application of exclusion criteria substantially reduced the number of patients in the study, impairing validity of some results.
- After data collection, four groups were identified into which the sample could be distributed, in this case, according to the homogeneity of the sequence of treatment techniques performed in the first radiotherapy treatment and re-irradiation. The four treatment groups were more heterogeneous and less balanced, which may have compromised the statistical robustness of the comparisons. Additionally, the assessment of radionecrosis was particularly limited, as, in many cases, this data was unknown because some patients did not undergo radiographic surveillance after re-irradiation.
- Lack of imaging techniques at the time of the study to differentiate between brain progression, radionecrosis, or pseudoprogression.
- The study assumed an essentially descriptive character, given the small sample size and the heterogeneity of the treatments that made it impossible to carry out univariate or multivariate analyses and restricted the conclusions obtained.

6 CONCLUSION

This retrospective study provides an overview of re-irradiation practices in patients with recurrent or progressive brain metastases, analysing the combination of different treatment techniques on clinical follow-up and survival.

In general, re-irradiation appeared to prolong survival in these patients, particularly when compared with the absence of treatment, in which median survival is typically limited to 1–2 months. [16] Repeated WBRT (Group 1) was associated with lower survival rates (without statistical significance) and higher rates of neurocognitive decline, although it retained a relevant role in controlling distant intracranial progression. In contrast, repeated SRT (Group 3) demonstrated a tendency toward improved overall survival, despite a higher incidence of radionecrosis. Notably, all patients treated with SRT, whether in the first RT treatment or re-irradiation, showed higher survival rates.

Our findings are consistent with the existing literature and suggest that SRT may represent the preferable technique whenever clinically feasible. Although the risk of radionecrosis is increased, this is often considered acceptable when compared with the potential neurocognitive deterioration and reduced quality of life observed in long-term WBRT survivors. These results emphasize the importance of individualized and multidisciplinary decision-making and highlight the need for prospective studies with larger cohorts and standardized imaging follow-up to validate these preliminary findings and optimize future therapeutic strategies.

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