



Whole Brain Irradiation or Stereotactic RadioSurgery for five or more brain metastases (WHOB-STER): A prospective comparative study of neurocognitive outcomes, level of autonomy in daily activities and quality of life

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ABSTRACT

Aims: To evaluate neurocognitive performance, daily activity and quality of life (QoL), other than usual oncologic outcomes, among patients with brain metastasis ≥ 5 (MBM) from solid tumors treated with Stereotactic Brain Irradiation (SBI) or Whole Brain Irradiation (WBI).

Methods: This multicentric randomized controlled trial will involve the enrollment of 100 patients (50 for each arm) with MBM ≥ 5 , age ≥ 18 years, Karnofsky Performance Status (KPS) ≥ 70 , life expectancy > 3 months, known primary tumor, with controlled or controllable extracranial disease, baseline Montreal Cognitive Assessment (MoCA) score $\geq 20/30$, Barthel Activities of Daily Living score $\geq 90/100$, to be submitted to SBI by LINAC with monoisocentric technique and non-coplanar arcs (experimental arm) or to WBI (control arm). The primary endpoints are neurocognitive performance, QoL and autonomy in daily-life activities variations, the first one assessed by MoCa Score and Hopkins Verbal Learning Test-Revised, the second one through the EORTC QLQ-C15-PAL and QLQ-BN-20 questionnaires, the third one through the Barthel Index, respectively. The secondary endpoints are time to intracranial failure, overall survival, retreatment rate, acute and late toxicities, changing of KPS. It will be considered significant a statistical difference of at least 30% between the two arms (statistical power of 80% with a significance level of 95%).

Discussion: Several studies debate what is the decisive factor accountable for the development of neurocognitive decay among patients undergoing brain irradiation for MBM: radiation effect on clinically healthy brain tissue or intracranial tumor burden? The answer to this question may come from the recent technological advancement

Abbreviations: RT, Radiation Therapy; MBM, Multiple Brain Metastases; SBI, Stereotactic Brain Irradiation; QoL, Quality of Life; MoCA, Montreal Cognitive Assessment; KPS, Karnofsky Performance Status; EORTC QLQ-C15-PAL, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 15 for Palliative Care; QLQ-BN20, Quality of Life Questionnaire - Brain Neoplasm 20; SRS, Stereotactic RadioSurgery; OS, Overall Survival; FSRT, Fractionated Stereotactic Radiation Therapy; BSC, Best Supportive Care; MRI, Magnetic Resonance Imaging; GTV, Gross Tumor Volume; CTV, Clinical Target Volume; PTV, Planning Target Volume; OAR, Organ At Risk; CT, Computerized Tomography; SRT, Stereotactic Radiation Therapy; NCCN, National Comprehensive Cancer Network; LINAC, Linear Accelerator; 3D-CRT, 3Dimensional-ConformalRadioTherapy; VEGF, Vascular Endothelial Growth Factor; CRF, Case Report Form; RTOG, Radiation Therapy Oncology Group.

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that allows, in a context of a significant time saving, improved patient comfort and minimizing radiation dose to off-target brain, a selective treatment of MBM simultaneously, otherwise attackable only by WBI. The achievement of a local control rate comparable to that obtained with WBI remains the fundamental prerequisite.
Trial registration: NCT number: NCT04891471.

Introduction/rationale

In the last few decades novel therapies and new combined approaches have prolonged survival among patients affected by several different solid tumors, resulting in higher incidence of brain metastases (BM).

In this patient setting, Whole Brain Irradiation (WBI) represents the gold standard for treating five or more brain metastases. Instead, the Stereotactic Brain Irradiation (SBI) finds a role in the treatment of oligo-progressive or oligo-metastatic cerebral disease. The current literature about SBI for high number of metastases (i.e. = 10 metastases) is promoting such a treatment as an alternative therapy to WBI because the latter therapeutic approach could lead to a neurocognitive deterioration, as reported by DeAngelis et al. [1]. Similar results have been observed by Kocher, Brown, Soffiatti, et al. in three different comparative studies between WBI and SBI with the same median survival in both groups [2–4].

Conversely, Li et al. [5] argued that cognitive performance depends on brain tumor burden, as could be inferred from the observed clinical improvement following a metastases volume reduction of about 45% compared to baseline. Subsequently, Yamamoto et al. [6,7], in the JLGK0901 trial, demonstrated the feasibility of GammaKnife-Stereotactic RadioSurgery (SRS) in the treatment of ten or more brain metastases, with better results in terms of preservation of the neurocognitive performance with respect to WBI [8].

The literature data are still controversial regarding the clinical outcomes and time to cognitive decline [9,10]. For the latter, Trifiletti et al. showed a latency period of 10,2 months after WBI [11]. In contrast, Cheng et al. reported early cognitive impairment at one month after WBI, likely due to the frontal lobe damage [12]. Between these opposing positions, Kepka et al. [13] supported that the omission of WBI after post-operative SRS delivered to the tumor bed affected the quality of life (QoL) and survival rates due to a poor sub-clinical disease control. These data have also been observed by Aoyama et al. [14] in a prospective study.

In another prospective trial, Minniti et al. proved that radiosurgery for ten synchronous cerebral metastases was feasible with a cognitive deterioration ranging from 4,7% to 18,7% when the cumulative target volume was <15 cc. [15]. Nicosia et al. [16] reported a one-year overall survival (OS) of 77% for the SRS group versus 34,6% for the WBI group. Interestingly, this difference in survival rate could lead to significant doubts and concomitantly increase debate among insiders.

These preliminary results on the potential opportunities offered by stereotactic radiotherapy in terms of neurocognitive preservation through selectively targeting multiple brain metastases (MBM), prompt us to draw a prospective randomized study on these issues. The WHOBI-STER is a multicentric trial that aims to address these needs through the evaluation of neurocognitive outcomes, daily activities, and quality of life in patients who have five or more brain metastases treated with Whole Brain Irradiation (WBI) or Stereotactic Brain Irradiation (SBI).

Methods

The purpose of this study is to define if the SBI is able to offer an actual advantage both in terms of preservation of neurocognitive performance and quality of life over WBI in patients with five or more brain metastases.

The control arm will be treated with WBI, i.e. the standard of care in this clinical scenario, while the SBI will be delivered to the experimental

arm.

Neurocognitive functional status, daily activity and QoL evaluations will be the primary endpoints.

Time to local failure, Overall Survival, Re-treatment rate, acute and late toxicities, and changing of Karnofsky Performance Status (KPS) will be evaluated as secondary endpoints (Table 1).

Design

Before starting treatment, the radiation oncologist has no predictive models to base a hypothesis about the best radiotherapy option to treat multiple brain metastases. This issue is related to contradictory findings in current literature on SBI use in those clinical scenarios where five or more metastases are detected. It is still unclear if such a therapeutic approach is able to better preserve the patients' neurocognitive capabilities, autonomy in activities of daily living, and quality of life.

The WHOBI-STER study is similar to the ENCEPHALON trial and CAR-studies but presents some substantial differences in comparison with these [17,18]. In fact, the ENCEPHALON- Trial (SRS vs WBI for patients with 1–10 BM) enrolls Stage IVB Small Cell Lung Cancer patients only; CAR- A and CAR- B have the aim to evaluate cognitive performance in patients with 1–10 and >10 BM after GammaKnife radiosurgery. The results obtainable from WHOBI-STER could further substantiate or disprove those from CAR study B through a larger sample size (100 vs. 46). The WHOBI-STER has a study design similar to the trial NCT01592968; early results of this study have been recently presented ([https://www.redjournal.org/article/S0360-3016\(20\)33527-6/fulltext](https://www.redjournal.org/article/S0360-3016(20)33527-6/fulltext)).

Our study is based on accrual of stage IV patients with different histological diagnoses, five or more brain metastases. In the experimental arm, the Stereotactic RadioSurgery or Fractionated Stereotactic Radiation Therapy (FSRT) with a mono-isocentric technique will be used in making the comparison with the control arm that will be treated with WBI.

After all, achieving an optimal locoregional control while limiting the onset of treatment-related adverse events, especially among frail patients ineligible for other treatments, is usually the main goal of current radiotherapy practice [19,20].

Registration

This Trial has been registered with a NCT number: NCT04891471 (<https://clinicaltrials.gov/ct2/show/NCT04891471>).

Participants

Participants must have five or more brain metastases to be candidates to Whole Brain Irradiation (WBI) or Stereotactic Brain Irradiation (SRS for single shot treatments or FSRT, if a fractionated schedule is used). For the duration of the radiotherapy course, all patients, unless

Table 1
Study Endpoints.

PRIMARY ENDPOINTS	SECONDARY ENDPOINTS
Neurocognitive functional status	Time to local failure
Autonomy in daily activities	Overall Survival
Quality of Life	Re-treatment rate
	Acute and late toxicities
	Changing of Performance Status

there are contraindications, will take a dexamethasone dose of 4 mg b.i.d. which will be tapered slowly until the discontinuation within two weeks after treatment ends. Although there is no actual evidence of a benefit related to such a preventive administration [21], we justify this therapeutic choice by the fact that even the irradiation of a low tumor burden may produce symptomatic swelling of quite an amount of healthy brain tissue.

Inclusion criteria

Age > 18 years old, life expectancy > 3 months, brain metastases number ≥ 5 , histologically confirmed primary tumor diagnosis, appropriate extracranial disease staging, baseline Montreal Cognitive Assessment equal to at least 20/30, Barthel Index for Activities of Daily Living not <90/100, Karnofsky Performance Score (KPS) ≥ 70 and signed informed consent.

Exclusion criteria

Brain-Magnetic Resonance Imaging (MRI) contraindications, contraindications to SBI for critical area involvement, pregnancy, hemorrhagic or miliary cerebral metastases, hippocampal metastases, massive perilesional edema, leptomeningeal involvement, previous brain irradiation, dementia, brain colonization by non-solid tumors, germ cell tumors, recent ischaemic cerebral event, alcohol and/or drug abuse, established diagnosis of anxiety and depression.

Moreover, the present study will exclude patients with KPS ≤ 60 and life expectancy < 3 months according to the QUARTZ trial [22], which has not shown a relevant difference between best supportive care (BSC) and WBI in terms of OS and QoL in case of patients' limited life expectancy.

The eligibility criteria for participating in the present study do not include a maximum number of brain metastases: the needed requirement is that the V12 of brain less PTVs should not exceed 10 times the number of metastases. Such a 1:10 ratio means that for each lesion is permitted an average of 10 cc of healthy brain that absorbs a 12 Gy dose, i.e. 7 lesions = maximum 70 cc of healthy brain tissue exposed to a dose of 12 Gy is allowed. The same is for V14Gy but in a 1:7 ratio, i.e. 7 lesions = maximum 49 cc exposed to a dose of 14 Gy is allowed. The minimum distance of metastases from hippocampal regions should be of 5 mm. Otherwise, the patient is not eligible for trial enrollment and will be treated with standard WBI.

Eligibility criteria are shown in Table 2.

Table 2
Inclusion and Exclusion Criteria.

INCLUSION CRITERIA	EXCLUSION CRITERIA
Age > 18	Brain-MRI contraindications
Life expectancy > 3 months	Contraindications to SBI
Brain metastases number ≥ 5	Pregnancy
Primary tumor histological diagnosis	Haemorrhagic cerebral disease or Ischaemic event
Appropriate Extracranial disease staging	Miliary metastases
Montreal Cognitive Assessment $\geq 20/30$	Hippocampal metastases
Barthel Activities of Daily Living $\geq 90/100$	Massive perilesional oedema
KPS ≥ 70	Leptomeningeal involvement
Signed Informed consent	Previous brain irradiation
	Dementia
	Non solid brain tumors
	Germ cell tumors
	Alcohol and/or drug abuse
	Anxiety or depression
	KPS ≤ 60
	Life expectancy < 3 months

Randomization

Following the assessment of the eligibility to this trial and obtainment of signed informed consent, participants will be randomized by the involved centres. Patients undergo randomization (WBI vs SBI) by means of a random number generator: the even patients will be assigned to control arm and the odd ones to experimental arm. This method allows to remove randomization bias. The final allocation group will be known to the investigator and patient.

Radiotherapy

Patients candidates to WBI will be treated using a 3Dimensional-ConformalRadioTherapy (3D-CRT) technique. The 3D-Computerized Tomography (CT) scan images will be acquired without contrast medium, using a thermoplastic mask as immobilization support.

The brain will represent the Clinical Target Volume (CTV) that, by a 5 mm uniform expansion, will result in the Planning Target Volume (PTV) in order to account for any setup uncertainties.

The total dose delivered for the WBI will be 30 Gy (3 Gy/day) [23,24].

For patients assigned to radiosurgery, the dose prescription was standardised among the participating institutions and it ranges from 15 Gy to 24 Gy: the smallest dose size is for lesions with diameter from 31 to 40 mm, the largest for diameter <20 mm, an intermediate dose of 18 Gy is for lesions with diameter between 21 and 30 mm. The single-shot treatment of lesions with diameter >3 cm located near critical structures, such as brainstem, optic nerves, tracts and chiasm, could be difficult due to the possible violation of the QUANTEC dose-volume constraints: Dmax = 10 Gy for chiasm/optic nerves and 12,5 Gy for brainstem. For normal brain tissue we consider V12 < 10 cc and V14 < 7 cc as acceptable. When these goals are not achievable, FSRT (i.e. 27 Gy in 3 fractions) may be used as an alternative to SRS [25]. The 3D-CT scan images will be acquired without contrast agent, using a thermoplastic mask for immobilization, and subsequently merged with a thin-slice brain MRI performed with contrast agent. For SRS and FSRT, the Gross Tumor Volumes (GTVs) will be defined as the target lesions and any clinically suspected adjacent findings on the contrast-enhanced T1-weighted 3D FSPGR sequence. An isotropic expansion of 2 mm will be applied to GTV for delineating the PTV. The latter volume can be manually trimmed to spare any neighboring critical Organs at Risk (OARs). The treatment will be delivered using five non-coplanar arcs and a mono-isocentric technique supported by a dedicated Treatment Planning System (TPS), that is the BrainLab Elements MultiMet™. In case of many lesions (>10–15) this TPS allows to achieve a highly conformal dose distribution in a similar peak-valley fashion to another radiotherapy technique, that is the Spatially Fractionated one, characterized by a steep dose fall-off between high dose subvolumes within extracranial bulky tumors [26]. The daily portal images (EPID) matched with the Digital Reconstructed Radiographs (DRRs) will be employed for an accurate patient set-up (ExacTrac™ X-ray system).

Allowed medications

Concomitant immuno- and radiotherapy administration is feasible and able to evoke abscopal effect [27,28]. Particular attention is paid to the radiation treatment for EGFR-mutated or ALK-translocated Non-Small Cell Lung Cancer (NSCLC) and melanoma brain metastases, since the literature data have shown early and lasting benefits in patients treated with combined therapy (that is radiotherapy/targeted therapy). In these stage IV patients, local response rates ranging from 74% to 89% and survival rates of 45 months have been observed [29,30]. Experiences that reported a significantly greater (but still acceptable, <14%) rate of brain radionecrosis for combination of immunotherapy (IT) and SRT with respect to SRT alone [31] are counter-balanced by as many which denied such a risk [32,33], some of these with quite large

population [33]. However, all of them agree that IT/SRT association improves survival outcomes. As no time interval between SRT and IT administration was identified as less risky for intracranial complications [34], targeted therapies will be started before or concomitantly to RT in this trial. Approved agents for combination with RT will be PD1-, PDL1-, CTL4-, BRAF- and MEK-inhibitors [35].

Interventions and follow-up

All patients will be submitted to a baseline evaluation, which includes clinical/biochemical parameters, Brain-MRI, cognitive assessment, interview about daily activities and perceived quality of life. The MoCA score and Hopkins verbal learning test-revised (HVLt-R) will be used for reporting neurocognitive functional status, while the Barthel Index for Activities of Daily Living and the EORTC QLQ-C15-PAL, QLQ-BN-20 questionnaires will be administered to evaluate the level of autonomy and QoL, respectively. The patients will be submitted to Brain-MRI every three months after radiation treatment. Also, based on the data of Mitchell, Pospisil et al. [36,37], both functional magnetic resonance imaging (fMRI) and spectroscopy will be performed to evaluate the cerebral network change (i.e. hippocampal region).

Besides, cognitive performance, autonomy in daily activities and quality of life will be investigated at the same three month interval. These data will be collected up to the patient's exitus. In case of intracranial disease progression, the therapeutic approach will follow the workflow in Fig. 1.

Statistical analysis

Fifty patients for each arm are planned to be enrolled. Statistical purpose is to identify a neurofunctional difference with an expected size of at least 30% between subjects of the two arms starting 6 months or more later, with 80% power and a significance level of 0,05. The G*Power software and ANOVA one-way test have been used to calculate this sample size.

The primary endpoints variation will be evaluated with the parametric and nonparametric tests (i.e., T-Test/Wilcoxon-Mann-Whitney test). The results will be considered as significant with the p-value < 0,05.

The secondary endpoints will be evaluated with the Kaplan-Meier estimator and the log-rank test. The significance of covariates will be evaluated through Principal Component Analysis and the correlation between covariates and primary endpoints through uni- and multivariate analyses. Even then, the results will be considered significant if the p-value < 0,05.

Discussion

Outcomes and toxicities

Achieving a better patient tolerance to treatment allows to define a reliable outcomes assessment after radiation therapy in the two study arms. The clinical scenario here investigated can alter the patients' quality of life by causing a variation of Karnofsky Performance Status (KPS) and favouring the worsening of autonomy in daily activities. Frequently, these changes, when of a particularly detrimental impact, may be responsible for patients' non-cancer-related death. Moreover, metastatic progression of cancer in the brain greatly affects patients' life expectancy: when this stage happens the median OS is about 11 months, which are a time frame that could be further reduced by intracranial failure due to an ineffective therapy. Finally, the re-treatment rate can be correlated with specific tumor biological characteristics and sensitivity to radiation therapy. By using brain-MRI every three months after radiotherapy, it is possible to obtain an early predictive and prognostic value for response to treatment. Functional magnetic resonance imaging (fMRI) will also be integrated with spectroscopic analysis for the assessment of the cerebral network change (i.e. hippocampal region). Regarding neurocognitive and quality of life studies, the use of specific questionnaires can permit to evaluate any deterioration of the patient's intellectual abilities and well-being. Some of these tests have been already used in this patient setting [17,18].

There are still few prospective literature data evaluating patients with five or more brain metastases from both a neurocognitive and quality of life point of view by comparing stereotactic radiotherapy and Whole Brain Irradiation. Our choice to recruit patients with at least 5 brain metastases is in keeping with the debate on the definition of "extensive brain metastases" as called for by NCCN [38] and with the patient grouping of experiences such as that of Yamamoto et al. [7], given that the usefulness and preferability of stereotactic RT compared with WBI is already well-established for limited brain metastases (≤ 4). Moreover, the cut-off of 5 secondary lesions fits the definition of oligometastatic and oligoprogressive cancer among Italian radiation oncologists [39] and agrees with the resulting current clinical practice [40].

Some risk for adverse events is peculiar to the stereotactic technique, which is an approach effectively used also in other metastatic or primary sites [41–44] in order to prevent the characteristic side effects of less conformal types of external beam radiotherapy [45,46]; this therapeutic option allows to use a high radiation dose in a single fraction or short fractionated radiotherapy schedule. Kano et al. [47] conducted a retrospective study involving 755 patients who have been submitted to a median single radiosurgery dose of 20 Gy. Following treatment, 55 patients (7.3%) showed acute and late toxicities, resulting irreversible in

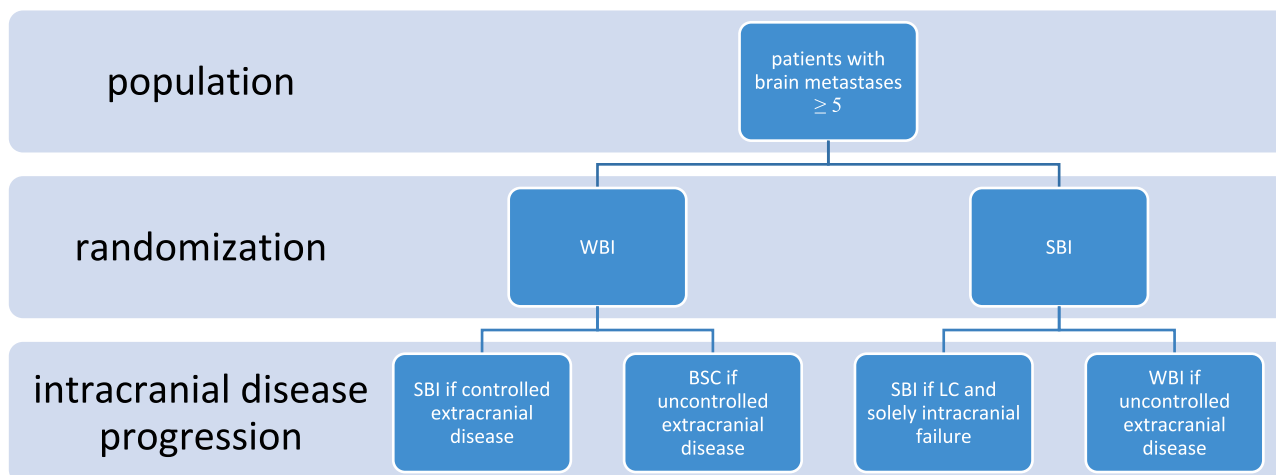


Fig. 1. WBI, Whole Brain Irradiation, SBI, Stereotactic Brain Irradiation, LC, local control, BSC, Best Supportive Care.

19/55 cases (2.5%). These toxicities were correlated to target location and volume, and off-target brain volume that received ≥ 12 Gy. At 6, 12, 18 and 24 months, the cumulative rates were 1.9%, 3.2%, 5% and 5.8%, respectively. However, the highest incidence of these events was registered at 60 months, resulting in a cumulative rate of 7.5%. Such an experience was based on the use of Gamma Knife radiosurgery whose excellent conformity index, Paddick index, dose fall-off and gradient index, especially in challenging situations (i.e. irradiation of adjacent or critically located targets [48–50]), characterize a different dose distribution in healthy brain tissue with respect to the LINAC-based stereotactic technique, thus being able to produce different neurocognitive outcomes [51]. An evaluation of these is therefore useful and should be carried out for both techniques.

The protocol proposed by Shaw et al. [52] correlated the dose/volume ratio with an increase of adverse events. A total dose of 15 Gy for tumor diameter between 30 mm and 40 mm showed better results in terms of chronic toxicities (14%).

Moreover, acute cerebral oedema is a brain irradiation toxicity, which can arise during or after therapy. It is provoked by the blood–brain barrier damage or possible alteration of drainage caused by mechanical occlusion. Regardless of pathogenesis, the clinical symptoms are headache, asthenia, somnolence, nausea, vomiting and region-specific neurological deficits. In our research, all patients will use corticosteroids as supportive care during the treatment.

In addition, radionecrosis is a side effect of radiation therapy and can occur after a long time from treatment. This biological event occurs more often after SRS. Radionecrosis incidence has been studied by Peng et al. [53], who proposed a V14 Gy ≤ 20 cc, such a limit being associated with grade 1–2 radionecrosis rate of about 12.1% and grade 3 of 3.4%. In the WHOBI-STER protocol, for the patients who will show a radiological diagnosis of radionecrosis or who will have symptomatic disease, the therapeutic approach will include the administration of corticosteroids. The refractory cases will be treated with surgery or with a monoclonal antibody for VEGF-A and hyperbaric oxygen [54–58].

Lastly, SBI could sporadically elicit some symptomatic events in distant previously irradiated body sites, thus evoking radiation recall phenomena [59]. At such occurrences, the need for any therapeutic interventions will be considered on a case-by-case basis.

Cost and financing analysis

The trial is based on two therapeutic approaches accepted as evidence-based medicine and can be proposed to a specific population affected by metastatic cancer. This study does not involve additional costs, other than those already included in normal clinical practice. The investigators will receive no financial support and declare no conflict of interest.

Ethical considerations

The present trial will be conducted in compliance with the approved protocol, the Declaration of Helsinki 2008, the principles of Good Clinical Practice (GCP) and the Italian National Normative for clinical experimentation. Fondazione Istituto Oncologico di Mediterraneo promotes the multicentric trial with REM (Viagrande – Italy) collaboration. The local Ethics Committee has approved the protocol. The other involved centers are represented by Azienda Universitaria “G. Martino” (Messina – Italy) and Azienda Universitaria “P. Giaccone” (Palermo – Italy). Both centers have submitted the protocol to its own ethics committee for approval before accrual. The involved centres have received a dedicated electronic case report form (CRF). Eligible participants who will have provided consent and will have been pseudonymously registered on the CRF, will be assigned to a numeric code.

Collection and confidentiality of data

The centers will use a dedicated electronic case report form (CRF).

Eligible participants who will have provided consent and met the inclusion criteria will be registered pseudonymously on the CRF by assigning an identification number.

Final consideration

Concerning intracranial metastases, most of the current literature agrees on the fact that improvement in survival outcomes correlates with total tumor volume reduction. Indeed, the amount of brain tissue affected by metastases before stereotactic radiotherapy could influence the outcomes and the neurocognitive performances, as reported by Habets et al. [60]. Their data demonstrated that patients with larger brain tumor volume, prior to radiation treatment, showed verbal memory decline and worse speed of information processing. Instead, these elements were not present in patients with lower brain tumor burden, irrespective of the total number of metastases and the extracranial disease status [61–63]. These findings were not consistent with those of Schimmel et al. Indeed, these authors reported a number- and volume-independent impairment of cognitive functioning at baseline among BM patients with respect to healthy controls. This calls into question some others confounding and likely determinant factors such as chemotherapy for worsening of immediate and delayed memory and psychomotor speed [64]. The first prospective evidence about patients' quality of life, after stereotactic radiation therapy, derived from a study performed on limited number of metastases (=3). In these reports, the SRS would represent a better therapeutical approach to preserve physical and communicative functions [30]. Ideally, this treatment should be as short as possible, subsequently referring patients to systemic therapies. Therefore, a single fraction or ultra-hypofractionation regimens must be used to deliver a clinically useful dose during this therapeutical approach. In patients with a more favorable prognosis, SBI could alleviate the possible onset of acute and late complications compared to WBI.

Nevertheless, for the WBI setting, there is agreement in the literature reports, which indicate the dose prescription of 30 Gy (3 Gy/day) as preferable because it produces a better result in terms of toxicity and clinical outcomes compared to the shorter course of 20 Gy in 5 fractions [65]. Conversely, about what is the better dose prescription for SRS, the literature data are still unclear. According to RTOG 90-05 the radiation doses to be administered are different with the changing metastasis diameter [52].

Therefore, by sticking as closely as possible to the current literature recommendations, the prospective WHOBI-STER study will employ the use of the single fraction approach, or alternatively the fractionated one, for the stereotactic arm. In particular, in the first case, a single dose between 15 Gy and 24 Gy will be delivered, while the FSRT will be used for lesions with diameter > 3 cm (i.e. 27 Gy in 3 fractions).

Regarding irradiation of the whole brain, the patients will be submitted to 30 Gy in 10 fractions.

Conclusion

The WHOBI-STER study aims to determine if the stereotactic radiation therapy for multiple brain metastases better preserves the pre-RT neurocognitive status, autonomy in daily activities and the QoL compared to Whole Brain Irradiation. As far as we know, this trial is the first study to provide a prospective comparative evaluation between the two techniques with the simultaneous assessment of neurocognitive functions, daily activity and QoL in patients with multiple brain metastases greater than or equal to five.

Trial status

Patient recruitment is not completed.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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