

A Systematic Review of Multimodal Treatment for 1 to 4 Brain Metastases

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Abstract: Treatment of brain metastases are controversial, being the optimal therapeutic combination still unknown. The aim of the present work was to determine the outcome differences among Whole Brain Radiation Therapy, Stereotactic Radiosurgery and Surgical Resection in terms of Overall Survival, Functional Independence, Local Control, Neurological Death and Neurocognitive Impairment. A systematically review of the pertinent literature was performed by using the Cochrane Register of Controlled Trials (CENTRAL/CCTR), MEDLINE, EMBASE, CINAHL and the ISRCTNR (International Standard Randomised Controlled Trial Number Register) databases. A total amount of 971 articles were encountered, including 19 Randomized Clinical Trials. High bias risk studies were excluded based on the Cochrane Bias Risk Tool and 14 RCT with low bias risk were selected. The combination of surgical resection and Whole Brain Radiation Therapy resulted in longer overall survival than Whole Brain Radiation Therapy alone. The combination of Whole Brain Radiation Therapy and Stereotactic Radiosurgery resulted in better Local Control and Overall Survival than Whole Brain Radiation Therapy alone. Significant differences were not found in terms of Local Control and Overall Survival between the combination of Whole Brain Radiation Therapy plus Stereotactic Radiosurgery and Stereotactic Radiosurgery alone but Neurocognition was less affected in patients treated with Stereotactic Radiosurgery. Current studies that compare different therapeutic modalities for 1 to 4 brain metastases are not conclusive. The best treatment for patients with 1-4 brain metastases remains controversial.

Keywords: Brain metastasis, Multimodal treatment, Radiosurgery, Whole brain radiation therapy, Surgical resection.

INTRODUCTION

The incidence of brain metastases (BM) in patients with cancer account for 10 to 40 % in the course of their illness [9], although some authors report this number higher than 40 % [19, 20]. Such disease represents the most frequent Central Nervous System lesion, being its incidence ten times higher than primary brain tumours [9] Furthermore, this pathology carries a poor prognosis for most of the patients [19].

About 170,000 new cases with BM are diagnosed every year in the United States [15]. The incidence of this pathology has increased during the last 40 years 2 to 5 times despite recent scientific advances. Various factors seem to be responsible for such an increase: the development of new diagnostic modalities, the increasing of survival rate for cancer patients and the diffusion of some chemotherapy agents, able to weak the blood-brain barrier. The most frequent primary tumour localization is the lung, 40 to 50%, followed in order by breast, melanoma, renal, colorectal and choriocarcinoma [10].

Metastases can be single or multiple, where the multiples represent approximately 50% of all cases. With the term oligometastases are generally considered patients harbouring 1 up to 4 BM [16].

As for the majority of patients with a cancer, the treatment of oligometastases is palliative and multimodal, addressing to reduce the symptoms, to improve the Local Control (LC), Survival with Functional Independence (SFI), and Overall Survival (OS).

Actually, conventional treatment modalities such Whole Brain Radiation Therapy (WBRT), Stereotactic Radiosurgery (SRS) and Surgical Resection (SR) have reached new levels of refinement. However, these achievements are somewhat muted by the emergence of Magnetic Resonance (MR)-guided laser interstitial thermal therapy or MR-guided focused ultrasound surgery, a minimally invasive neuroablative techniques [16, 23].

WBRT is used to treat noted metastases or as a prophylactic cranial irradiation against micrometastases not detected by neuroradiologic investigations. WBRT constitutes the standard palliative treatment for oligometastases and increases up to 3 times the OS average when compared with steroid treatment alone

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(OS from 3 up to 9 month) [5]. Best results are obtained in patients younger than 60 years, with a Karnofsky Performance Status (KPS) score of 70 or higher, a radiosensitive primary tumor and controlled primary disease. The optimal dose remains uncertain and delivery schemes have changed widely in the literature [10].

The SRS is an interdisciplinary procedure that requires the use of high resolution anatomical images, specialized instrumentation and rigid immobilization. It combines stereotactic principles with high intensity focal radiation. High ionizing radiation doses are delivered to the target through beams generated with a Linear Accelerator (LINAC) or Cobalt multisource devices (Gamma Knife) while sparing normal tissue. The total dose is normally applied in one session, although is possible to apply up to five sessions [23]. SRS is frequently used for initial handling or adjuvant therapy after SR or WBRT [22]. It has been reported as having successful LC rates up to 70-80% of patients [4].

Focal treatment of oligometastases with SR has shown an improvement in tumor LC and extension of OS, especially when combined with WBRT. Indications for SR as primary therapeutical modality include one or some of the following circumstances: unknown primary tumour; significant mass effect including edema that requires rapid relieve; symptomatic lesions, localized in no eloquent areas, and surgically accessible (not deep situation) [17]. However, SR can be contraindicated in many patients due to co morbid associated conditions or non resectable lesion. Potential benefits of SR must be counterbalanced with morbidity risks and after surgical mortality.

WBRT utilization is also controversial because of the potential neurocognitive damage that it produces [23].

Taking into account these elements, we made the following question: what is the therapeutic modality that offers the best results attending to OS, SFI, LC, Neurological Death (ND) and Neurocognition?

METHODS

It was made a qualitative systematic review retrospective study.

Study Selection Criteria

Randomized Control Trials (RCT) that compare SR, SRS and WBRT alone or in combination, in patients

older than 18 years with oligometastases, histologically confirmed, regardless primary tumor localization were selected.

Study Exclusion Criteria

RCT in patients with no controlled primary tumor, as well as those without a Computed Tomography (CT) or a Magnetic Resonance Image (RMI) diagnosis, mainly before the 1980's. High bias risk studies were excluded.

Therapeutic Modalities

The considered therapeutic modalities were:

- SRS with rigid frame or mask, in single or repeated fractions, with LINAC or Gamma Knife
- SR
- WBRT alone or associated to another modality

Variables

Primary Variable

OS, as defined from the time of patient inclusion in the study

Secondary Variable

1-SFI: The time that the patient remained with a KPS equal to or higher than 70 or with a rating lower than or equal to 1 according to the World Health Organization (WHO) scales.

2-LC: Lesion recurrence rate

3-Neurocognitive damage as measured by the Hopkins Verbal Learning Test (HVLT) [3].

4-ND: Death rate due to brain disease progression.

Search Strategies and Studies' Selection

The search was made in the following electronic databases: Cochrane Register of Controlled Trials (CENTRAL/CCTR), MEDLINE, EMBASE, CINAHL and the ISRCTNR (International Standard Randomised Controlled Trial Number Register).

The following terms were used, in english as well as spanish.

In english: solitary/ single/oligo-brain/cerebral metastasis/metastases, surgery/ neurosurgery/micro-

surgery, radiosurgery/stereotactic radiosurgery, whole brain radiotherapy/radiation therapy/ irradiation and randomised/controlled trial/ Gamma knife/ recursive partitioning analysis.

In spanish: enfermedad metastásica cerebral/ metástasis cerebral/ cirugía/ radiocirugía/ radioterapia holocraneal/ reirradiación/ radionecrosis/ análisis de particionamiento recursivo/ bisturí de rayos gamma/ escalación de dosis/ lesiones radioresistentes/ oligometastasis/ factores pronósticos.

The references lists of the identified studies were also checked to search additional studies. There was not language limitation.

REVIEW METHODS

Bias Risk in the selected studies was based on the Cochrane Bias Risk Tool [6].

The following exclusion criteria were considered:

- 1-Improper randomization
- 2-Lack of blinding methodologies for participants
- 3-Incomplete data

With respect to these criteria, studies were divided into

- 1-Yes (low bias risk)
- 2-No (high bias risk)
- 3-Unknown (unknown bias risk)

Only the "Yes" studies were accepted for our analysis.

The treatment modalities were classified as follows:

- 1-SR alone
- 2-SR and WBRT
- 3-SRS alone, including all techniques: Gamma Knife, LINAC, with rigid or reconfigurable frame.
- 4-SRS, all techniques, plus WBRT
- 5-WBRT alone

RESULTS

The search initially found 971 published articles.

Among them, there were 19 RCT. When the Cochrane Bias Risk Tool was applied, a sample of 14 RCT with low bias risk was selected (Table 1).

SR PLUS WBRT VS WBRT

In 1990, in a RCT with 48 patients (25 with SR plus WBRT and 23 with WBRT alone) in Kentucky, USA, Patchell *et al.* [13] founded an increase in OS (40 weeks versus 15, $p < 0.01$), better LC (20% recurrence versus 52%, $p < 0.02$) and longer SFI, determined as the time that the patient retained a KPS equal or higher than 70 (38 weeks versus 8 weeks, $p < 0.005$) with the combination of SR plus WBRT.

In 1993, Vetch *et al.* [21] conducted a multicenter study with a sample of 66 patients. WBRT was delivered in 2 Gy sessions, twice a day, for 2 weeks. In this trial, OS was established since the randomization time. SFI was evaluated according to the WHO scale. Before randomization, patients were classified according to the primary tumor localization (lung versus not lung) and extracranial disease level (stable or progressive). Mean OS was 10 months in patients treated with SR plus WBRT and 6 months in those treated with WBRT alone ($p < 0.04$). Results were similar in lung or not lung groups. For those cases with progressive primary disease, OS was low in both groups, with a mean value of 5 months. SFI was longer in the group that received combined treatment ($p < 0.06$). The authors concluded that patients with stable primary disease and 1-4 brain metastases had to be treated with SR and WBRT, while WBRT alone was acceptable for patients with progressive primary disease during the previous three months.

In 1994, Noordjik *et al.* [11] published a similar study with 66 patients. SR and WBRT were similar to the Vetch's study [21]. Combined treatment allowed a longer mean OS (12 months vs 7 months, $p = 0.02$). Patients with extracranial active disease had a mean OS of 5 months, independently of the therapeutic modality. As for the SFI, the achieved results were similar for both groups.

In 1996, Mintz *et al.* [7] published another multicenter study with an 84 patient's sample. WBRT was administered up to a total dose of 30 Gy, in 2 Gy daily sessions for 2 weeks. It was not found a significant improvement in any of the two groups. 36 patients with the combination of WBRT and SR and 30 patients with WBRT alone died in the course of the year, $p = 0.24$. ND and SFI were similar in both groups.

Table 1: Summary of the RCT Selected

Authors and Year	Arms	OS	LC	SFI	ND	Neurocognition
Patchell et al. 1990	SR plus WBRT (n = 25) versus WBRT (n = 23)	9.2 months versus 3.5 months (p < 0.01)	13.6 months versus 4.8 months (P < 0.0001)	NE	80% versus 87%	NE
Vetch et al. 1993	SR (n = 32) plus WBRT vs WBRT (n = 31)	10 months versus 6 months (p < 0.04)	NE	NE	NE	NE
Noordijk et al. 1994	SR plus WBRT vs WBRT (n = 66)	12 months vs 7 months, p = 0.02	NE	NE	NE	NE
Mintz et al. 1996	SR plus WBRT vs WBRT (n = 84)	NE	NE	NE	NE	NE
Patchell et al. 1998	SR plus WBRT vs SR (n = 95)	11 months vs 10 months, p = 0.39	10% recurrence rate vs 46%, p < 0.001	KPS equal or higher than 70 during 8.5 vs 8 months, p = 0.61	14% vs 44%, p = 0.003	NE
Andrews et al. 2004	SRS +WBRT (n = 164) versus WBRT (n = 167)	5.7 months versus 6.5 months (p = NS)	82% versus 71% (p = 0.01)	43 versus 50	39 versus 46	Worse or Unchanged: 38% vs. Worse or unchanged: 48%
Aoyama et al. 2006	SRS +WBRT (n = 65) SRS alone (n = 67)	8.0 months 7.5 months (P = NS)	53.2% 23.6% (P < 0.001)	NE	NE	3 point deterioration in MMSE
Muacevic et al. 2008	SR plus WBRT vs SRS (n = 70)	9.5 months versus 10.3 months (P = NS)	82% versus 97% (P = NS)	NE	NE	NE
Chang et al. 2009	SRS (n = 30) vs WBRT p SRS (n = 28)	63% vs 21% (p = .003)	67% vs 100% (p = 0.12)	NE	NE	Mean posterior probability of decline at 4 months: 24% vs 52%

*Abbreviations: OS: Overall Survival; SFI: Survival with Functional Independence; NE: Not evaluated; LC: Local Control; MMSE: Mini Mental Exam. ND: Neurological Death; NS: Not Significant.

SR PLUS WBRT VS SR

In 1998, Patchell *et al.* [12] published a RCT with 95 patients with oligo brain metastases. They compared evolution of patients with SR plus WBRT 28 fractions, 54 Gy each one vs SR alone. They found that addition of WBRT improved LC (10% recurrence rate vs 46%, p < 0.001) and neurological death rate (14% vs 44%, p = 0.003) but it did not influence OS (mean values of 11 months vs 10 months, p = 0.39) or SFI (KPS equal or higher than 70 during 8.5 vs 8 months, p = 0.61).

Roos *et al.* in 2006 [18], evaluated the effect of adjuvant WBRT after SR or SRS in 19 patients with solitary brain metastases, 17 patients had SR and one in each arm had SRS. They didn't observe significant differences in OS SFI but tendency was observed to reduce the ND. This RCT was suspended by the Trial Management Committee on 31 July 2000 due to slow accrual and closed on the recommendation of the

Radiation Therapy Oncology Group (RTOG) Scientific Committee on 14 October 2000.

SR PLUS WBRT VS SRS

In a multicenter study reported by Muacevic *et al.* [8] with a sample of 70 patients, there were not significant differences found with respect to LC (p = 0.08) and neurological death (p = 0.3).

SR PLUS WBRT VS WBRT PLUS SRS

There are no studies with low bias risk.

WBRT PLUS SRS VS WBRT

In 2004 a phase III RCT involving 331 patients with 1 to 3 metastases was conducted by Andrews, Scot *et al.* [1] from RTOG. They compared the results in a phase III study including 331 patients with 1 to 3 metastases. There was no difference in OS, neither in

mental status between the 2 arms based on the Mini-Mental Status Exam (MMSE). No patient experienced acute grade 3 or 4 toxicities in the WBRT alone arm, however, 2% grade 3 and 1% grade 4 acute toxicities were observed in those treated with WBRT and SRS.

Patil and Pricola *et al.* [14] compared the results between WBRT and WBRT plus SRS in single and multiple metastases. They concluded that SRS plus WBRT showed no benefits over WBRT. However, SRS plus WBRT improved the SFI and LC.

WBRT PLUS SRS VS SRS

Roos *et al.* [18], in 2006 compared 19 patients that received WBRT with 30 to 36 Gy doses supplemented with SRS, with 9 patients that received SRS alone. Even though differences between both arms were not found, this RCT was abandoned without conclusions.

Aoyama *et al.* [2], in a RCT with a sample of 128 patients, did not find statistically significant differences concerning OS. Nevertheless, in a more recent RCT carried out by Chang *et al.* [3], in 2009, enrolling 58 patients with 1 to 3 metastases treated with SRS plus WBRT (30 Gy in 10 fractions) versus SRS, the SRS arm increased the OS.

Chang *et al.* [3] assessed Neurocognition using HVLT-Revised. Patients who received WBRT (30 Gy in 12 fractions) plus SRS showed a significant decline in learning and memory function compared with the group that received SRS alone.

SR VS SRS

There are no studies with low bias risk.

DISCUSSION

SR Plus WBRT Vs WBRT

The results of the studies that compare SR plus WBRT with WBRT were not consistent due to several reasons. Samples sizes were smaller (48, 63, 66, 84, respectively). There were significant differences among the volume baseline information. All the patients from the Patchel study were diagnosed through Magnetic Resonance Imaging (MRI) [12]. In Noordijk's study MRI was optional and no biopsy was obtained [11]. Mintz patients were confirmed by Computerized Axial Tomography (CT) and biopsy was obtained only when diagnosis was not clear [7].

The studies showed different ratios of number of patients regarding both arms. Studies exhibited different eligibility criterion: Mintz *et al.* [7], selected patients with a scale of performance status of KPS of 50 or higher, Patchell *et al.* [12] selected patients with KPS of 70 or higher while Noordijk *et al.* [11] selected patients using the scale of World Health Organization (WHO) equal 1 or lower. In addition, they studied different ratios of patients with extracranial tumors. None of them assess the LC.

It is remarkable that in 3 of 4 studies, longer OS were observed in the SR plus WBRT arm.

These results could be related with the decrease of the neurological death.

According with Chang analysis [3], the OS is determined by powerful prognostic factor such as: primary tumor type, systemic stage of the disease, and the systemic chemotherapy effect.

SR Plus WBRT Vs SR

Only one comparative RT between SR plus WBRT and SR showed benefits related to combination over the SR, concerning the LC and neurological death, with no differences regarding OS. SRS could show the same results as SR but with less morbidity because complications during and after the SR are lower. In addition, SRS offers more comfort to the patient requiring a shorter hospital stay, with lower costs.

SR Plus WBRT Vs SRS

Only one comparative RCT between SR plus WBRT and SRS was found [8]. The results exhibit no statistically significant differences between both modalities. However this study had some limitations: it was prematurely abandoned.

WBRT Plus SRS Vs WBRT

Only two comparative RCT, performed by RTOG, between these modalities was found [1, 14]. An advantage was reported favouring patients treated with WBRT plus SRS regarding LC.

These results showed that LC variable depends on the dose. LC increases when radiobiological dose increase, like in SRS-WBRT combination. According with these evidences we could assume that increasing the SRS dose we can obtain the same LC as in SRS-WBRT combination. OS was statistically significant

higher in patients with good prognostic (less than 65 years old, KPS \geq 70, and stable primary tumour, without extracranial metastases) treated with the SRS-WBRT combination than in patients with a poor prognostic.

WBRT Plus SRS vs SRS

Three RCT, which compare these combinations, were found [2, 3, 18].

The Aoyama group assessed the neurocognitive functions through the Mini-Mental Status Exam (MMSE) without detecting differences between the two arms [2]. However these results are questionable since MMSE is not a useful tool to evaluate neurocognitive damages. Although WBRT improved the LC, Aoyama *et al.* [2] and Patil *et al.* [14] concluded that SRS alone should be considered as a routine treatment due to the low neurocognitive damage, low risk of adverse effects and does not affect the SFI. These evidences favored the usage of SRS.

As conclusion, the addition of SRS to the WBRT improved a litter bit the OS, LC, and the Quality of life with regard to WBRT alone. Some physicians defend the usage of SRS alone since adding WBRT to SRS provokes a deterioration of the neurocognitive function and there are not benefits in the OS with respect to the SRS alone, therefore they prefer to apply repeated SRS or subsequent WBRT in case of progression of the disease [10].

Some authors affirm that LC failure with WBRT alone affect the neurocognitive function more than the WBRT effects [3, 19]. Although the authors of the present study think that WBRT are effective to avoid new lesions but, in spite of that, it has less effectiveness in LC than SRS so we can obtain less neurocognitive damage without WBRT.

It has to be taken into account that SRS could be repeated in the time, (repeated SRS) avoiding the cerebral damage caused by WBRT. However, while SRS is performed in one session, WBRT requires several sessions.

On the other hand, histology should be always considered before to choose any treatment. In fact, several types of lesions have higher frequency of relapse, or are radioresistant, being WBRT not useful.

The comparison between WBRT added to SRS and SRS or SR alone in patients with few BM and

controlled primary tumor, remain controversial. National Comprehensive Cancer Network (NCCN) guides [9] suggest three different therapeutic options to patients with 1-3 resectable metastases and limited systemic disease:

- 1- SR plus WBRT
- 2- SRS plus WBRT
- 3- SRS.

WBRT, SRS or both can be used in case of non resectable lesions. There is no general consensus within the American College of Radiology about the therapeutic recommendation to single brain metastases mainly because of the adverse effect of WBRT on the neurocognitive function.

We have to highlight that HVLt-R is the most frequently used test to evaluate neurocognitive damages in patients with brain metastases, although it mainly measures the memory functions missing others neurocognitive functions.

We consider that neurocognitive functions should be measured with a more comprehensive group of tests since the commonly used tests prove to be incomplete.

CONCLUSION

This retrospective study compares different therapeutic modalities for 1 to 4 brain metastases treatment. However, the optimal treatment is not well defined yet and remains a controversial topic. Further researches should assess some controversial variables we highlighted in order to increase the quality of clinical evidence.

CONFLICT OF INTEREST

None

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