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Refining radiation techniques: Focus on hippocampal sparing WBRT.

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Abstract

Whole brain radiotherapy (WBRT) has been considered the standard treatment in patients with multiple brain metastases. In patients with a limited number of brain metastases, the use of more aggressive treatment, including stereotactic radiosurgery with or without WBRT has been proposed. Moreover, technological improvement allows clinicians to deliver simultaneously WBRT and a boost dose to brain metastases. In the last decades, WBRT has been questioned due to the presumed late decline in neurocognitive functions (NCFs); moreover, several clinical trials found relationships between hippocampal deterioration and NCFs decline after WBRT. New clinical trials are evaluating the use of hippocampal avoidance in WBRT. Nevertheless, the benefit on NCFs deficit remains unclear. Aim of the review is to analyse the role of hippocampal avoidance, the impact of technology and the current clinical trials on going for hippocampal sparing radiotherapy.

Keywords: Brain radiotherapy; Hippocampal sparing; Radiation techniques.

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Introduction

Introduction on the Role of Whole Brain Radiotherapy in the Treatment of Brain Metastases

1. Prognostic classification (GPA and RPA) in patients with good prognosis and brain metastases

Brain metastases (BMs) are the most common intracranial tumors in adults, in fact, about 20-40% of patients affected by cancer will develop brain metastases during their oncological history [1]. Non-small lung cancer (NSCLC) is the most common primary tumor in patients with BMs, which occur in up to 40% of patients [2,3]. Historically, whole brain radiotherapy (WBRT) with or without surgical resection has been considered the standard treatment for solitary BM patients and WBRT alone for those with multiple BMs [4,5]. For instance, WBRT is proposed for brain metastasis/metastases, also, for the setting of prophylactic cranial irradiation (PCI) especially for patients with limited or extensive-stage small cell lung cancer [6]. However, the outcome for such patients remains poor, local control (LC) probability was up to 71% of cases and median overall survival (OS) is estimated to be 4-6 months [7-9].

In the last decades, the implementation in neurosurgical techniques and radiotherapy (RT), including radiosurgery (SRS) or stereotactic fractionated radiotherapy (SRT), has allowed offering more aggressive local treatment to BMs patients in order to increase LC probability and potentially OS. To date, a statistical advantage on OS was reported only for patients with a single BM treated with a combination of WBRT and SRS compared with WBRT alone, while, in patients with more than one BM, WBRT plus SRS showed an advantage in terms of LC probability, intracranial time to progression, performance status improvement and decrease in corticosteroid use [10]. The most common prescribed schedule for WBRT is 30 Gy in 10 fractions for a Biological effective dose (BED) of 39 Gy10. When dose/fractionation was evaluated, stratifying the data by low or high BED dose (the low dose regimens as a BED inferior to 39 Gy10, and high dose as superior to 39 Gy10), none trials demonstrated an improvement in terms of outcomes (LC and OS) [11]. In fact, there is a class I evidence that WBRT with altered dose/fractionation schedules does not result in significant differences in OS, LC or neurocognitive function respect to ‘‘standard’’ WBRT dose/fractionation [11]. To date, unfortunately, no evidences are available to define the impact of tumor histopathology on WBRT treatment outcomes. Only one retrospective study with 75 cases tries to solve this issue, but no statistically significant differences in OS was reported by tumor histology. Nevertheless, it is well recognized that the prognosis was not similar for all patients with BMs [12].

Moreover, nowadays, improvement in technology represented by volumetric modulated arc therapy (VMAT) technique and other rotational intensity modulated radiotherapy (IMRT) associated with the introduction of image guided radiotherapy (IGRT) allows the possibility to offer several treatment options, including surgery, WBRT, and SRS or

some combination thereof. Thus, the subsequently clinical evaluation about the proper treatment(s) for the proper patient is still not so definitive [13].

In the last years, to better understand the role of prognostic factors for BMs patients, the prognostic scores has been aroused increased interest, because they could guide the clinicians for the appropriate clinical decision making. Several indexes exist, including the recursive partitioning analysis classes (RPA), the graded prognostic assessment index (GPA), or the Diagnosis-Specific Graded Prognostic Assessment (DS-GPA) [9,14-17].

In 1997, Gaspar et al. [9] proposed the prognostic index scoring model RPA, evaluating 1200 BM patients, that received RT. Based on RPA scores, patients were classified into 3 classes: class I for patients with age $\leq$ 65 years old, KPS $\geq$ 70, and controlled primary tumor without extra cranial metastasis; class III for patients with KPS score <70; and class II for the other cases. The results showed that RPA classes were associated with prognosis: median survival of patients in class I, II and III were 7.1, 4.2 and 2.3 months, respectively [9,18-21].

Recently, Sperduto et al. [15] based on an analysis of 1960 patients' data collected from 5 randomized RTOG trials, found a new prognostic index (GPA) which takes into account also BM numbers. The rationale for this index derived from the RTOG 9508 results, in which the number of BM correlated with outcome. In fact, the latter trial randomized patients to receive WBRT alone or WBRT plus SRS, showing a statistically significant survival advantage (p=0.04) for patients with solitary BM when treated with WBRT plus SRS, but no such benefit for patients with 1-3 BMs. GPA index analyzed 4 clinical criteria (age, Karnofsky Performance Scale score, number of BMs, and presence/absence of extra cranial metastases) for which a score of 0, 0.5 or 1.0 was given. A GPA total score of 3.5-4.0 had the best prognosis with a median survival of 11 months, while for GPA 0-1, OS was 2.6 months; for GPA 1.5-2.5, 3.8 months and for GPA 3, 6.9 months. Based on this analysis, it has been suggested that prognostic factors and the applicability of prognostic systems could be different by primary diagnosis, thus a site-specific prognostic systems was developed [22].

A retrospective database of 4,259 patients treated for BMs was used to define diagnosis specific prognostic factors. The DS-GPA score was calculated and correlated with the outcomes, stratified by diagnosis and treatment. The original GPA was confirmed in this larger database as the best index for NSCLC and SCLC: based on the DS-GPA score, patients with NSCLC and SCLC and GPA 3.5-4 reported a median survival of 14 and 17 months, respectively [16]. The trial emphasized the heterogeneity of patients with BMs and confirmed that the diagnosis specific prognostic factors indexes correlated with outcome. Moreover, in order to evaluate the proper treatment choice, the usefulness of DS-GPA for the clinicians, in the present treatment scenario, remains undisputed.

2. Neurocognitive deficit in patients with brain metastases and role of hippocampal sparing

Despite the local control of BMs after RT could be useful to stabilizing neurocognitive functions (NCFs) [23], WBRT has been questioned due to its association to late paradoxical decline in NCFs [24]. Clinical complications of RT include acute, delayed and late side effects [25]. Acute and delayed injury may result from RT-induced cerebral edema [26,27] and could be partially due to the oligodendrocyte injury and the subsequently transient interruption of myelin synthesis. Both acute and delayed toxicities may be reversible and recover spontaneously [28,29]. In contrast, the late side effects could be irreversible and progressive. The most severe symptoms are RT-induced necrosis and the possibility of potential progressive NCFs deterioration [30,31]. Moreover, for BMs patients, multiple factors may contribute to NCFs deterioration: disease progression, RT, surgery, chemotherapy, medications (e.g. Anti-epileptic drugs), or paraneoplastic effects, but brain tumour progression seems to adversely affect NCFs more than WBRT dose [32]. However, the exact mechanism of RT-induced learning and memory decline in BM survivors is unclear: probably, it could relate to the limbic system as well as to hippocampus malfunctioning [33].

The hippocampus is believed to be responsible for the formation of verbal memory, so its dysfunction could decrease patient ability to consolidate short-term with long-term memory [34]. RT-induced vascular damage [35] could lead to hippocampus impairment. Additionally, some evidences suggest that impaired hippocampal neurogenesis due to RT [36-39] should be strongly correlated to NCFs impairment [40,41].

Some clinical studies hypothesized that RT-induced damage to neuronal progenitor cells in the subgranular zone of the hippocampi may increase cognitive decline in BMs patients [42,43]. As a result, it has been hypothesized that conformal hippocampal sparing during the course of WBRT would provide meaningful preservation in terms of NCFs [44-47]. Moreover, due to the low incidence of metastases within 5 mm of hippocampi (roundly 3.3%), hippocampal sparing is considered safe [44]. Ghia et al., in fact, analysed 272 BMs patients, suggesting that the use of hippocampal sparing was not associated with a decrease in central nervous system control probability [44]. Recently, a mathematical model is under investigation to calculate the radiation dose distributions near the hippocampi, establishing the benefit in the use of hippocampal sparing approach in whole brain treatment and clinical benefit in terms of outcomes and neurocognitive preservation [45].

To date, thanks to the great advancement in RT techniques, including volumetric-modulated arc therapy (VMAT) and helical tomotherapy, it is feasible to achieve conformal avoidance of the centrally located hippocampus while maintaining uniform dose delivery to the remaining brain tissue [48-50]. In fact, the feasibility of delivering WBRT with hippocampal avoidance for BMs has been reported using different rotation IMRT techniques [51-53]. Aim of the present review is to analyse the role of hippocampal avoidance, the impact of technology and the current clinical trials on-going for hippocampal sparing RT.

3. Technical aspects in hippocampal sparing and whole brain radiotherapy

Traditionally, the use of 3D conformal radiotherapy (3D-CRT) has been considered the standard technical approach in patients with multiple BMs eligible to WBRT. Different publications demonstrated that hippocampal-dependent functions are preferentially affected by RT, and consequently exposing to a risk of NCFs decline [54,55].

Moreover, recent preliminary results from a Phase III trial conducted by Brown et al. (ASCO 2015 oral presentation) confirmed that the combination of WBRT and SRS is associated with a higher risk of NCFs dysfunction [56]. In the last decade relevant technological improvement have been introduced in clinical practice, including IMRT, VMAT, helical tomotherapy, which allow sparing hippocampal structure from high dose of radiation and theoretically to prevent NCFs deficit. Several dosimetric experiences have been published, reporting the feasibility of WBRT, hippocampal sparing with or without simultaneous integrated boost to the BMs.

4. Whole brain radiotherapy and hippocampal sparing

Rong et al. compared the use of three different radiation techniques for WBRT with a dose prescription of 30 Gy in 10 fractions: Step and shoot intensity modulated radiotherapy (IMRT), VMAT, and helical Tomotherapy. All treatment plans were calculated according to the RTOG 0933 criteria. In dosimetric comparisons, Tomotherapy has a significantly superior homogeneity index of 0.15 ± 0.03, while VMAT has the fastest average delivery time of 2.5 min compared to the other modalities (15 min for IMRT and 18 min for Tomotherapy). Analysing hippocampal avoidance, Tomotherapy was superior to IMRT and VMAT in terms of mean D100% with a dose of 8.0 Gy, 8.7 Gy and 8.6 Gy respectively. Moreover, VMAT had a significantly lower Dmax (13.6 Gy) when compared to Tomotherapy ($p<0.001$) and IMRT ($p<0.05$) in terms of average hippocampal doses [57].

Different results have been published by Gondi et al., 5 patients were considered for a planning study, based on helical Tomotherapy and Linac-based IMRT with a dose prescription of 30 Gy in 10 fractions to whole brain. Analysing helical Tomotherapy approach, hippocampus received a median dose and maximum dose of 5.5 Gy and 12.8 Gy respectively, while Linac-based IMRT reported a median dose of 7.8 Gy and maximum dose of 15.3 Gy. In particular, normalizing to 2 Gy fractions, the mean dose to the hippocampus was reduced by 87% using helical Tomotherapy and by 81% using Linac-based IMRT. In terms of brain target coverage and target homogeneity, there were acceptable with both approaches, though a more rapid dose fall-off was obtained in helical Tomotherapy [48].

Marsh et al., using Tomotherapy techniques, studied the sparing of limbic circuit in WBRT treatment and PCI. Dose prescription was 35 Gy/2.5 Gy per fraction in WBRT and 30 Gy/2 Gy per fraction in PCI, respectively. Authors reported a mean dose and equivalent uniform dose to the hippocampus of 17.9 Gy/20.74 Gy in WBRT and 12.5 Gy/14.23 Gy in PCI and good results in terms of brain target coverage [58].

Lee et al. selected 3 patients evaluating the use of VMAT and IMRT approach. Both treatment plans obtained a hippocampal sparing with whole brain, though VMAT approach was associated with a more homogenous dose distribution to the PTV, decreasing the maximal dose to the target [59].

A recent publication by Kim et al. studied the use of inclined head positioning to facilitate dose distribution during WBRT and hippocampal sparing, using VMAT approach. Dose prescription was 30 Gy in 10 fractions to the whole brain and maximum dose to the hippocampi was limited to 16 Gy. Interesting results in terms of whole brain target coverage and hippocampal sparing have been obtained with the use of inclined head position approach compared with non-inclined head position [60].

5. Whole brain radiotherapy, simultaneous integrated boost and hippocampal sparing

Gutiérrez et al. evaluated in 10 patients the planning feasibility of WBRT with simultaneous integrated boost (SIB) using a single helical Tomotherapy plan [61]. Whole brain dose prescription was 32.25 Gy in 15 fractions, while boost prescription, according to brain metastases diameter, were 63 Gy and 70.8 Gy respectively. The mean dose to the hippocampus was approximately 6.0 Gy. Authors obtained good results in terms of homogeneous dose distribution to the whole brain when compared to 3D-CRT and dose distribution to brain metastases and conformal hippocampal avoidance. Hsu et al. evaluated the feasibility of VMAT-WBRT approach, hippocampal avoidance and simultaneous integrated boost in 10 patients in one to three brain metastases. The whole brain prescription dose was 32.25 Gy in 15 fractions, while and SIB doses were respectively 63 Gy to lesions ≥ 20 mm and 70.8 Gy in all other lesions. The mean hippocampal dose (normalized total dose Gy2) was 5.23 Gy and adequate target coverage to the whole brain and metastases have been obtained. Moreover, this experience confirmed the limited treatment time with the use of VMAT (<4 min) [52].

Prokic et al. compared the use of WBRT–SIB and WBRT sequential SRS associated with hippocampal sparing with VMAT technique. The study enrolled 10 cases with 57 BMs (range 2-8). The dose prescription was: 30 Gy (EQD2=31.25 Gy) on WBRT and 51 Gy (EQD2=60.56 Gy) on BM–SIB in 12 fractions. The results reported a HI on WBRT: 0.54 ± 0.04 and TC 0.96 ± 0.01. HI on brain metastases was 0.11 ± 0.02and TC 0.95 ± 0.01. Mean dose to hippocampus was 7.55 ± 0.62 Gy. The use of SIB achieved better sparing of the hippocampus compared with sequential approach [50].

Kim et al. reported a clinical study of 11 patients with 70 BMs (range 2–15) treated with hippocampal sparing WBRT-SIB. Median brain metastases volume was 0.235 cc (range 0.020-10.140 cc). The dose prescription was 25-28 Gy on WBRT (EQD2=26.04 Gy-28 Gy) and 30-42 Gy on BMs (EQD2=32.5 Gy-45.5 Gy) in 10-14 fractions. On whole brain, HI was 0.52 ± 0.16, TC 0.89 ± 0.05; while on BMs, HI was 0.17 ± 0.04, TC 0.99 ± 0.02 and CI 0.48 ± 0.16. Mean dose on hippocampus was 13.65 Gy. After a median follow-up of 14 months, a complete remission was observed in 33% of lesions and a partial response in 45%

with a 65% reduction of tumor volume. The study did not report any data about neurocognitive functions [62]. Awad et al. analysed in 35 patients the use of VMAT treated with WBRT with hippocampal avoidance, SIB or both. WBRT was prescribed in 23 patients with a median dose of 30 Gy, whole the median dose to brain metastases was 50 Gy (range: 20-70.8 Gy), delivered in a median of 15 fractions. The mean hippocampal dose for these patients ranged from 4.3 to 18.0 Gy and the maximum dose ranged from 8.4 to 32.2 Gy [63]. Giaj-Levra et al. evaluated the feasible of VMAT-WBRT with SIB and hippocampal sparing in 10 patients with BMs. A hypofractionated dose prescription of 20 Gy to the whole brain and 40 Gy in 5 fractions to BMs was prescribed. Mean and maximum doses to hippocampus were 7.7 Gy and 10.5 Gy. For WBRT mean dose to 90% was 19.8 ± 0.2 Gy, mean HI 0.42 ± 0.12 and target coverage 0.78 ± 0.11. A phase II trial is ongoing to establish the clinical impact of this approach [54].

In conclusion, according to the literature, all modern radiotherapy approaches are able to guarantee acceptable target coverage to the brain and metastases with hippocampal sparing. In particular a slight superiority in terms of target homogeneity has been reported in Chemotherapy approach, while treatment time delivery was less with VMAT.

6. Quality of life and Neurocognitive preservation after whole brain radiotherapy and hippocampal sparing

Initial results on the impact in neurocognitive preservation and quality of life of hippocampal avoidance in patients treated with whole brain radiotherapy have been reported in the literature. In the phase II clinical trials (RTOG 0933), Gondi et al. reported no alteration in quality of life and a significant lower neurocognitive impact in patients treated with hippocampal avoidance and WBRT with a mean relative decline of 7% (C.I. -4.7% to 18.7% - $p<0.001$) compared to the historical control [47].

More recently, Tsai et al. analysed in 40 patients, the impact of the delivery of WBRT associated with hippocampal sparing, using VMAT techniques. The prescribed dose was 25 Gy in 10 fractions for prophylactic brain irradiation or 30 Gy delivered in 10 to 12 fractions for therapeutic or adjuvant WBRT. The corresponding EQD2 values of 0, 10, 50, 80 % irradiating the composite hippocampal structure with <12.60 Gy, <8.81, <7.45 Gy and <5.83 Gy respectively were significantly associated with neurocognitive preservation [64]. The phase II/III clinical trial-NRG (National Surgical Adjuvant Breast and Bowel Project, Radiation Therapy Oncology Group, and Gynecological Oncology Group) CC (Cancer Control) 003 and the phase III clinical trial NRG-CC001 are going to define the impact of WBRT and hippocampal avoidance in terms of quality of life and neurocognitive preservation.

Future Directions

The use of SRS and SFRT represents an intriguing approach in patients with multiple brain metastases in order to maximize locale control and prevent the potential neurocognitive dysfunction associated to WBRT. A multi institutional Japanese trial compared the use of SRS alone to WBRT and SRS [10,24].

The study enrolled 132 patients with one to four metastases and comparing SRS and WBRT group, the median survival time was not statistically significantly higher in the SRS alone treated patients (7.5 vs. 8 months; $p=0.42$). Furthermore, using the Mini-Mental State Examination, the authors showed a greater average time until neurocognitive decline in the WBRT and SRS group compared with SRS alone (16.5 vs. 7.6 months; $p=0.05$). These results suggested that the neurocognitive decline in SRS alone group was correlated to an intracranial disease recurrence/progression that could be reversed by salvage therapy (WBRT). On the other side an upfront use of WBRT and SRS was correlated to a better intracranial control of brain metastases at the expense of potential and irreversible neurocognitive decline in some patients.

A phase III study evaluated neurocognitive outcomes for patients with one to three brain metastases randomized to SRS alone or WBRT and SRS [65]. A total of 58 patients were accrued and the trial was stopped early because interim analyses showed that patients treated with SRS and WBRT reported a statistically significantly propensity to show cognitive decline and memory deficits, using the Hopkins Learning Test-Revised, compared with patients treated with SRS alone (52% and 24%, respectively). Moreover, 1 year survival was higher for the SRS alone group than for patients in the SRS and WBRT group (63 and 21%, $p=0.003$) and authors concluded that SRS alone and close clinical monitoring were acceptable to preserve long-term memory and cognitive abilities.

The European Organization for Research and Treatment of Cancer (EORTC) conducted a randomized controlled trial - 22952-26001 - to evaluate whether adjuvant WBRT increased functional independence and quality of life in patients previously treated for brain metastases with SRS or surgical resection [66].

WBRT arm had a statistically significant detriment in quality of life score and also had lower cognitive function at 8 weeks and 1 year, even though only a 45% completed the tests at 1 year. The results of current studies about the effects of WBRT on neurocognitive functions and the role of SRS treatment in patients with limited brain metastases opened the relevant issue about the use of local treatment in 4-10 brain metastases setting. The rationale of the use of WBRT in patients with multiple brain metastases is to eliminate the microscopic spread not detectable by Magnetic Resonance Imaging. American Society for Therapeutic Radiation Oncology (ASTRO) had confirmed the role of SRS treatment in patients with a limited number of brain metastases [67]. Moreover, National Comprehensive Cancer Network (NCCN) proposed SRS treatment in patients with a limited brain metastases presentation, without a specific recommendation in the maximum number [68].

Recently, Yamamoto et al. published a multi-institutional prospective study, analyzing the role of SRS in patients with multiple brain metastases from 1 to 10. This study enrolled over 1100 and patients have been divided in single brain metastases, 2 to 4 metastases and 5 to 10 metastases. Median survival for the three groups was: 13.9 months in the single

metastasis, 10.8 months in those with 2-4 and 5-10 lesions (p=0.0004). The risk of intracranial progression (new sites) was lower in the single brain metastases group compared to the others (p<0.0001) and overall survival was comparable between patients with 2-4 brain metastases and with 5-10 [69]. Moreover, analyzing neurocognitive preservation, assessed by Mini Mental State Examination no treatment-related adverse events for patients with two to four and five to 10 lesions was reported. The North American Gamma Knife Consortium is prospective randomized trial with the goal to establish the impact of SRS treatment on neurocognitive function for patients with more than 5 metastases (ClinicalTrials.gov NCT01731704).

Conclusion

The eternal debate in regard to the optimal radiation approach for brain metastases, especially in case of multiple intracranial lesions, remains unresolved. Available literature data evidenced a potential detrimental effect of WBRT in neurocognitive functions. Nevertheless, WBRT alone or in association to focal aggressive treatment represents a milestone of treatment strategy for metastatic intracranial disease. Technical advancements in radiation therapy, including several intensity modulated techniques are now able to obtain dose painting in strategic areas and hippocampi sparing seems to be a feasible and a promising option for selected cases where optimal intracranial control needs to be assured but neurocognitive decline is to be minimized. Further studies in this direction can confirm the value of hippocampal sparing techniques in clinical practice.

Conflicts of Interest

The author has no conflicts of interest to declare.

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