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RESEARCH ARTICLES

Radiosurgery and whole brain therapy in the treatment of brainstem metastases

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Abstract
Purpose The incidence of brainstem metastasis (BSM) accounts for 1–3% of brain metastases (BM). They are often associated with multiple BM and produce significant neurological symptoms. We retrospectively analyse the results of treatment with stereotactic radiosurgery (SRS).
Methods and material We included the medical records of 28 patients aged 52.86±11.29 years; 17 (60.7%) were women. The most frequent primary tumours were breast (*n*=11), lung (*n*=9) and melanoma (*n*=4). A total of 30 BSM were treated with radiosurgery (SRS) with a linear accelerator (Linac Scalpel, University of Florida). The 3D planning was with image fusion.
Results The mean time from the diagnosis of the primary tumour to the BM was 3±3.35 years; 5 cases were diagnosed simultaneously. Twenty-seven patients (96.4%) received whole brain radiotherapy, 19 before SRS and 8 after. The most usual dose was 30 Gy. Three patients underwent another SRS for other BM. The medium volume of BSM was 1.86±2.31 cc. The mean prescribed dose was 1114.33±315.6 cGy. The tumour volume did not change significantly with SRS but there was neurological improvement in 13 patients (41.9%). Twenty-four patients (85.7%) died, 22 (78.5%) due to the primary tumour: 12 cases (42.8%) due to progression of BM, 1 case due to progression of BSM and 10 due to local tumour progression or extra-cerebral metastases. Mean survival from diagnosis of BM was 22.8±32.4 months and from SRS of BSM, 16.8±31.56 months (1 month to 13.54 years).
Conclusion The combined treatment of SRS and whole brain radiotherapy treatment is effective in the control of BSM (only one patient died due to progression of BSM), improving the neurological symptoms in 41.9% of patients; therefore an early diagnosis and treatment is important. Many patients die due to causes other than the BSM.

Keywords Brainstem metastasis · Stereotactic radiosurgery

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Introduction

Since MRI has become routine in the follow-up of patients with brain metastases (BM), more asymptomatic lesions have been diagnosed and consequently the number of asymptomatic BSM being diagnosed has increased.

Between 20% and 40% of patients with cancer develop BM in the course of their disease. The most common primary tumours are lung cancer, breast cancer and gastrointestinal tumours. The majority (85%) of BM are located in the brain hemispheres, 10–15% in the cerebellum and 1–3% in the brainstem [1]. The most important prognostic factors in

patients with BM include, age, performance status, number of lesions and whether there is extracranial disease. The Radiation Therapy Oncology Group (RTOG) has developed three prognostic classes using recursive partitioning analysis (RPA), which is associated with survival [2].

BSM are often associated with multiple BM and produce significant neurological symptoms, mainly affecting the long pathways and the cranial nerves. Surgical treatment in this location involves a high morbidity and mortality. Treatment with stereotactic radiosurgery (SRS) with or without whole brain radiotherapy is another therapeutic option, but given the low incidence in this location, there are not many series published on this either. The objective of this study is to analyse our experience in the treatment of BSM with SRS and whole brain radiotherapy.

Methods and material

An analysis was made of 28 patients with 30 BSM, treated with SRS, from June 1993 to September 2006.

The mean age was 52.86±11.29 (range 33–73 years). There were 17 (60.7%) female patients and 11 (39.3%) males. The primary tumour was breast cancer in 11 cases (39.3%), lung cancer in 9 cases (32.1%), melanoma in 4 cases (14.3%), and in one case each (3.6%), Ewing sarcoma, cervical cancer, ovarian cancer and adenocarcinoma of unknown origin. The oncology treatment was standard, depending on the tumour type and the stage of the disease, which was generally multidisciplinary with surgery, chemotherapy, radiotherapy, hormone therapy and/or immunotherapy.

The symptomatology previous to the diagnosis of BM often included several symptoms, depending on the location, such as long pathways involvement in 14 patients (50%), cerebellar syndrome in 11 patients (39.3%), cranial nerve involvement in 9 patients (32.1%), migraine in 7 patients (25%), higher cognitive changes in 4 patients (14.3%) and behavioural changes in 1 patient (3.6%). One patient was asymptomatic.

In 13 of the cases (46.4%) there was only one BM located in the brainstem, with the rest of the patients having several brain lesions, from 2 to 7; 2 lesions in 6 cases (21.4%), 3 lesions in 5 cases (17.8%), 4 lesions in 1 case (3.5%), 6 lesions in 1 case (3.5%) and 7 lesions in 2 cases (7.14%).

There were a total of 64 BM, of which 30 were brainstem, located in: pons 20 lesions (66.7%), upper brainstem 8 lesions (26.7%) and medulla oblongata 2 lesions (6.6%). In 3 cases the brainstem metastasis (BSM) developed after the diagnosis and treatment of BM. The time from the diagnosis of the BM to the diagnosis of BSM was 14 months, 16 months and 41 months in three patients; in the rest of the patients they were diagnosed simultaneously. Two patients presented 2 metastases of the brainstem.

In all patients, the SRS treatment was performed with a linear accelerator, with a high precision positioning system with mechanical fixation by tertiary collimator, SRS200 system (University of Florida), with photons of 6 MV. To locate the lesion, MR images were obtained; the stereotactic frame was positioned under local anaesthetic, in order to perform the planning of CT scans. An image fusion program was used to delineate the planning target volume. Treatment planning was made in 3D in all cases, but using different planners throughout the period of the study (BRAIN LAB, PLATO-Nucletron, ERGO-3D Line, PINACLE and Adac-Philips).

After performing the SRS treatment, all the patients received prophylaxis with dexamethasone and remained in hospital for 24 h. Follow up was carried out with MRI every 3 months.

The most usual dose in the whole brain radiotherapy was 30 Gy, with 3 Gy per fractions and 10 fractions, and rest during weekends.

The SPSS program version 12.0 was used for the statistical analysis. Given the sample size, no parametric tests were used for between-group comparisons. The Kaplan–Meier method was used for the survival curves.

Results

The BM were diagnosed simultaneously with the primary tumour in 5 cases (17.8%), 4 cases corresponding to lung cancer and 1 case to an adenocarcinoma of unknown, but probably lung, origin. In the rest of the cases the BM appeared during follow up of the disease. The mean time from the diagnosis of the primary tumour to diagnosing BM was 3±3.35 years (range from 0 to 12.67 years). The mean time from the diagnosis of BM to the diagnosis of BSM was 0.44±0.69 years (range from 0 to 3.52 years)

At the time of diagnosis of the BSM, 24 patients (85.7%) had a locally controlled primary tumour and 9 patients (33.3%) had a metastasis in one or several extra-cerebral locations (bone metastases 6 patients, hepatic 4 patients, lung 4 patients and ganglionar 2 patients).

External whole brain radiotherapy treatment (WBRT) was applied in 27 patients (96.4%): before SRS in 19 cases (67.8%) and after in 8 cases (28.6%). Three patients with small cell lung cancer had received prophylactic cranial irradiation, as part of their initial radical treatment, with a total dose of 20–24 Gy with 5 fractions of 200 cGy per week. In the remaining 24 patients, whole brain radiotherapy was performed as treatment of BM, in 21 cases as palliative (total dose 30 Gy with 10 fractions of 300 cGy in 19 cases, or 20 Gy with 5 fractions of 400 cGy in 2 cases) and in 3 cases as radical, treatment (40–46 Gy dose in conventional fractions). The majority of WBRT has been made out of our hospital, different doses has been carried out.

Surgical extirpation of a non-brainstem cerebral metastasis was performed on 2 patients before radiosurgery. Radiosurgery was also performed on the other brain metastatic lesions in 3 patients.

A total of 30 brainstem metastatic lesions were treated with SRS. The mean lesion volume before treatment was

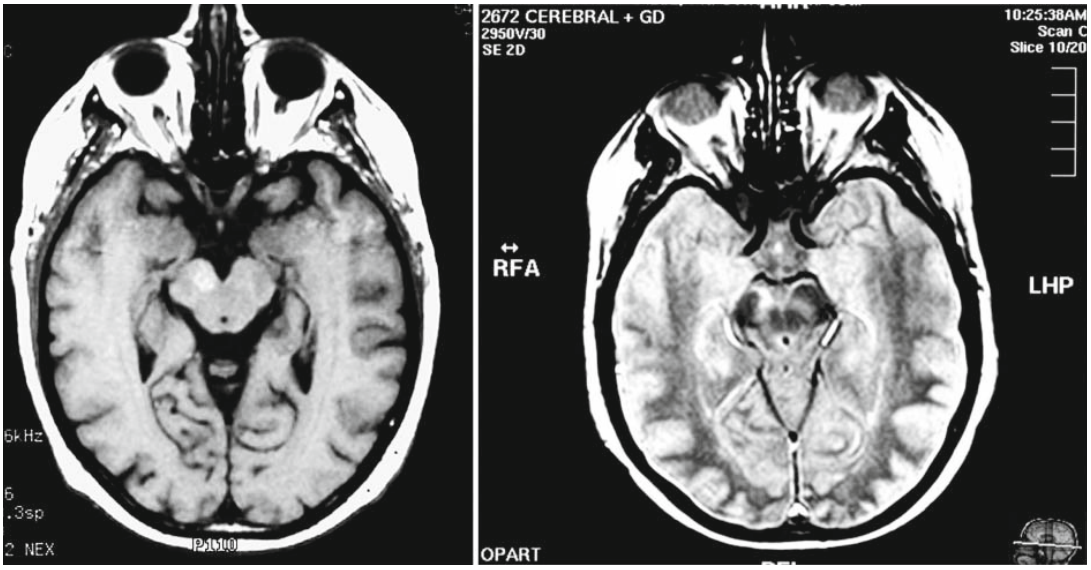

Fig. 1. Magnetic Resonance image in October 2003 *(left)* and August 2009 *(right)*

1.86±2.31 cc (from 0.01 to 7.78 cc). The mean prescribed dose was 11.14±3.156 Gy (range 5–20 Gy) at an isodose of 89.6±1.8% (range from 80 to 90%). The mean maximum dose was 12.72±3.698 Gy (range from 5.57 to 22.28 Gy). Of the 30 lesions, 29 were treated with 1 isocentre and one lesion with 2 isocentres. A collimator was used in 26 lesions and 2 were used in 4 lesions. The prescribed dose completely covered the tumour volume in 25 cases (80.6%).

The mean final volume of the brainstem lesions was 1.94±2.21 cc (range from 0 to 5.06 cc). No statistically significant differences were observed compared to the initial volume. The progression of one of the patients can be observed in Fig. 1.

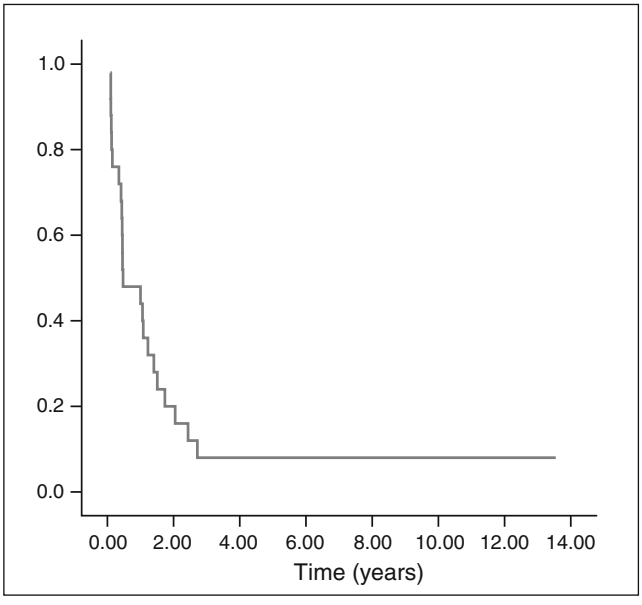

Fig. 2. Survival curve from the diagnosis

The initial clinical symptoms improved with treatment in 13 patients (46.4%) and progressed in 5 (17.8%). No toxicity associated with SRS was observed.

During the follow-up period, 5 patients (16.1%) developed new BM. There were 24 (85.7%) deaths, 2 patients are still alive and 2 patients were lost. Twenty-two (78.5%) of 24 patients had died from the tumour and 2 by other causes: 1 case due to toxicity to chemotherapy and a heart attack in the other. Of the 22 patients who died due to tumour progression, the cause of death was brain tumour progression in 12 cases (42.8%), only in one patient was it due to progression of the BSM and in the 10 remaining patients death was associated with the progression of an extra-cerebral metastatic tumour or local progression of the primary tumour.

The mean survival from diagnosis of the BM was 22.8±32.4 months (range from 3.48 months to 13.62 years). The mean survival from SRS treatment of the BSM was 16.8±31.56 months (range from 1 month to 13.54 years). The survival curve after treatment with SRS is shown in Fig. 2.

Discussion

WBRT [3] has been used for decades as the standard treatment for BM. Since radiosurgery has been used widely in the treatment of brain lesions, many studies have demonstrated the positive influence of combine treatment on clinical status and the survival of those patients. From the randomised and meta-analysis [1] studies currently available, the following conclusions can be drawn: (1) In patients with a single BM, with a good performance status with no evidence of extracranial disease, surgical extirpation followed by WBRT improves survival compared to radiotherapy alone. (2) The use of altered fractionation in WBRT does not improve survival or neurological function compared with standard fractionation schemes. (3) The use of WBRT

and boost with SRS improves survival compared to WBRT alone in selected patients with a single BM (RTOG 9508) [4]. (4) No benefit in survival is obtained with the use of WBRT and boost with SRS vs. WBRT alone in patients with multiple BM, although this treatment improves local brain tumour control and the quality of life in patients with 2 or 4 metastases [4]. (5) The use of WBRT plus SRS does not improve survival compared to SRS alone in patients with 1–4 metastases, but it decreases intracranial recurrences and rescue treatments [5].

As regards the role of SRS in the treatment of BM, ASTRO has published an evidence-based review, which reaches the same conclusions [6].

As many patients with BM are not suitable candidates for surgery, as is the case for metastases located in the brainstem, SRS emerges as a very effective alternative. The primary objective of SRS, as a combine treatment with WBRT, is to improve the control of the local brain tumour, and in selected patients, those with a single metastasis, at the same time lead to improve the survive. In the randomised study by Kondziolka et al. [7] comparing WBRT with or without an SRS boost in patients with 2–4 metastases, the local failure at one year in the treated with WBRT alone was 100% compared to 8% with an SRS boost; the mean time to local failure was 6 months vs. 36 months. In patients with 4 or more BM, Bhatnagar et al. [8], in a retrospective study, reported that treatment with SRS alone, in combination with WBRT, or as a rescue treatment to WBRT, appears to improve survival compared with a historic series in which the treatment was only WBRT.

The choice of BM treatment depends on prognostic factors: age, performance status and location of the primary tumour, the RPA classification defined by RTOG [2] being of great use.

In our series, 13 patients (46.4%) had a single BM (located in the brainstem) and only 3 cases (17.8%) had more than 4 BM; the majority of patients, 22 (78%), were less than 65 years, 24 patients (85.7%) had their primary tumour controlled at the time of the diagnosis of the BSM and 9 patients (33.3%) had extra-cerebral metastases. We were unable to use the RPA classification as a Karnofsky score was not available in all patients, but in those that it mentions in the history it was >70% in all cases.

BSM are rare; there are few publications on this subject. Hussain et al. [9] have recently published their experience of treatment with SRS with a gamma-knife in 22 patients, a series very similar to ours. In their series the patients received a mean dose of 16 Gy (range 14–23 Gy) at an isodose of 50% in the majority of patients, higher than ours, which was 11.14 Gy (range 5–20 Gy) at an isodose of 90% in the majority of cases. This is because 27 patients in our series (96.4%) also received WBRT treatment, while in the Hussain et al. series only 3 patients received it. They achieved local control in all patients, whereas in our series only one patient had a progression of the BSM, which was the cause of death. In our study patients received SRS with a linear accelerator, with a high-precision positioning system with mechanical fixation by the tertiary collimator, SRS200 system (University of Florida), with an accuracy of 0.2±0.1 mm, comparable with the gamma-knife accuracy. Hussain et al. [9] reported a mean survival of 8.5 months from treatment with SRS, whereas in our series it was 16.8 months, although we do have one patient with a survival of 13.54 years. If we exclude this patient the mean survival was 11.16 months.

The initial clinical symptoms improved after treatment in 13 patients (46.4%), with no appearance of associated toxicity. Of the 22 patients who died due to tumour progression, the cause of death was cerebral tumour progression in 12 cases (42.8%). Only in one patient was it due to progression of the BSM. In the remainder, death was associated with extra-cerebral tumour metastatic progression or local progression of primary tumour. Therefore, SRS is a minimally invasive technique that may help to improve the quality of life in these patients, who often die due to extra-cerebral tumour progression.

Conclusions

Combined treatment, SRS and WBRT is effective in the local control of BSM, improving the neurological symptoms in 41.9% of patients. In those treatments, it is essential to reduce the dose to minimise treatment toxicity. The favourable effects of SRS are often limited by the progression of the systemic disease, which determines the survival in many of these patients. Extra-cerebral tumour control is increased with improvements in systemic therapies; therefore it is very important to increase local control of BM and in this sense SRS could play a significant role.

Conflict of interest The authors declare that they have no conflict of interest relating to the publication of this manuscript.

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