Guidelines for the treatment of central nervous system metastases using radiosurgery

Diretrizes para tratamento de tumores metastáticos de sistema nervoso central com radiocirurgia

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The Guidelines Project, an initiative of the Brazilian Medical Association, aims to combine information from the medical field in order to standardize procedures to assist the reasoning and decision-making of doctors.
The information provided through this project must be assessed and criticized by the physician responsible for the conduct that will be adopted, depending on the conditions and the clinical status of each patient.

Grades of recommendation and levels of evidence

- **A:** Experimental or observational studies of higher consistency.
- **B:** Experimental or observational studies of lower consistency.
- **C:** Cases reports (non-controlled studies).
- **D:** Opinion without critical evaluation, based on consensus, physiological studies or animal models.

Objective

The purpose of this guideline is to evaluate the radiosurgery technique for the treatment of patients with central nervous system (CNS) metastatic tumors.

Description of evidence collection method

Through the elaboration of six relevant clinical questions related to the proposed theme, we sought to present the main evidence regarding safety, toxicity and effectiveness of radiosurgery in the treatment of CNS metastases. The study population consisted of male and female patients of all ages, with metastatic CNS cancer independent of histological type and presence or absence of comorbidities. For this, a systematic review of the literature was carried out in primary scientific databases (Medline – PubMed; Embase – Elsevier; Lilacs – Bireme; Cochrane Library – Record of Controlled Trials). All articles available through Thursday, April 2, 2015 were considered. The search strategy used in Medline searches is described in Appendix 1. The articles were selected based on critical evaluation, seeking the best evidence available. The recommendations were elaborated after discussion with the elaboration group composed by three members of the Brazilian Society of Radiotherapy. The guideline was reviewed by an independent group, which specializes in evidence-based clinical guidelines. After completion, the guideline was released for public consultation for 15 days, the suggestions obtained being forwarded to the authors for evaluation and possible insertion in the final text.

Introduction

Brain metastases are the most frequent intracranial tumors in the adult population. It is estimated that 6 to 30% of patients diagnosed with malignant systemic disease will have cerebral metastases at some point in their natural progression.[1-3]

In recent years, the incidence of brain metastasis has been increasing mainly due to the implementation in clinical practice of cranial magnetic resonance imaging (MRI), which has good accuracy in detecting early neoplastic lesions in the CNS. In addition, there was a significant improvement in the control of extracranial disease, something associated with the use of new systemic therapies available for the treatment of several cancers.[4-6]

In the adult population, the primary tumors most frequently related to the development of CNS metastases are lung, melanoma, kidney, breast and colorectal cancer.[7]

Regarding pathogenesis, CNS metastases are most commonly due to hematogenous spread. Metastases are usually located directly at the junction of the gray matter and white matter where the diameter of the blood vessels is reduced favoring the clusters of tumor cells; 80% of metastases appear in the cerebral hemispheres.[8]

Clinical manifestations vary according to the number, volume, and location of CNS metastases. The main symptoms described are headache, nausea, vomiting, focal neurological dysfunction and cognitive dysfunction.[9]

Local treatment for CNS metastases depends primarily on the prognosis of the clinical condition and age of the patient. There are several tools available to aid in the classification of patients with brain metastasis regarding prognostic factors and their possible impact on median survival. These tools may therefore facilitate the decision of the most appropriate local treatment for cancer.[10,11]

For patients considered to have poor prognosis, treatment should be focused on the control of symptoms caused by cerebral metastasis aimed at maintaining neurological functioning and quality of life. For those with good prognosis, local treatment should aim to eradicate and control metastatic CNS disease. In this scenario, the options available are surgical resection and radiotherapy (whole brain radiotherapy or radiosurgery), either alone or combined.

Radiosurgery is a radiotherapy technique that is capable of delivering high doses of radiation at pre-defined small target volumes. It is a complex technique that utilizes multiple treatment fields (coplanar and non-coplanar beam plans) that converge to the desired target(s), allowing adjacent healthy tissues to be significantly spared and treatment to be performed quickly, non-invasively and safely.[12]

1. What is the toxicity of radiosurgery for brain metastases?

Toxicity after the use of radiosurgery is generally low. Patients are unlikely to have side effects that negatively impact their quality of life.

Fokas et al. showed levels of acute toxicity grade 3 (headache, nausea and vomiting) as low as 3% in patients undergoing radiosurgery. Similarly, rates of chronic toxicity grade 3 (alopecia, headache, motor and neurocognitive deficits, visual and auditory deficits) of only 6% were observed.[13] (**B**)

Kim et al. used the Common Terminology Criteria for Adverse Events, version 3.0 to measure the toxicity of 58 patients who underwent radiosurgery for the treatment of CNS metastases. Ten patients had some degree of toxicity identified (five patients with grade 1 toxicity, one patient with grade 2 toxicity, and four patients with grade 3 toxicity). The events observed included headache, vertigo, hemiparesis, visual acuity deficit or cerebral necrosis.[14] (**B**)

Flickinger et al. demonstrated that only four patients out of 116 evaluated developed perilesional edema with worsening of neurological symptoms requiring the introduction of supportive therapy with steroids. Of the entire cohort of patients, intracranial tumor hemorrhage occurred in only three (2.5%) patients.[15] (**B**)

Lim et al. conducted a randomized phase 3 clinical trial with patients diagnosed with non-small cell lung cancer with 1 to 4 brain metastases who underwent radiosurgery followed by chemotherapy, or chemotherapy alone. Treatment with radiosurgery was well tolerated and there was no difference in neurocognitive function between the two study groups.[16] (**A**)

Even when the tumor is located in critical areas, radiosurgery is feasible. Luther et al. observed that motor function improves by 31% or remains stable in 50% of patients with brain metastases located in the motor cortex treated with radiosurgery.[17] (**B**) Other authors have evaluated the role of radiosurgery in patients with brainstem metastases. Asymptomatic perilesional edema occurred in 4%, while 2.4% of the patients developed tumor hemorrhage at the treatment site.[18,19] (**B**)

Recommendation

Radiosurgery has low morbidity and is associated with low rates of side effects.

2. What is the maximum number and size of metastatic lesions in the brain for radiosurgery treatment to be performed?

Empirical doses and volume thresholds were established for single dose radiosurgery in order to minimize the risks of side effects. Existing recommendations define up to four lesions and a maximum diameter of 4 cm as the ideal group for the indication of primary radiosurgery, or dose boost after whole brain irradiation[20-23] (**A**) (Table 1). Nevertheless, there are retrospective series of patients with up to 15 metastatic lesions treated with radiosurgery who had clinical progression, complications and responses similar to those treated with up to four lesions.[24,25] Some authors suggest that total tumor volume is more important than the absolute number of lesions,[26-28] but this statement requires further investigation. (**B**)

TABLE 1 Main studies recommending adequate number and size of lesions to indicate radiosurgery.

Study	Grade of recommendation	Number of lesions	Size (diameter)
RTOG 90-05[23]	A	1	< 4 cm
RTOG 95-08[20]	A	1-3	3 cm
Kondziolka[21]	A	2-4	≤ 25 mm
Mehta[22]	A	3-4	4 cm

Recommendation

Radiosurgery should preferably be performed in patients with up to four lesions and a maximum diameter of 4 cm.

3. What are the advantages of radiosurgery compared to whole brain radiotherapy?

Radiosurgery has the advantage of offering a more conformed and localized treatment, with larger ablative doses than whole brain radiotherapy.[29-32]

Thus, it minimizes the deleterious effects of whole brain radiotherapy with regard mainly to neurocognitive deficit and declining quality of life.[22,30,32-34] (**A**)

Another important point is that radiosurgery offers higher rates of local control, even in patients with histologically radioresistant tumors (requiring higher doses of ionizing radiation, e.g., melanoma, renal tumors, and sarcoma) compared with whole brain radiotherapy.[35,36] (**B**)

Recommendation

Radiosurgery decreases the risk of neurocognitive decline and can positively impact the patients' quality of life.

4. What is the effectiveness of radiosurgery in the approach of patients with brain metastases?

Radiosurgery alone for the treatment of brain metastases produces local control rates ranging from 65 to 94%.[15,37,38] (**B**)

The main factors related to local control after radiosurgery are: characteristics of tumor lesion and treatment dose. Doses lower than 14 Gy and cystic and necrotic lesions are associated with a greater likelihood of recurrence.[39,40] (**B**)

The efficacy of radiosurgery does not depend on the histological type of the primary tumor since local control rates are similar in both radiosensitive and radioresistant tumors.[41-43] (**B**)

Recommendation

Radiosurgery is effective for the treatment of patients with brain metastases, even in those with histologically radioresistant primary tumors.

5. What are the benefits and disadvantages of performing two treatment modalities involving radiosurgery and whole brain radiotherapy in patients with brain metastases?

There have been some randomized phase 3 trials evaluating the use of radiosurgery (RS) associated with whole brain radiotherapy (WBRT) or WBRT alone in patients with brain metastases and limited disease (1 to 4 intraparenchymal lesions).[20,21]

Aoyama et al. reported a 12-month CNS recurrence rate of 46.8% for the WBRT+RS group and 76.4% for RS alone ($p<0.001$), and 73 and 89% ($p=0.002$) of local control for the RS and WBRT+RS groups, respectively. However, there was no difference in overall survival between groups.[29] (**A**)

Chang et al. reported that patients treated with WBRT+RS have a rate of learning decline and mean functional memory of 52 versus 24% in the RS group. Although brain metastasis-free survival rates at one year were higher in the WBRT+RS (73%) than in the RS (23%) group, there was no difference in overall survival and RS patients were easily rescued with new therapy.[30] (**A**)

Brown et al. presented data according to which the addition of WBRT to RS, despite improving local control (50.5 x 84.9% at one year with RS alone and WBRT+RS, respectively), did not lead to an increase in overall survival and was negatively correlated with some cognitive decline, especially for memory, verbal fluency and immediate memory in the WBRT+RS group ($p<0.05$).[44] (**A**)

In a systematic review that included the meta-analysis of individual data from randomized clinical trials, the authors noted that in patients aged less than 50 years, with 1 to 4 lesions and good performance, the use of RS alone led to longer overall survival, whereas the initial omission of WBRT did not produce any more failures in CNS.[45] (**A**)

In addition, despite worse local control rates and higher rates of salvage treatment, RS proved in the economic analysis to be more cost effective than WBRT+RS.[46] (**B**)

Recommendation

The addition of whole brain radiotherapy in patients treated with radiosurgery allows greater intracranial local control, despite no positive impact on overall survival. The use of whole brain radiotherapy may be related to worsening of cognition, verbal function and memory.

6. After surgical resection of brain metastases, is there a role for adjuvant radiosurgery in the surgical bed?

In the postsurgical adjuvant scenario, one of the standard treatment regimens is to perform whole brain radiotherapy.[47-48]

However, in order to avoid the detrimental effects of whole brain radiotherapy, some authors advocate the use of adjuvant radiosurgery in the surgical bed.

A phase 2 clinical study evaluated the use of radiosurgery with a median dose of 18 Gy in patients with performance status ≥ 70 and ≤ 2 resected brain metastases. Local and regional failure rates of 22 and 44%, respectively, were demonstrated at 12 months. There was more benefit for lesions < 3 cm and deep.[49] (**B**) Several other studies with patients treated similarly showed local control rates of approximately 75 to 90% and 60 to 80% after one and two years of follow-up, respectively. These results are comparable with the local control achieved in patients who received postoperative whole brain radiotherapy.[50-54] (**B**)

Moreover, postoperative radiosurgery improves local control compared with observation alone for completely resected brain metastases. Data from a randomized phase 3 trial demonstrated that local control rates are statistically significant higher in patients who received radiosurgery (local control rates in 6 months and 12 months were 83%, 57% and 72%, 45%, for radiosurgery and observation groups, respectively).[55] (**A**)

Recently, two important studies were presented in ASCO and ASTRO. Kayama et al. conduced a non-inferiority phase 3 trial (JCOG0504) to assess the effectiveness of radiosurgery for residual and recurrent brain metastases after surgical resection. Patients were randomized to receive radiosurgery or whole brain radiotherapy. The overall survival rates were similar in both groups.[56] (**A**) Similarly, Brown et al. randomized patients with 1 to 4 brain metastases to either whole brain radiotherapy or radiosurgery after surgical resection. More cognitive deterioration was observed in whole brain radiotherapy group. No differences in overall survival were demonstrated between the groups and better quality of life was reported in the radiosurgery arm.[57] (**A**)

Recommendation

After surgery, adjuvant radiosurgery may be employed to replace whole brain radiotherapy.

Appendix 1

Search strategy – MEDLINE

(Central Nervous System [Mesh] OR Central Nervous Systems OR Nervous System, Central OR Nervous Systems, Central OR System, Central Nervous OR Systems, Central Nervous) AND (Neoplasm Metastasis [Mesh] OR Metastases, Neoplasm OR Neoplasm Metastases OR Metastasis OR Metastases OR Metastasis, Neoplasm) AND (Radiosurgery [Mesh] OR Radiosurgeries OR Radiosurgery, Stereotactic OR Radiosurgeries, Stereotactic OR Stereotactic Radiosurgeries OR Stereotactic Radiosurgery OR Gamma Knife Radiosurgery OR Gamma Knife Radiosurgeries OR Radiosurgeries, Gamma Knife OR Radiosurgery, Gamma Knife OR Stereotactic Body Radiotherapy OR Body Radiotherapies, Stereotactic OR Body Radiotherapy, Stereotactic OR Radiotherapies, Stereotactic Body OR Radiotherapy, Stereotactic Body OR Stereotactic Body Radiotherapies OR CyberKnife Radiosurgery OR CyberKnife Radiosurgeries OR Radiosurgeries, CyberKnife OR Radiosurgery, CyberKnife OR Radiosurgery, Linear Accelerator OR Linear Accelerator Radiosurgeries OR Radiosurgeries, Linear Accelerator OR Linear Accelerator Radiosurgery OR Radiosurgery, Linac OR Radiosurgeries, Linac OR LINAC Radiosurgery OR Radiosurgeries, LINAC)

Conflict of interest

The authors declare no conflict of interest.

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