

Management of Cerebral Metastases—About 25 Cases

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How to cite this paper: Hemama, M., Mrichi, S., El Fatemi, N. and El Maaqili, M.R. (2022) Management of Cerebral Metastases—About 25 Cases. *Open Journal of Modern Neurosurgery*, 12, 160-166. <https://doi.org/10.4236/ojmn.2022.123017>

Received: March 30, 2022

Accepted: July 25, 2022

Published: July 28, 2022

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Abstract

Approximately, 20% of all cancer patients will end up having brain metastases. This is especially the case of patients in which the primary tumor is lung cancer, breast and colorectal cancers, melanoma, or renal cell carcinoma. Development of brain metastases contributes substantially to overall cancer mortality in patients with advanced-stage cancer given the associated poor prognosis despite multimodal treatments and advances in systemic therapies. The objective of this retrospective single center study is to describe the experience of the Department of Neurosurgery of the Ibn Sina University Hospital in Rabat in the management of patients with brain metastases, highlighting the therapeutic choices as well as the various challenges encountered during treatment.

Keywords

Brain, Metastases, Therapeutic Management

1. Introduction

An estimated 20% of all patients with cancer will develop brain metastases. Even though any type of cancer can metastasize to the brain, the three most common primary tumors associated with brain metastases are lung cancer (20% - 56% of patients), breast cancer (5% - 20%) and melanoma (7% - 16%) [1] [2] [3] [4]. Lung cancer is the most frequent to metastasize to the brain irrespective of patient gender and is the most common brain metastasis occurring in men. In women, breast cancer is the most commonly occurring brain metastasis [5].

The incidence of brain metastases is increasing due to earlier detection and better systemic therapies leading to an improvement of overall survival of cancer patients. Brain metastases are often associated with high morbidity and mortality. Median survival after diagnosis is approximately 1 month without treatment

[6].

Appropriate management of patients with brain metastases requires an evaluation of all the independent prognostic factors in order to maintain the neuro-cognitive function and the quality of life of the patients while avoiding useless treatments. Therapeutic options include whole-brain radiation therapy (WBRT), surgical resection, stereotactic radiosurgery (SRS), and systemic therapies. With appropriate management, the overall survival rate increases to 10 - 12 months, although some patients show remarkable responses to treatment [6] [7] [8]. As a result, there is an ongoing debate regarding the most effective treatment regimen.

Stereotaxic surgery and radiosurgery are currently the treatment of choice for preselected patients. However, the use of encephalic radiation therapy *in toto*, a standard treatment for multiple metastases, alone remains controversial at the present time.

The objective of this paper is to describe our experience with the management of patients with brain metastases, highlighting the therapeutic choices as well as the various challenges encountered during treatment.

2. Methods

This was a retrospective, single center study that included all the cases of brain metastases treated within the Department of Neurosurgery of the Ibn Sina University Hospital in Rabat between 2014 and 2019. Medical charts of these patients were retrospectively reviewed to collect study relevant information such as demographic (gender, age), clinical (symptomatology, type of the primary tumor, time to diagnosis, KPS score) and radiological data (single or multiple metastases, localization of the metastases in the brain). Therefore, no formal sample size calculation was performed.

All patients underwent computed tomography (CT) and cerebral magnetic resonance imaging (MRI). The spread of the disease was assessed in all patients using breast ultrasound, a thoraco-abdomino-pelvic CT scan, and a bone scan (in some selected patients). In addition, the patients' hematological and biochemical profiles were also reviewed. All patients had histological confirmation from the primary tumor or after stereotaxic biopsy (in case of an unknown primary tumor).

Patients were classified according to the location of the tumor (supratentorial or infratentorial), and the type of the primary tumor. The prognosis was assessed mainly on the basis of the Karnofsky score and the Recursive Partitioning Analysis (RPA) score (Table 1). At the time of diagnosis, all patients were receiving dexamethasone which was continued throughout radiotherapy and then discontinued.

Within our department, surgery is usually carried out for brain metastases in patients with none or limited systemic disease and good performance status. However, surgical resection is generally undertaken for unique metastases that are large and accessible or in case of multiple metastases (<4 lesions), the most

Table 1. Recursive Partitioning Analysis (RPA) score.

Class	Variables
I	Age < 65 years old, KPS ≥ 70, controlled primary tumour, no extracranial metastases
II	All others
III	KPS < 70

KPS: Karnofsky performance status.

large and accessible lesion is resected. In case of multiple metastases with 4 or more lesions, surgery is usually not performed. Additionally, surgical resection is preferred when tumors display cystic or necrotic aspect with important edema or when located in eloquent areas or cortico-subcortically. Otherwise, the patient is treated by radiosurgery or radiotherapy.

Data collected during this study were analyzed descriptively using the statistical package SPSS®.

3. Results

In our patients' population, the median age was 40 years (range: 28 - 65 years) while the male to female ratio was 1.2/1 (male = 14, female = 11). On the other hand, the pre-diagnosis interval ranged from 3 months to 1 year. The clinical presentation depended on the location of the metastatic lesion.

Hemiparesis was noted in 56% of cases (n = 14), intracranial hypertension in 52% of cases (n = 13) while convulsions were observed in 24% of patients (n = 6) (Table 2). Multiple brain metastases were observed in 68% of cases while in 32% they were unique (Figure 1). On the other hand, 20% of the lesions were infratentorial and 80% were supratentorial. About 80% of the infratentorial lesions were in the cerebellar hemisphere and the rest (approx. 20%) in the vermis. Regarding the supratentorial lesions, 20% were located in the frontal lobe, 25% in the temporo-occipital junction, 20% were located in the parietal lobe, 15% in the temporal lobe, 15% in the occipital lobe and 5% in the Rolando suture region (Table 3).

Lung cancer was the most common primary tumor followed by breast cancer with 60% and 16% of cases, respectively (Table 4).

In more than 72% of patients, the Karnofsky's performance index was below 70, which had an important impact on the RPA prognosis score. As a result, 52% of the patients were classified as RPA II while 24% were proportionally equally RPA I and III.

Due to the multiplicity of metastases and the low Karnofsky index, stereotaxic biopsy followed by total brain radiotherapy (WBRT) was the most frequently undertaken therapeutic choice (68% of cases, n = 17). Radio-chemotherapy was given in 16% of the cases (n = 4). Only two patients (8%) underwent total tumor excision followed by radiotherapy. Radiosurgery was used in 8% of cases (n = 2). Early postoperative KPS improved in 87% of the patients.

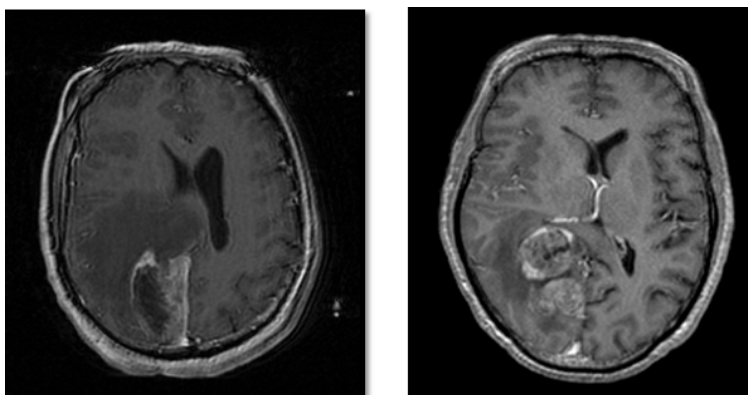


Figure 1. T1-weighted brain MRI + GADO illustrating various unique and poorly limited supratentorial lesions with a necrotic centre, gaining contrast in the periphery. Note the presence of perilesional edema. Appearance in favor of a cerebral metastasis or high-grade glial tumor. Patient who underwent a stereotactic biopsy. The histological study came back in favor of a metastasis.

Table 2. Clinical characteristics.

Clinical signs	n	%
Intracranial hypertension	13	52
Neurologic deficit	14	56
Epilepsy	6	24
Neuricognitive alterations	1	<1
Others	2	<1

Table 3. Localization of the metastases in the brain.

Localisation	n	%
Infratentorial	5	20
Cerebellar hemisphere	4	80
Vermis	1	20
Supratentorial	20	80
Frontal lobe	4	20
Temporo-occipital junction	5	25
Parietal lobe	4	20
Temporal lobe	3	15
Occipital lobe	3	15
Rolando suture region	1	5

Table 4. Localization of the primary tumours.

Lung cancer	N = 14	56%
Breast cancer	N = 4	16%
Melanoma	N = 1	4%
Kidney	N = 2	8%
Other cancers	N = 4	16%

The median duration of the short-term follow-up was 2.5 months (range: 1 - 4 months). During this period, 48% of the patients had died. We have no documentation regarding neurocognitive impairment after radiotherapy. Two groups stand out according to the Karnofsky index, the first group with the lowest index (<70%) was associated with a mortality rate close to 100% compared to the KPS group > 70% where mortality had occurred in almost 27% of cases. When considering the RPA score, Class III patients showed a 100% mortality at 3 months, while survival of RPA Class I patients was 100% at 6 months. At 1-year follow-up, 24% survival rate was observed.

4. Discussion

Brain metastasis is a deleterious complication of systemic malignancy that can be seen in a relatively high number of patients with cancer. Appearance of brain metastases is most often a sign of poor prognosis and is associated with a poor survival time [5]-[10].

In the last twenty years, increased global incidence of malignancy improved systemic disease treatment with prolonged survival, and increased central nervous system (CNS) surveillance in cancer patients have led to higher rates of observed cerebral metastatic disease [8] [9] [10].

Patients with brain metastases often exhibit neurologic manifestations such as headache, seizures, focal deficits, and cognitive changes, which severely impair patients' quality of life [9]. The overall prognosis depends mainly on age, the extent and activity of the systemic disease and the number of brain metastases [10].

Treatment of brain metastases aims to improve quality of life, provide local tumor control, prevent death from neurological causes, and improve therefore overall survival [10]. The use of WBRT became standard of care in the 1980s. It improved survival from 1 month to 3 - 6 months and remained a mainstay treatment for patients with brain metastases for a long time. The role of surgery has been very well described in the literature and surgical management of brain metastases has evolved significantly during the last two decades thanks to the development of new techniques and technology in neurosurgery. However, the role of surgical resection for multiple brain metastases remains controversial even if its value has been well defined for single metastases. In addition, stereotactic radiosurgery started to be considered starting from the early 90s as a complement to therapy [5]-[10].

Nowadays surgery is in competition with stereotactic external irradiation in number of patients. Prospective and randomized studies comparing the two treatments are in progress. Retrospective comparisons of surgery plus WBRT versus single-dose stereotactic irradiation plus WBRT failed to show a clear advantage of one treatment over the other. However, neurosurgery retains its own indications in accessible tumors larger than 3 cm in diameter, and in lesions producing large mass effect and/or shift in midline superior to one centimeter [6] [7] [8] [9].

Response to treatment may differ among patients, and surgical candidates should be carefully selected. The characteristics of both the patients and their tumors should be investigated for their prognostic significance in patients with brain metastases. These factors include age, patient's functional status (mainly evaluated by KPS score), status of primary cancer, activity of systemic disease, neurocognitive function, number of brain metastases, histology of the primary tumor, and interval between the initial cancer diagnosis and detection of brain metastases [7] [8] [9] [11]. The most favorable prognosis, with median survival of 7.1 months, is seen in Class 1 patients who have a Karnofsky performance score (KPS) of ≥ 70 , age < 65 , and controlled primary tumor without extracranial metastases. Class 3 patients have KPS < 70 and a median survival of 2.3 months and are considered poor prognosis. All other patients fall into Class 2, including those with KPS ≥ 70 but other unfavorable characteristics, such as uncontrolled primary tumor, extracranial metastases, or age ≥ 65 ; these have a median survival of 4.2 months. This is in agreement with the results observed from our study.

In about 50% of the patients, death is directly related to extraneural lesions, and treatment of the cerebral disease does not significantly improve survival. In these cases, the objective of treatment is to improve the neurologic deficit and maintain the quality of life. Corticosteroids and WBRT can be used for this purpose. Contrarily, patients with a limited number of brain metastases, and well controlled or limited systemic disease may benefit from aggressive treatment of brain lesions as both the quality of life and survival are primarily related to treatment of CNS disease [6]. The role of medical therapies in brain metastases was limited due to multiple factors that included a lack of blood brain barrier (BBB) penetration, protein binding, and efflux pumps. In the last decade, our understanding of molecular drivers of brain metastases and CNS penetration of drugs across the BBB has improved. The molecular targeted tyrosine kinase inhibitors have shown effectiveness in cerebral metastases with activating mutations with NSCLC, breast cancer, and melanoma. More recently immunotherapies have shown efficacy in the management of these patients. These agents can be effective for both intracranial as well as extracranial disease and are being actively employed in this patient population.

Our study has several limitations that are mainly due to its retrospective nature and the low sample size involved. Despite these, a clear conclusion can be drawn in relation to the fact that management of cerebral metastases depends on several factors and should be adapted to the objective of the treatment. A thoroughly multidisciplinary approach is required for comprehensive and effective management of these tumours.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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