CLINICAL INVESTIGATIONS

Medicina (Kaunas) 2012;48(6):281-5

Postoperative Survival in Patients With Multiple Brain Metastases

Kaspars Auslands, Daina Apškalne, Kārlis Bicāns, Rolfs Ozols, Henrijs Ozoliņš

Neurosurgery Department, Riga East Clinical University Hospital "Gailezers," Latvia

Key words: *multiple brain metastases; surgery, survival.*

Summary. *Background and Objective. Although surgery is traditionally performed for patients with a single brain metastasis, an increasing number of patients with multiple brain metastases may also be treated surgically. The objective of the study was to analyze postoperative survival results and the clinical factors affecting these results.*

Material and Methods. The records of the patients who underwent surgical resection of 2 or more lesions between January 2005 and January 2010 were retrospectively reviewed. Survival was calculated from the date of surgery to the last follow-up evaluation or death, and different clinical factors were analyzed in regard to patient survival.

Results. In total, 36 patients underwent one or more craniotomies. The survival of the total group ranged from 16 days to 37.5 months (mean, 29 months). There were 4 deaths within 30 days. When divided into Radiation Therapy Oncology Group RPA classes, the survival time was 11.75, 8.58, and 5.31 months for classes 1, 2, and 3, respectively. Regarding an impact on the survival, a significant association with a favorable outcome was found for the following factors: the number of brain metastases (2–3 vs. 4–6, P=0.046), RPA classes (1 vs. 2 or 3, P=0.0192), and extent of metastasis resection (all vs. partial, P=0.018).

Conclusions. Well-selected patients with multiple brain metastases appear to benefit from surgery compared with historical controls of patients treated with whole-brain radiotherapy alone.

Introduction

With an increase in the early detection of primary tumors and longer survival in patients with cancer, the incidence of brain metastases is rising. The most common primary sites of brain metastases are lung (17%), renal cell (10.5%), and breast (5.2%) cancer and melanoma (8%) (1). Melanoma also has the highest frequency of presentation with multiple metastases of all primary tumors (2). Prognosis for patients with brain metastases is generally poor (median survival, 2.3–7.1 months), and therapy is aimed at providing optimum quality of life while reducing the rates of tumor relapses (3).

For many decades, whole-brain radiotherapy (WBRT) has been the gold standard treatment for patients with cranial metastases (4). Although surgery is traditionally performed for patients with a single brain metastasis, an increasing number of patients with multiple brain metastases are also treated surgically (5).

Historically, patients with multiple brain metastases were considered good candidates for aggressive surgical treatment because it was thought that they were likely to die before obtaining benefit (6–8). Now, with more advanced procedures (image guidance, intraoperative ultrasound, and functional neuronavigation), surgical approaches can be more aggressive and can provide a better outcome, such that multiple metastatic lesions are no longer an automatic barrier to craniotomy.

With a proper patient selection and operative and postoperative management, resection continues to play a significant and evolving role in the care of patients with metastatic brain tumors.

The aim of the present study was to analyze the clinical factors affecting postoperative survival results in patients with multiple brain metastases.

Material and Methods

The records of the patients with multiple brain metastases who underwent surgical resection of 2 or more lesions in the Neurosurgery Department, Riga East Clinical University Hospital, between January 2005 and January 2010 were retrospectively reviewed.

Patient's age, gender, type of primary cancer, Karnofsky Performance Status (KPS), time from the first diagnosis of cancer to the diagnosis of brain metastases, number of metastases at the time

Correspondence to K. Auslands, Neurosurgery Department, Riga East Clinical University Hospital "Gailezers," Hipokrāta 2, 1038 Riga, Latvia. E-mail: ka75@inbox.lv

of surgery, presence or absence of systemic diseases, number of craniotomies, and postoperative complications were entered into a computer database.

The patients were divided into Radiation Therapy Oncology Group (RTOG) recursive partitioning analysis (RPA) classes according to Gaspar et al. (9): class 1, patients under 65 years with a KPS score of at least 70 and who had a controlled primary disease and no evidence of extracranial metastases; class 3, patients with a KPS score of less than 70; and class 2, all the remaining patients.

All the patients underwent surgery as an elective procedure and received antibiotic prophylaxis, perioperative anticonvulsants, and corticosteroids. The goal of all the surgical procedures was gross total excision. Image-guided surgical navigation and Cavitron ultrasonic systems were used in all the patients. Complications related to surgical resection sites were scored. The KPS score was evaluated before surgery and at hospital discharge.

The following criteria were used to define the cases of the patients without systemic metastases as having a "controlled" primary disease: patients presenting with brain metastases alone when no primary site could be identified after a thorough investigation, patients presenting with synchronous brain metastases if the primary site was surgically resected or treated with radiotherapy/chemotherapy, and patients with metachronous brain metastases when no evidence of primary tumor recurrence was identified.

The survival was calculated from the date of surgery to the last follow-up evaluation or death. Deaths within 30 days after surgery were considered as perioperative mortality.

Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS) and MedCalcfor Windows software. Survival curves were estimated by the Kaplan-Meier method. A univariate analysis was conducted using the Mann-Whitney *U* test, and a multivariate analysis was performed to determine which variables were significantly associated with a difference in the survival under a Cox regression model.

The following factors were analyzed in regard to patient survival using the Mann-Whitney *U* test and Cox regression model: patient's gender (male vs. female), patient's age (⩾65 vs. <65), histology (melanoma and breast metastases vs. all other), presentation (synchronous vs. metachronous), KPS (⩾70 vs. <70), RTOG RPA class (1 vs. 2 or 3), number of tumors (2–3 vs. 4–6), extent of resection (resection of all lesions vs. resection of some, but not all lesions), and controlled primary tumor (yes vs. no).

Table. Patients' Characteristics and Survival Time by Different Groups

Variable	n	Survival Time, Months	*P*
Gender			
Male	18	7.83±1.53	0.134
Female	18	6.76±2.20	
Age, years			
⩾65	10	4.64±1.73	0.340
<65	26	8.32±1.34	
Presentation			
Synchronous	10	7.80±1.74	0.258
Metachronous	26	7.10±1.65	
Primary tumor controlled			
Yes	21	7.72±2.13	0.677
No	15	6.70±1.19	
No. of brain metastases			
2–3	27	8.59±1.65	0.046
4–6	9	3.42±1.28	
Site of primary tumor			
Melanoma	15	7.83±1.78	0.360 (melanoma vs. all other)
Breast	9	7.88±4.11	0.266 (breast vs. all others)
Gastrointestinal tract	3		
Lung, small cell	2		
Ovary and cervix	2		
Kidney	1		
Unknown	4		
KPS score			
⩾70	15	10.06±2.69	0.173
<70	21	5.32±1.09	
RPA class			
1	7	11.76±4.84	0.390
2, 3	29	6.22±1.14	
Extent of metastasis resection			
All	15	10.94±2.64	0.018
Partial	21	4.69±0.98	

Values are mean ± standard error.
KPS, Karnofsky Performance Status; RPA, recursive partitioning analysis.

Results

During the 6-year period, 36 patients diagnosed with multiple brain metastases underwent 1 or more craniotomies at our institution.

There were 18 men and 18 women with a mean age of 58.47 years (range, 35 to 82 years; SD, 10.98). Fifteen patients had metastatic melanoma. Besides, 26 patients developed metachronous metastases, whereas the others developed synchronous metastases (Table).

More than half of the patients (n=20) presented with neurological deficits, whereas other patients were neurologically intact preoperatively, only exeperiencing symptoms of raised intracranial pressure (n=9) or seizures (n=5) or were incidentally diagnosed with their primary malignancy (n=2) during workup. Besides, 15 patients (41.66%) had a KPS score of at least 70.

There were 18 patients with 2 metastases, 9 patients with 3 metastases, 6 patients with 4 metastases, and 3 patients with 5 or more metastases.

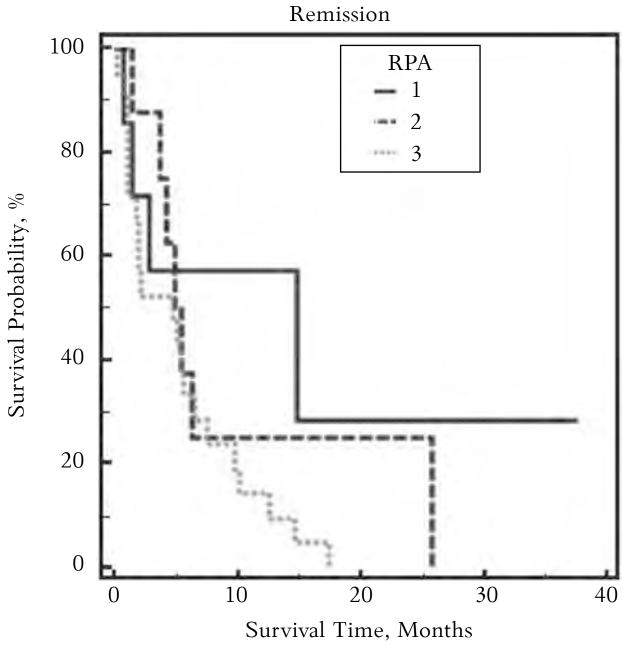

Fig. Survival times by recursive partitioning analysis (RPA) classes 1, 2, and 3

Moreover, 20 patients had metastases located in the cerebral hemispheres; metastases of deep location (referring to tumors located within the basal ganglia, thalamus, brainstem, corpus callosum, or cerebellar hemispheres) were seen in 3 patients, whereas 13 patients had metastases in both locations. The size of metastatic lesions ranged from 1.2 cm to 4.6 cm.

All the lesions were removed in 15 patients; 21 patients did not undergo resection of all known lesions. Furthermore, 28 patients underwent 1 craniotomy, 7 patients underwent 2 craniotomies in a single operation, and 1 patient underwent 3 craniotomies in a single operation.

There were 3 postoperative complications (1 infection due to cerebrospinal fluid leak and 2 due to local hematomas), and 4 deaths occurred within 30 days.

The survival time ranged from 16 days to 37.5 months (mean, 7.29 months; 95% CI, 4.60–9.98; SD, 7.95; SE, 1.33). When divided into RTOG RPA classes, the survival time was 11.75, 8.58, and 5.31 months for classes 1, 2, and 3, respectively (Fig.).

The use of adjuvant WBRT remains controversial; therefore, only 7 patients (19.44%) with radiosensitive tumors (breast, lung, etc.), a stable systematic disease, and a good performance status (KPS $\geqslant$70) received WBRT (median dose, 30 Gy) 2 weeks after surgery. Systemic chemotherapy is known to be largely ineffective for brain metastases because of the inability of most agents to penetrate the blood-brain barrier, and it was used only for the systemic disease treatment.

Because many of the patients died in other hospitals or at home, it was impossible to determine precisely whether they died from cerebral or extracerebral progression. For this reason, the cause-specific survival was not calculated.

Regarding a potential impact on the survival and using a univariate analysis, a statistically significant association with a favorable outcome was found for the following factors: number of brain metastases (2–3 vs. 4–6, P=0.046) and extent of metastasis resection (all vs. partial, P=0.018). A multivariate analysis was conducted using the same criteria, and a significant effect was demonstrated only for RPA (P=0.0192).

Discussion

Although surgery is known to play a limited role in patients with multiple metastases, studies have demonstrated its feasibility and suggest that it may be an effective option. This is particularly important for patients who have multiple metastases with a mass effect. In a retrospective study by Bindal et al. (10), 56 patients with multiple brain metastases were surgically treated. The investigators found that in the cohort of the patients who had all metastases resected, the prognosis was similar to that of a matched cohort of the patients with a resected solitary metastasis. There was no increase in morbidity. On the other hand, the cohort of the patients who did not have all the metastases surgically removed had a poorer prognosis. Our study showed similar data: significant differences in the survival were noted among the patients who had all metastases resected versus those who did not have all metastases surgically removed (10.94 months vs. 4.68 months, P=0.018). In other study, Wronski et al. (11) found no difference in the overall outcome comparing patients with a single metastasis with patients multiple brain metastases, all being surgically treated. However, not all studies confirm this experience (12), and a randomized study could help clarify this.

Patients with 4 or more brain metastases remain to have a particularly poor prognosis and are usually not treated surgically (13). Those patients with 4 or more metastases who were surgically treated in our clinic also had a statistically significantly worse prognosis regarding the median survival compared with those who had 2 to 3 metastases removed (P=0.046).

It is important to recognize that not all patients will benefit from the surgical removal of brain metastases, and a number of factors should be carefully considered when developing a treatment plan (5). Traditional criteria for selecting patients who will benefit from surgery include a good physical function as assessed by the KPS score, a single and surgically accessible metastasis, and stable or absent extracranial metastases. The KPS ranks patients on their ability to carry out activities of daily life, with the scores of 70 or above having the best outcome after surgery (14). More recently, the RTOG has developed recursive partitioning analysis, a statistical method of classifying patients that includes the KPS score, patient's age, and the status and extent of extracranial disease (9). Patients in RPA class 1 status are the best candidates for craniotomy. These patients are characterized by the age of 65 years or less, the KPS score of 70 or more, the absence of extracranial metastases, and a good control of their systemic disease. RPA class 2 patients have the KPS score of 70 or more, but may also be aged over 65, and have an uncontrolled systemic disease and other systemic metastases. The selection of these patients for surgical treatment requires a careful consideration of their likely duration of survival and their operative risks. Patients in RPA class 3 status have the KPS score of less than 70; these patients have the poorest prognosis and are usually not selected for surgery (15). In the current series, the median survival time for RPA class 1 patients with multiple metastases was 11.75 versus 6.21 months for patients in less favorable RPA classes (P=0.098). Logically, a more aggressive treatment should be reserved for patients who are functionally independent with a good systemic disease control. For patients in less favorable prognostic groups (⩽RPA class 2) and with multiple lesions, the choice is either WBRT alone or a stereotactic radiosurgery (SRS) boost, according to clinical judgment. Moreover, adjuvant WBRT after surgery or SRS significantly reduces intracranial relapse and neurological death rates, but does not improve functional independence or overall survival (16).

Patients with multiple metastases often have lesions located too far apart to allow resection with a single craniotomy. Accurate localization of subcortical lesions is now possible with image-guided stereotaxy, smaller cranial and dural openings, and minimal exposure of normal brain. Our data indicate that multiple craniotomies are not associated with an increased complication rate per craniotomy or with higher 30-day mortality rates. However, patients undergoing multiple craniotomies have a higher cumulative probability of developing a complication. In general, the need for multiple craniotomies should not be a major deterrent to the decision to operate.

During the last 20 years, radiosurgery, in addition to surgery and WBRT, has emerged as one of the key options for patients with brain metastases because of its noninvasive nature and high lesion control rates (17). Since 2010, the Novalis frameless image-guided radiosurgery system has been applied at Riga East Clinical University Hospital. We have data on our initial experience in the treatment of patients with single or multiple brain metastases, and further studies are needed to match the treatment results. However, surgery continues to play an essential role in the management of lesions that are complicated by a mass effect or after failure of less invasive treatment methods (18).

Conclusions

Well-selected patients with multiple brain metastases appear to benefit from surgery compared with historical controls of patients treated with whole-brain radiotherapy alone. Further prospective series are needed to optimize and individualize the care of patients with multiple brain metastases.

Statement of Conflict of Interest

The authors state no conflict of interest.

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Received 27 January 2012, accepted 12 June 2012