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# Surgical management of 39 patients with metastatic brain tumor

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## Abstract

**Objective:** In this study, we aimed to investigate the factors that affect surgical outcome and survival duration of the patients with metastatic brain tumors, and compare the literature with our results.

**Methods:** Clinical and radiodiagnostic data of thirty nine patients with metastatic brain tumor who underwent surgery between January 2011 and December 2013 were analyzed, retrospectively. Factors related to the patients, the metastatic lesions and the primary disease were evaluated with respect to postoperative outcome and survival.

**Results:** The mean survival duration relative to prior diagnosis, eloquent location, size and number of the lesions, operative technique, and Recursive Partitioning Analysis (RPA) classes were not different. Nine patients who had lesions in the posterior fossa tended to have a shorter mean survival of 8.3 months compared to those with functional grade I, II, and III lesions. Karnofsky Performance Score (KPS) scores significantly improved in 72% of the patients operated. Patients with a KPS score ≥70 at discharge had a mean survival of 9.8 months compared to 4 months of those with a KPS score below 70 at discharge.

**Conclusion:** Patients that were in a higher RPA class tended to have shorter survival in comparison to those in lower classes. Surgical management provided a significantly higher KPS scores at discharge relative to the initial scores. Higher KPS scores at discharge were associated with a longer survival duration unlike the preoperative KPS scores that did not estimate predict the survival duration.

**Keywords:** Brain tumor, metastasis, therapeutics, outcome, surgery

## INTRODUCTION

Metastatic brain tumors develop in approximately 30% of systemic cancer diseases and have been reported to be the most frequent intracranial tumors in adults, partly due to the advanced imaging modalities and to the increase in survival of cancer patients in recent years (1, 2). Since the first report on technical details by Grant et al. in 1926, it has been accepted that surgical intervention has role in the treatment of metastatic brain tumors (3). However, total whole brain radiation (TWBR) plus corticosteroids was the prominent therapeutic modality until the mid-1900s due to the high surgical morbidity and mortality. Improvement of surgical techniques in every aspect, development in neuroanesthesia and appropriate patient selection gave rise to better outcome after surgical resection (4). Randomized, controlled, prospective clinical studies conducted in 1990s have indicated that surgical intervention was one of the main therapeutic options in the management of metastatic brain tumors (5-7).

In order to obtain the best surgical outcome, recent treatment algorithms included factors related to patient (age, neurologic status), metastatic lesion (number of metastases, eloquent/noneloquent location), and status of the primary disease (controlled/uncontrolled, prognosis) (8, 9). In this study, we aimed to investigate some of these factors that were expected to be influential on the postoperative outcome in our patients with metastatic brain tumors, and to interpret our results in the light of data from the literature.

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## METHODS

We retrospectively investigated 39 patients with metastatic brain tumors admitted to our clinic and opted for surgical treatment between January 2011 and December 2013 (Table 1). Cranial computerized tomography (CT) followed by a contrast magnetic resonance imaging (MRI) were the initial imaging modalities. All patients obtained thorax, abdomen and pelvis CT as well as radionuclid bone screening and positron emission tomography (PET) scan for the diagnosis of the primary disease. Pre- and postoperative neurologic status and cognitive functions were evaluated via Karnofsky Performance Score (KPS).

**Table 1. Characteristics related to the patients and the lesions**

| | n |
|---|---|
| Age | |
| < 65 | 31 |
| ≥ 65 | 8 |
| Sex | |
| Male | 27 |
| Female | 12 |
| Histologic diagnosis | |
| Lung | 28 |
| Breast | 5 |
| Melanoma | 2 |
| Thyroid | 2 |
| Kidney | 1 |
| Unknown | 2 |
| Size | |
| < 3 cm | 7 |
| 3-5 cm | 24 |
| >5 cm | 8 |
| Number | |
| Single | 25 |
| Multiple | 14 |

**Table 2. Definition of RPA class**

| RPA class | Patient characteristics |
|---|---|
| I | KPS > 70 |
| | Age < 65 |
| | Primary disease under control |
| | No extracranial metastasis |
| III | KPS < 70 |
| II | KPS > 70 |
| | Age > 65 |
| | Primary disease uncontrolled |
| | With extracranial metastasis |

RPA: Recursive partitioning analysis; KPS: Karnofsky performance score

For survival analysis, the criteria based on recursive partitioning analysis (RPA) defined by Gaspar et al. were used to comprise the classes (Table 2) (10). The mean survival in the study groups was compared to the RPA class and the KPS score (Table 3). The size and the number of the lesions were measured on contrast MRI images by a radiologist. Tumors located in noneloquent areas were considered functional grade-I, and those near and in eloquent areas (motor or sensory cortex, visual cortex, expressive or receptive language centers), grade-II and III, respectively (8). The location and the number of the lesions were compared to the mean survival (Table 3). Morbidity and mortality related to surgery were outlined in Table 4.

### Statistical Analysis

A student's t-test or Mann Whitney U test was used in order to compare two groups based on the distribution of parameters. Kruskal Wallis was used for the comparison of groups of three or above. For numerical data, Pearson chi square, Fisher's exact test and Fisher-Freeman-Halton test were used. $P<0.05$ was considered statistically significant.

## RESULTS

Patient age at the diagnosis varied between 34 and 82 with a preponderance of male sex. Thirty patients had a KPS of 70 and above, whereas 9 patients were below 70. Presenting symptoms

**Table 3. Comparison of number and location of the lesions, and the RPA class and KPS score of the patients with survival duration**

| | n | Survival (months) | p |
|---|---|---|---|
| **Number** | | | 0.837 |
| Single | 25 | 9.12±6.31 | |
| Multiple | 14 | 9.07±5.03 | |
| **Location** | | | 0.773 |
| Functional grade I | 10 | 10.70±6.24 | |
| Functional grade II | 11 | 8.45±4.11 | |
| Functional grade III | 9 | 8.89±7.17 | |
| Posterior fossa | 9 | 8.33±6.32 | |
| **RPA** | | | 0.375 |
| Class I | 22 | 10.09±5.82 | |
| Class II | 11 | 8.55±6.52 | |
| Class III | 6 | 6.50±4.09 | |
| **KPS score** | | | |
| Preoperative | | | 0.452 |
| < 70 | 8 | 7.38±4.27 | |
| ≥ 70 | 31 | 9.55±6.13 | |
| Postoperative | | | 0.021* |
| < 70 | 5 | 4.00±3.16 | |
| ≥ 70 | 34 | 9.85±5.76 | |

RPA: Recursive partitioning analysis; KPS: Karnofsky performance score included headache, upper or lower limb weakness or numbness, impaired consciousness, difficulty speaking, imbalance, tinnitus, visual disturbance, difficulty swallowing, hoarseness or urinary incontinance. Three patients presented with seizure. Fourteen patients had ongoing medical treatment for the systemic co-morbidities. There were lung carcinoma in 27, breast carcinoma in 5, malignant melanoma in 2, renal carcinoma in 1, and thyroid carcinoma in 1 patient. Three patients had metastatic tumors of unknown origin. There was no difference in mean survival in terms of histopathological type of the malignancy.

All patients underwent gross total microsurgical resection via a standart craniotomy except for 6 with functional grade-II or grade-III lesions requiring stereotaxic localization, 6 of which had the removal of a free 3x3 bone flap and one of which had stereotaxic needle biopsy. Three patients with functional grade-III had the removal of a bone flap with pedicle. The mean survival in patients of functional grade I, II, III, and posterior fossa location were 8.7, 8.4, 8.7 and 8.3 months, respectively, which were not statistically different, although patients who had lesions in posterior fossa appeared to have slightly shorter mean survival. Six patients were still alive on their follow-up longer than 12 months.

In 25 of 39 patients, primary disease was diagnosed at the time of presentation during the preoperative workup, whereas 14 patients had already been followed up with a prior diagnosis of primary disease. Mean survival in the group with prior diagnosis was 9.2 months, and this was not different than that in all patients, which was 9.3 months.

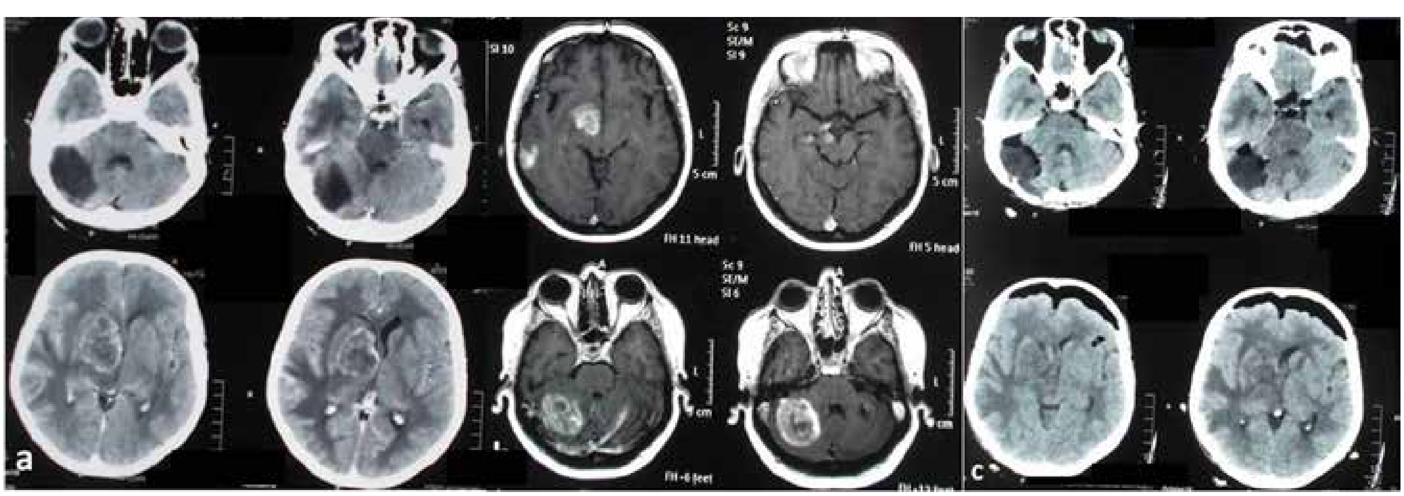
There was a single lesion in 25 (64%), and were multiple lesions in 14 (36%) of 39 patients (Figure 1). There was no difference in mean survival, RPA class, pre- and postoperative KPS scores, and functional grade in terms of lesion multiplicity versus singularity.

**Table 4. Morbidity and mortality related to surgery**

| Age/Sex | Primary disease | Location | Local surgical or neurologic complication | Hospital stay | KPS score at discharge |
|---|---|---|---|---|---|
| 65/M | Lung ca | Left frontal | Hematoma in tumor bed | 8 days | 90 |
| 55/M | Lung ca | Posterior fossa | Pneumocephalus and CSF fistula at PO day 4 | 21 days | 90 |
| 58/F | Lung ca | Right frontal and temporal | Epidural hematoma at PO day 1 | 8 days | 90 |
| 61/M | Lung ca | Left temporal | Subgaleal CSF collection | 8 days | 90 |
| 51/F | Breast ca | Left parietal | Status epilepticus and left parietal hematoma at PO day 8 | 29 days | Expired |
| 61/M | Lung ca | Right fronto-temporal | Pneumocephalus and CSF fistula at PO day 34 | 62 days | 60 |
| 43/F | Breast ca | Posterior fossa | CSF fistula at PO day 3 | 65 days | Expired |
| 39/F | Breast ca | Posterior fossa | Paraparesis at PO day 2<br>Seeding metastasis at Th6-L1 | 9 days | 60 |

CSF: Cerebrospinal fluid; PO: Postoperative; KPS: Karnofsky performance score

**Figure 1. a-c.** Multiple metastatic lesions in the right temporal lobe, the right basal ganglia and the right cerebellar hemisphere seen in cranial CT (a) and MRI (b). Postoperative cranial CT following removal of the lesion in the cerebellum (c).



Five (22.7%) of 22 of RPA class I, 5 (50%) of 10 of RPA class II and 4 (57.1%) of 7 of RPA class III died within the first six months of postoperative period. There was a strong trend for an increase in mean survival of the patients that had lower preoperative RPA classes, which did not reach statistical significance. Of 37 patients that were discharged, KPS scores improved in 27 (72%), same in 9 (33%) and worse in 1 (0.3%) patient, which was statistically significant. Higher KPS scores at discharge were associated with longer survival duration unlike the preoperative KPS scores that did not predict the survival duration.

Seventeen (73%) of 23 patients who were RPA class I, 6 (60%) of 10 patients who were RPA class II, and 2 (28.5%) of 7 patients who were RPA class III at the initial presentation were discharged within a week. No difference was found in the time to discharge relative to RPA class.

Five patients developed pneumonia, 4 patients deep vein thrombosis, 2 patients pulmonary embolism, 2 patients electrolyte imbalance and one patient urinary tract infection, postoperatively. Two patients died at postopeartive day 13 and day 20 due to intracerebral hematoma, and pneumonia as well as renal failure, respectively. There was no significant effect of location of the metastatic lesions on the complications developed postoperatively.

## DISCUSSION

Brain metastases are frequently encountered mainly in patients with malignant melanoma, as well as in those with lung, breast, kidney and colon carcinoma, whereas metastases from gastrointestinal (GI), female reproductive, prostate and hematological malignancies are relatively rare (11). The average survival of untreated patients with cerebral metastasis is around one month (12). This duration can be extended up to two months with corticosteroids. Addition of whole-brain radiation therapy (WBRT) provides survival up to 3 to 6 months. If a surgical resection is included in the treatment plan, then, a 9 to 14 month survival may be expected (8). Today, surgical resection has been the first choice among the other modalities (2, 13, 14).

Factors related to the patient, metastatic lesion and status of the primary disease have been investigated in order to predict the outcome of surgical management (15). In our study, we looked into location, size and number of the lesions, status of the primary disease, surgical technique and RPA class as well as KPS score of the patients.

Surgical resection should be considered as a means of cytoreduction to decrease the size of the mass as much as possible (11, 15). The size and the number of the lesions are two main tumoral characteristics that influence the surgical decision along with several other factors. For the lesions larger than 2 cm in diameter, surgery is mostly the first line treatment (16). Surgery is also recommended for the lesions smaller than 3 cm in diameter in posterior fossa or temporal lobe. Due to the fact that these two compartments are less compliant, if stereotactic radiosurgery (SRS) is planned as the initial treatment, usually, there is no time for the effect of SRS to take place. Today, SRS is recommended for the metastatic lesions smaller than 3 cm diameter (17). In addition to the size of the lesion mentioned above, other factors that prompted us for surgical intervention included those with intratumoral hemorrhage, compressive effect causing hydrocephalus and/or neurological deficit, or when there is no information regarding primary disease with an accessable metastatic lesion and a biopsy is needed.

Only 37 to 50% of brain metastases present as a single lesion (15). The management of multiple metastatic brain tumors may vary depending on the location of the lesions. Multiple craniotomies are not generally pursued for the lesions at different locations. For the lesions one of which is larger and has a mass effect, or for the lesions close to each other, a one-stage or combined surgical approach is recommended (8, 9). If the source of primary disease with multiple lesions is not known, then, a biopsy is considered as an initial diagnostic step (18). In our series, two metastatic lesions in a patient with lung cancer were removed gross totally in one stage via a wide frontotemporal craniotomy. Another patient who had a surgery for the posterior fossa lesion a month before, and whose lesions in the right parietal lobe and right lateral ventricle that had been grown on follow-up underwent a single stage surgery with gross total removal of these lesions.

Sawaya subclassified the metastatic brain tumors according to their localization relative to eloquent areas (19). Numerous intraoperative imaging or electrophysiologic techniques such as neuronavigation, MRI, ultrasonography, awake craniotomy and cortical mapping have been developed especially for functional grade II and III patients in order to delineate the optimal route to the tumor, safely (20, 21). However, since there is not yet enough data to conclude that these modalities improve surgical outcome, most medical centers lack these sophisticated setups, and they are relatively time consuming, their use is somewhat limited (2). We used transcortical ultrasonography in one patient for a left frontal lesion with a size of 3.5 cm diameter.

Bidal et al. concluded that reoperation in their 48 patients with recurrent metastatic disease, especially in those that were young and have good medical condition, improved the quality of life and the survival, and made the adjuvant treatment options possible in some of these patients with no definite diagnosis radiologically only, by providing histologic confirmation on necrosis and tumoral recurrence (1). We operated on one of our patients who had local recurrence, and removed the tumor gross totally. The patient still has 8 month follow-up.

A group of our patients with lesions that are radiosensitive, such as small cell lung cancer, lymphoma, germ cell tumor or multiple myeloma were considered for radiotherapy, whereas those with radioresistant lesions melanoma, renal cell carcinoma or sarcoma were managed surgically as a first line treatment. Patients with lesions that are in the intermediate zone in terms of responsiveness to radiotherapy, such as breast or large cell lung cancer, were evaluated with oncologists whether a surgical option or radiotherapy should be pursued.

Surgical technique may have some bearing on outcome. Removal of the tumor along with the infiltrated cerebral parenchyma surrounding the tumor significantly decreases the likelihood of recurrence (22). Lesions particularly in posterior fossa should be removed in an "en bloc" fashion as breaking into pieces during resection may result in "seeding" metastases (23, 24). We had one RPA class II patient with no neurologic deficit preoperatively, developing paraparesis in lower extremities postoperatively at day 3 and was found out to have a thoracolomber lesion, which suggested a "seeding" metastasis. It has been agreed on that surgical resection of metastatic brain tumors should be carried out gross totally without any harm to the surrounding normal parenchyma (25). If this could not be assured in functional grade II and III patients, postoperative SRS or WBRT should be considered (8). Our results suggested that surgical technique as well as eloquent location were not influential on survival, although patients that had craniectomy for metastatic posterior fossa lesions tended to have shorter survival.

The mortality in cerebral metastases develops due to the systemic effects of the primary tumor in 70% of patients (15). Therefore, the status of the primary disease is one of the key factors that influence the prognosis (4). Unless an emergent surgical intervention is necessary, the whole workup aimed for the primary source should be completed (18). Patients admitted to the hospital with a known primary source may bypass the diagnostic steps and right head to the operating room, although no evidence has been reported that this may have any influence on the postoperative outcome, as was, too, the case in our study.

We found, although not statistically significant, a similar relationship between the RPA class and the survival as reported in the literature. As the RPA scores increased, the survival of the patients tended to become shorter. Lack of significance may have been the result of our relatively smaller sample size. RPA class did predict KPS scores at discharge in our patients. Patients with lower RPA classes had a significantly better early postoperative course defined by higher KPS scores. Our results also indicated that surgical management in these patients provided a significantly better postoperative outcome characterized by higher KPS scores at discharge relative to the initial scores. Interestingly, higher KPS scores at discharge were associated with longer survival duration unlike the preoperative KPS scores that did not predict the survival duration. The involvement of comorbidities may complicate the surgical outcome and prolong the hospital stay, although they do not have a significant effect on prognosis (20, 26). Our results were consistent with the literature.

In conclusion; our results suggested that the number, size and eloquent location of the metastatic lesion, or the operative technique are not influential on postoperative outcome and survival. Patients who have metastatic lesions in posterior fossa tend to have shorter survival duration. Meticulous microsurgical resection in selected patients may improve overall performance status of patients with single or multiple metastases without significantly increasing surgical morbidity. Higher KPS score at discharge is associated with longer survival duration. Limitations of our study were its small sample size and relatively short follow-up period. More data with larger sample size and longer term follow-up are needed.

**Ethics Committee Approval:** Ethics committee approval was received for this study from the Medical Specialty Education Committee of İstanbul Haydarpaşa Numune Tranining and Research Hospital (62977267-771).

**Informed Consent:** Written informed consent was obtained from the parents of the patients who participated in this study.

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