Recursive Partitioning Analysis (RPA) Classification Predicts Survival in Patients with Brain Metastases from Sarcoma

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Key words
- Brain metastases
- Recursive partitioning analysis (RPA)
- Sarcoma
- Surgery

Abbreviations and Acronyms
GTR: Gross-total resection
KPS: Karnofsky Performance Status
MRI: Magnetic resonance imaging
RPA: Recursive partitioning analysis
RTOG: Radiation Therapy Oncology Group
SRS: Stereotactic radiosurgery
WBRT: Whole-brain radiation therapy


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■ OBJECTIVE: **Sarcoma rarely metastasizes to the brain, and there are no specific treatment guidelines for these tumors. The recursive partitioning analysis (RPA) classification is a well-established prognostic scale used in many malignancies. In this study we assessed the clinical characteristics of metastatic sarcoma to the brain and the validity of the RPA classification system in a subset of 21 patients who underwent surgical resection of metastatic sarcoma to the brain**

■ METHODS: **We retrospectively analyzed the medical, radiological, surgical, pathological, and follow-up clinical records of 21 patients who were operated for metastatic sarcoma to the brain between 1996 and 2012. Gliosarcomas, sarcomas of the head and neck with local extension into the brain, and metastatic sarcomas to the spine were excluded from this reported series.**

■ RESULTS: **The patients' mean age was 49.6 ± 14.2 years (range, 25–75 years) at the time of diagnosis. Sixteen patients had a known history of systemic sarcoma, mostly in the extremities, and had previously received systemic chemotherapy and radiation therapy for their primary tumor. The mean maximal tumor diameter in the brain was 4.9 ± 1.7 cm (range 1.7–7.2 cm). The group's median preoperative Karnofsky Performance Scale was 80, with 14 patients presenting with Karnofsky Performance Scale of 70 or greater. The median overall survival was 7 months (range 0.2–204 months). The median survival time stratified by the Radiation Therapy Oncology Group RPA classes were 31, 7, and 2 months for RPA class I, II, and III, respectively ($P = 0.0001$).**

■ CONCLUSIONS: **This analysis is the first to support the prognostic utility of the Radiation Therapy Oncology Group RPA classification for sarcoma brain metastases and may be used as a treatment guideline tool in this rare disease.**

INTRODUCTION

Metastasis is the most common type of tumor in the brain (9). The incidence of brain metastatic disease gradually is increasing, most probably because of earlier detection, improvements in treatments leading to increased overall survival of patients with cancer, the increasing age of the population, and nonpenetration of chemotherapeutic agents into the brain (8). The current standard treatment of brain metastases includes surgical resection, whole-brain radiation therapy (WBRT), stereotactic radiosurgery (SRS), and various combinations of these therapies.

Prognostic factors play an important role in determining how aggressively to treat a patient's brain metastases. The Radiation Therapy Oncology Group (RTOG) developed 15 years ago the recursive partitioning analysis (RPA), a prognostic score based on data from 3 consecutive RTOG trials enrolling more than 1200 patients with brain metastases (4). The RPA is one of the first and the simplest methods to predict survival in patients with newly diagnosed brain metastases. Three prognostic classes were defined, including age, Karnofsky Performance Status (KPS), and control of primary disease. Current treatment paradigms largely are based on data from lung and breast carcinomas that are the most common origin for brain metastases.

Given that the natural history of each malignancy differs, it is more beneficial to analyze a uniform group of patients. There are several systemic cancers that rarely metastasize to the brain and for which management guidelines are lacking. We report our retrospective review to test the validity of the RPA classification system in a subset of 21 patients who underwent surgical resection of metastatic sarcoma to the brain and assess the clinical parameters that may affect patient's survival.

MATERIALS AND METHODS

The study was approved by the Tel-Aviv Medical Center Institutional Research Board (0188-13 TLV). The patients' medical, radiological, functional, surgical, pathological, and follow-up clinical records were reviewed. Patients with gliosarcoma, sarcoma of the head and neck with local extension into the brain, and metastatic sarcoma to the spine were excluded from this series. Pathological diagnosis was determined according to the World Health Organization criteria (5). Demographics and clinical and survival data were retrieved from the hospital database. Specifically, age, sex, clinical symptoms at presentation, type of sarcoma and other extracranial systemic metastases, previous treatment, and postoperative radiation treatment were documented. The KPS was used to assess

preoperative functional status, and the scoring was divided above and below 70. Computed tomography or magnetic resonance imaging (MRI) studies were obtained and reviewed, and maximal tumor diameter and tumor location was determined according to specific hemisphere and location for each patient. The extent of tumor resection was based on a postoperative MRI or Computed tomography scan performed within 48 hours after surgery. Gross-total resection (GTR; 95 % of the lesion) was defined by the absence of residual tumor enhancement on the postoperative MRI, and subtotal resection (90% of the lesion) by the demonstration of small residual tumor enhancement. Postoperative mortality and surgery-related complications were recorded if they occurred within 30 days after surgery. Survival was calculated from the diagnosis of brain metastasis to death.

Recursive Partitioning Analysis

Patients were classified based on the RPA scoring system. RPA class I patients included patients with KPS $\geq$70, age 65 years or younger, with controlled primary disease and no extracranial metastases. RPA class III patients included patients with KPS <70 and RPA class II included all the others.

Statistical Analysis

Descriptive statistics were given as median, mean and SD for continuous variables and frequency distribution for categorical variables. Median survival was calculated by using the Kaplan-Meier plots. Univariate and multivariate analyses were used to identify factors affecting survival and determined by Cox proportional-hazards model. Survival differences between groups were statistically analyzed by using the log-rank test. All statistical analyses were performed using SAS for Windows 9.2 (SAS Institute, Cary, North Carolina, USA).

RESULTS

Patient Population

Of 1115 patients with brain metastases who underwent surgical resection of their lesion during the specified time period of the study, we identified 21 (1.8%) patients who were treated for metastatic sarcoma to the brain. The mean age of the patients was 49.7 $\pm$ 13.6 years (range, 25–75, 10 females) at the time of diagnosis of brain metastases. Sixteen patients had a known previous diagnosis of sarcoma, including uterine leiomyosarcoma (n = 4), synovial sarcoma (n = 4), undifferentiated sarcoma (n = 3), pleomorphic sarcoma (n = 3), Ewing's sarcoma (n = 2), liposarcoma (n = 2), chondrosarcoma (n = 2), and osteosarcoma (n = 1). All 16 patients had been previously treated with systemic chemotherapy and local radiation therapy. Seven patients had no extracranial metastases at the time of brain metastases diagnosis. Seven patients harbored lung metastases at the time brain metastases were diagnosed. In 5 patients, brain metastases was the first manifestation of the sarcoma.

Headache was the most common presenting symptom (n = 10, 48%) followed by a new onset of seizures (n = 5, 24%), focal neurological deficits, such as hemiparesis (n = 4, 19%), and dysphasia (n = 3, 14%). In 14 patients, the tumor was located in the right hemisphere. The most common location was the parietal lobe (n = 8, 38%) followed by the frontal lobe (n = 6, 29%), the temporal lobe (n = 4, 19%), and the cerebellum (n = 2, 9%). At diagnosis, the group's median KPS was 80. The mean maximal tumor diameter was 4.9 $\pm$ 1.7 cm (range 1.7–7.2 cm). All tumors exhibited heterogeneous enhancement with a relatively mild degree of surrounding edema. Eighteen patients underwent GTR, 2 underwent subtotal resection, and 1 underwent brain biopsy only. One patient (4.7%) died within 1 week after surgery because of bone marrow aplasia and sepsis that was related to chemotherapy that had been administered preoperatively. Nine patients (42.9%) experienced tumor recurrence within 4 months from the first operation: multiple new brain metastases developed in 7 patients. Local recurrence occurred in only 2 patients. Four patients underwent recraniotomy for resection of a symptomatic recurrent tumor.

Adjuvant Therapy

Fourteen patients have received postoperative radiotherapy (71.4%). Seven (50%) patients received WBRT, 6 (43%) received SRS, 1 (7.1%) received combination of SRS and WBRT, and 4 patients did not receive postoperative radiation therapy.

Parameters That Enhanced Survival in Patients with Sarcoma Brain Metastases

The median overall survival of the 21 patients was 7 months (range, 0.2–204 months) (Figure 1). Table 1 summarizes the statistical analyses for survival data.

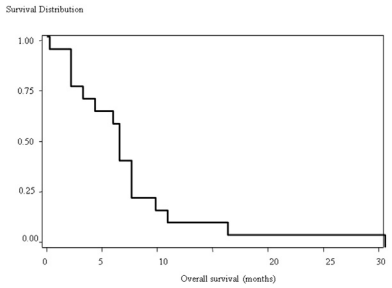

Figure 1. Kaplan-Meier plot showing the median overall survival of the 21 study patients.

RPA

Application of the RTOG RPA classification system to the current patients cohort reveled that RPA class I was associated with prolonged survival of 31 months (n = 8; range, 3–204 months) compared with survival of 7 (n = 9; range, 6–33 months) and 2 months (n = 4; range, 0.2 $\pm$ 5.5 months) for patients in RPA classes II and III, respectively (P = 0.0001) (Figure 2). (RPA classes I vs. II, P = 0.0038; RPA classes I vs. III, $P < 0.0001$; RPA classes II vs. III, P = 0.40). Patients with KPS <70 had a median survival of 5.7 months compared with 7 months for patients with KPS >70; this did not reach, however, statistical significance (P = 0.2).

Postoperative Radiation Therapy

Median overall survival in patients treated with combination therapy of surgical resection followed by WBRT was 31 months, 8 months for those who were treated with surgical resection followed by SRS, and 5 months for those who were treated with surgical resection without any further treatment. The overall survival in one patient treated with combination therapy of surgical resection followed by SRS and WBRT was 33 months. Unfortunately, data on postoperative radiation treatment were not available for 3 patients.

DISCUSSION

Brain metastases from sarcoma are rare and their clinical course and optimal treatment are not well described. Information in the literature relies mainly on anecdotal case reports or case series with a small number of patients. Herein, we present the clinical course of 21 patients with sarcoma brain metastases who underwent surgical resection during a period of 16 years.

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