Retrospective study of 229 surgically treated patients with brain metastases: Prognostic factors, outcome and comparison of recursive partitioning analysis and diagnosis-specific graded prognostic assessment

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Abstract

Background: Metastases are the most frequent tumors in the brain. Most often used scoring systems to predict the outcome are the RPA (Recursive Partitioning Analysis) classification and the DS-GPA (Diagnosis-Specific Graded Prognostic Assessment) score. The goal of our study was to determine prognostic factors which influence outcome in patients who undergo surgery for brain metastases and to compare different outcome scores.

Methods: Two hundred and twenty-nine patients who underwent surgery for brain metastases in our institution between January 2005 and December 2014 were included in the study. Patient data were evaluated retrospectively.

Results: The mean survival time was 19.2 months (median survival time, MST: 8 months), for patients with a single metastasis (n = 149) 17.6 months (MST: 8 months), and for patients with multiple metastases (n = 80) 17.9 months (MST: 6 months). Significant influence on MST had age <65 years (9 vs. 5 months, P = 0.002), female sex (10 vs. 6 months, P < 0.001), RPA Class I and II (11 vs. 4 months, P < 0.001), Karnofsky score >70% (11 vs. 4 months, P < 0.001), and postoperative radiotherapy (8 vs. 5 months, P < 0.002). To evaluate the diagnostic power of DS-GPA and RPA score in respect of survival, two Cox regressions were modeled, where the RPA classification showed a better predictive power.

Conclusion: Favorable factors for prolonged survival were KPS >70%, RPA Class I and II, age <65 years, female sex, a DS-GPA Score of 2.5–3 and 3.5–4, and adjuvant radiotherapy. The RPA Classification was more accurate in predicting the outcome than the DS-GPA score.

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INTRODUCTION

Almost 25% of all patients with oncological diseases present with cerebral metastases.\textsuperscript{[7,17]} Metastases are the most frequently occurring tumors in the brain, averaging about 30 to 40% of all cerebral lesions. Primary tumors include lung cancer (50%), including small cell (SCLC) and non-small cell (NSCLC) lung cancer, breast cancer (15–20%), gastrointestinal tumors (5–10%), melanoma (5–10%), urogenital tumors (5–10%), and carcinoma of unknown primary (CUP, 10%).\textsuperscript{[11,12,51,64]}

Surgery and radiosurgery are established treatment strategies for patients with single brain metastasis, followed by radiation therapy.\textsuperscript{[47]} In patients with multiple brain metastases whole brain radiation therapy (WBRT) is the gold standard and surgery is performed in selected cases, usually when there are large space-occupying lesions often in metastases of unknown primaries at the time of diagnosis.\textsuperscript{[46,47]} In the past decade stereotactic radiotherapy became part of the standard therapy.

Median survival time (MST) in patients with brain metastases without any therapy is 1 month only and with steroids around 2 months. MST after WBRT is 3–6 months. MST after resection of brain metastasis is differently reported in literature in the range of between 6 and 17 months.\textsuperscript{[11,12,51,64]}

Surgical resection plays an important role in relieving mass effects and decompressing eloquent areas of the brain causing improvement of the neurological status.\textsuperscript{[32]} To benefit from surgical resection, a patient must be medically suitable, with a disease prognosis amenable to benefit from local central nervous system tumor control.\textsuperscript{[35]} This has led to the formulation of prognostic indicators. Most often used scoring systems to predict the outcome are the RPA (Recursive Partitioning Analysis) Classification and the DS-GPA (Diagnosis-Specific Graded Prognostic Assessment) score. The RPA Classification was introduced by the RTOG (Radiation Therapy Oncology Group) in 1997 using retrospective data on 1200 patients.\textsuperscript{[16]} It recognizes three prognostic classes. The new Graded Prognostic Assessment as well as DS-GPA were established after data of 3940 patients from 1987–2007 were retrospectively analyzed.\textsuperscript{[58]} It recognizes four prognostic classes and is specific for the primary tumor.

The goal of our study was to determine prognostic factors which influence outcome in patients who undergo surgery for brain metastases and to compare different outcome scores.

MATERIALS AND METHODS

Two hundred and twenty-nine patients who underwent surgery for brain metastases in our institution between January 2005 and December 2014 were included in this study. The follow up period was extended to April 2017. Patient data were retrieved from charts and electronic databases. The patient data were evaluated retrospectively.

All patients were evaluated with respect to the following parameters: age, sex, primary tumor, presence of extracranial metastases assessed by contrast-enhanced computed tomography scan of thorax, abdomen, and pelvis, location of the metastasis (differentiating between supra- and infratentorial lesions as well as eloquent and non-eloquent region), number of metastases, number of resected lesions, MST, preoperative and postoperative Karnofsky Performance Score (KPS), RPA, DS-GPA, complications, postoperative radiotherapy, postoperative chemotherapy, and metastasis recurrence.

Two hundred and twenty-nine patients who underwent surgery for brain metastases in our institution between January 2005 and December 2014 were included in this study. Follow-up period ranged from 1 month to 126 months with a mean follow-up of 10.3 months. Until the end of the follow-up, 207 patients died and 22 patients (9.6%) were alive.

Surgery was performed for patients with symptomatic single or multiple brain metastases. The indications for surgery included large supra- and infratentorial space-occupying lesions and brain metastases of unknown primary at the time of the diagnosis (metastasis as the first symptom of the primary tumor).

Survival was calculated from the day of the resection of the brain metastasis until death or until the end of the follow-up period. Patients were followed by MRI at 3 months interval. Overall survival rates were calculated using the Kaplan–Meier method. Differences between the Kaplan–Meier curves were determined with the log-rank test (univariate analysis); only if Kaplan-Meier curves crossed the Tarone–Ware test was used. P values <0.05 were considered statistically significant. All statistical computations were performed using SPSS Statistics 23 (IBM, Germany).

To evaluate the diagnostic power of DS-GPA and RPA scoring systems with respect to survival, two Cox regressions were modeled. In the first Cox regression model, the predictor of survival is the DS-GPA score; in the second model, the predictor of survival is the
RPA Score. The model accuracy is assessed by means of the fit statistic – 2 log likelihood and the overall score (Chi-square).

RESULTS

Patient characteristics
Two hundred and twenty-nine patients who underwent surgery for brain metastases in our institution between January 2005 and December 2014 were included in the study. There were 114 male (49.8%) and 115 female (50.1%) patients. Patient age ranged from 26 to 86 years, with the medium age being 59.7 years. Table 1 summarizes the patient characteristics.

Follow-up period ranged from 1 month to 126 months with a mean follow-up of 10.3 months. Till the end of the follow-up 207 patients died and 22 patients (9.6%) were still alive.

One hundred and forty-nine patients (67 male and 82 female) or 65.1% underwent surgery for single metastasis, and 80 patients (47 male and 33 female) or 34.9% underwent surgery for multiple brain metastasis. Forty-one patients had two metastasis (12.0%), 10 had three metastases (4.4%), 7 had four (3.1%), and 22 more than four metastases (9.6%). Among 41 patients with two metastases, both lesions were resected in 9 patients and one lesion in 32 patients. From 10 patients with three metastases, in 1 patient all three metastases were resected, in 1 patient two out of three and in 8 patients only one metastasis. From 7 patients with four metastases, in 2 patients all four metastases were resected, in 1 patient two out of four, and in 4 patients one metastasis. From 22 patients with more than four metastases, all metastases were resected in 2 patients and in 20 patients only one metastasis was operated. The maximal number of metastases resected in 1 patient was five.

For 156 patients or 68.1%, surgery was performed due to a supratentorial lesion; in the remaining 73 cases or 31.9%, an infratentorial lesion was resected. In 91 cases or 39.7%, the lesions were located in an eloquent area, among them 35 operations or 15.3% were performed due to tumors located in the central region.

According to the primary tumor, we divided the patients into seven groups – lung cancer, breast cancer, melanoma, gastrointestinal tumors, renal carcinoma (including urothel carcinoma), carcinoma of unknown primary (CUP), and others. The most common primary tumors were lung cancer (SCLC and NSCLC, 86 or 37.5%), followed by breast cancer (50 or 21.9%). In 30 patients or 13.1%, tumors of the gastrointestinal tract were primary tumors (14 with rectal carcinoma, 8 with colon carcinoma, 2 each with hypopharynx carcinoma and esophagus carcinoma, and 1 each with hepatocellular, stomach, pancreas, and peritoneal carcinoma). Twenty-four patients

| Table 1: Patient characteristics |
|---------------------------------|
| Characteristic                  | Number of patients |
| Sex (M:F)                       | 114:115            |
| Age                             | Median 59.7 years (range 26-86) |
| Follow-up                       | Mean 10.3 months (range 1-126) |
| Number of metastases            |                   |
| Single metastasis               | 149               |
| Multiple metastases             | 80                |
| Tumor location                  |                   |
| Supratentorial                  | 156               |
| Infratentorial                  | 73                |
| Site of primary tumor           |                   |
| Lung carcinoma                  | 86                |
| Breast                          | 50                |
| Gastrointestinal tract          | 30                |
| Melanoma                        | 24                |
| Renal carcinoma                 | 15                |
| Ovarian carcinoma               | 6                 |
| Carcinoma of unknown primary (CUP) | 4            |
| Testicular carcinoma            | 2                 |
| Prostatic carcinoma             | 2                 |
| Others                          | 7                 |
| Extracranial metastases at the time of diagnosis | 126 |
| Symptoms                        |                   |
| Signs of elevated intracranial pressure | 117 |
| Motor neurological deficit      | 65                |
| Speech disturbances             | 25                |
| Visual disturbances             | 25                |
| Seizures                        | 27                |
| KPS Score preoperative          |                   |
| KPS <70                         | 87                |
| KPS >70                         | 142               |
| KPS Score postoperative         |                   |
| KPS <70                         | 86                |
| KPS >70                         | 143               |
| RPA Classes preoperative        |                   |
| Class I                         | 67                |
| Class II                        | 79                |
| Class III                       | 83                |
| RPA Classes postoperative       |                   |
| Class I                         | 66                |
| Class II                        | 80                |
| Class III                       | 83                |
| DS-GPA Classes preoperative     |                   |
| 0-1.4                           | 50                |
| 1.5-2                           | 65                |
| 2.5-3                           | 72                |
| 3.5-4                           | 42                |

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or 10.5% had a melanoma as the primary tumor and 15 or 6.5% had renal carcinoma (renal cell carcinoma in 10 and urinary bladder urothel carcinoma in 5 patients). There were 6 patients with ovarian carcinoma (2.6%), four patients with carcinoma of unknown primary (1.74%), 3 patients with cervical cancer (1.31%), 2 patients each with testicular cancer and prostatic cancer (0.87% each), and 1 patient each with chloroma, endometrium carcinoma, vulvar cancer, follicular carcinoma of thyroid gland, malignant trophoblastosis, malignant peripheral nerve sheath tumor, and leiomyosarcoma (0.4% each). At the time of operation, 126 patients or 55% had extracranial metastases.

The most common symptoms at the time of presentation were signs of elevated intracranial pressure, including headache in 66 patients (28.8%), often combined with nausea and vomiting (51 cases or 22.3%). Sixty-five patients or 28.3% had a motor neurological deficit (monoparesis or hemiparesis). Speech disturbances (motoric, sensory, or global aphasia, usually in lesions near classical Broca or Wernicke area) occurred in 25 patients (10.9%) and visual problems (usually retro orbital lesions or lesions involving the primary visual cortex in the occipital lobe) in another 25 patients. Twenty-seven patients or 11.8% presented with seizures. In 27 cases, the patients were asymptomatic and the metastasis was discovered during staging for metastasis of the known primary tumor. In 9 patients or 3.93%, hydrocephalus occurred with the need of implantation of ventriculoperitoneal or ventriculoatrial shunt. In all of these cases, occlusive hydrocephalus occurred due to infratentorial metastasis and did not resolve after the resection of the lesion. In 13 patients or 5.67%, patients presented with intracerebral hemorrhage due to hemorrhage in the metastasis; in 5 cases the primary tumor was melanoma, in 4 cases renal carcinoma, in 2 cases breast cancer, and in 1 each prostate cancer and NSCLC. In 76 patients or 33.2%, the cerebral metastasis led to the first diagnosis of the primary tumor.

### Mean survival time and median survival time

The mean survival time of the whole group was 19.2 months (SE 2.289 months, 95% CI lower bound 14.7, upper bound 23.7); MST was 8 months (SE 0.752 months, 95% CI lower bound 6.5, upper bound 9.4) [Figure 1]. For patients with a single metastasis (n = 136) mean survival time was 17.6 months (MST 8 months) and for patients with multiple metastases (n = 70) 17.9 months (MST 6 months) [Figure 2].

### Age

One hundred and thirty-seven patients or 59.8% were at the time of surgery younger than 65 years. Age <65 years had a significant influence on median survival time (9 months vs. 5 months, P = 0.002) [Figure 3].

### Sex

Female sex had a significant influence on median survival time (10 months vs. 6 months, P < 0.001) [Figure 4].

### Karnofsky performance score

One hundred and forty-two patients or 62% had a preoperative KPS >70% and 87 or 38% had KPS <70%. Preoperative KPS >70% had a significant influence on median survival time. There is a strong correlation between preoperative and postoperative KPS. Thirty-eight percent of our patients had preoperatively a KPS <70%. Ninety-four percent of patients with a KPS <70% preoperatively had KPS <70% postoperatively. Among all the patients with a preoperative KPS >70%, 97% had a postoperative KPS >70% and only 3% deteriorated. A postoperative KPS >70% also showed significant correlation to prolonged MST (11 vs. 4 months, P < 0.001) [Figure 5].

One hundred and forty-two patients with KPS >70% had a MST of 9 months (SE 0.827 months), there were 102 patients with single and 40 with multiple brain metastasis, with a MST of 10 and 8 months, respectively. The patients with single metastasis with KPS >70% had a significantly longer MST of 10 months.

### Recursive partitioning analysis

The patients with RPA Class I and II had the same median survival time (11 months). RPA Classes I and II showed significant correlation with a prolonged median survival time (11 months vs. 4 in RPA Class III, [Figure 1].

**Figure 1:** Kaplan–Meier curve with median survival time (MST) for the whole group.
One patient changed postoperative from Class I into Class II, 2 patients moved from class II to class III, and 3 patients due to a change in their KPS Score changed from Class III to Class II. In KPS Score, there was a strong correlation between preoperative and postoperative RPA Class, and the postoperative RPA class showed a significant correlation with prolonged MST ($P < 0.001$).

**Primary tumor and Diagnosis-Specific Graduated Prognostic Analysis**

According to the primaries, the observed differences in the MST did not reach statistical significance. Patients with breast cancer metastases had the longest median survival time of 8 months. SCLC and NSCLC, melanoma, and renal cancer had a MST of 7 months each, gastrointestinal tumors, as well as group of other tumors 6 months and CUP 2 months ($P = 0.030$). The longest MST of 11 months had a subgroup of 32 patients with single metastasis of the breast cancer. All 32 patients underwent adjuvant radiotherapy.

DS-GPA score showed a highly significant predictive power ($P < 0.005$). The patients with DS-GPA score of 0–1.4 had a median survival time of 4 months, score 1.5–2 MST of 7 months, the ones with a score 2.5–3 had MST of 9 and with DS-GPA score of 3.5–4 MST of 17 months. These differences were highly significant ($P < 0.0001$) [Figure 7].

**Neurological outcome**

One hundred and twenty-five patients (54.6%) had an acute neurological deficit before the surgery (motor deficit, speech deficit, visual disturbances). Among 125 patients which had a neurological deficit preoperatively, 98 patients or 78.2% improved after surgery, two worsened and 25 remained unchanged. Fifty-eight patients or 25.3% had a postoperative neurological deficit. Among these patients, in 33 patients, the neurological deficit improved after surgery and among 25 it remained unchanged.

Sixty-five patients had a preoperative motor neurological deficit (28.4%). In 19, the postoperative motor deficit didn’t resolve (29.2%). In 15 patients, the deficit was hemiparesis, and in 4 a monoparesis.
Aphasia occurred in 25 or 11% of patients. In 3 patients, the aphasia did not resolve after surgery. Only 6 patients (2.9%) deteriorated neurologically after surgery. In 2 patients, hemiparesis and in 4 patients hemianopsia occurred after surgery as a new neurological deficit.

Radiotherapy
Postoperative radiotherapy was performed in 182 patients (79.4%). Postoperative whole brain radiotherapy (WBRT) with total dose of 30 Gray (Gy) was performed in 160 patients (69.9%). Twenty-two patients (9.6%) underwent fractionated stereotactic radiotherapy (FSRT) postoperatively (single dose 3 Gy, total dose 30–36 Gy). In the remaining 47 patients (20.5%) radiotherapy was not performed due to low KPS or due to patient decision against radiotherapy. In 8 patients, FSRT was performed due to recurrence after WBRT. Six patients who were treated with FSRT due to single metastasis experienced permanent growth after the treatment with neurological deficits due to edema and then underwent surgery.

Postoperative radiotherapy had significant influence on MST compared to patients who did not receive any radiotherapy (8 months vs. 5 months, \( P < 0.02 \)) [Figure 8].

The number of metastases, postoperative chemotherapy, preoperative radiotherapy as well as presence of extracranial metastases were not significant in influencing median survival time \( (P > 0.05) \).

Complications and perioperative mortality
Eighteen patients (7.9%) died in the first 30 days after the surgery. Ten of these patients had a preoperative KPS <70% (RPA Class III). Causes of death were rapid progression of the primary disease \( (n = 8) \), sepsis due to pneumonia in mechanically ventilated patients \( (n = 6) \), and myocardial infarction with heart failure \( (n = 3) \). One patient died due to brainstem infarction as an operative complication after resection of an infratentorial metastasis.

We divided complications as surgical and nonsurgical. Surgical complications were divided into local and neurological. Nonsurgical complications were systemic. In 20 patients (8.7%), local complications leading to revision surgery occurred. In 16 patients, wound healing deficits occurred which needed to be reoperated (in 7 patients together with intracranial abscess or subdural empyema), in 3 patients cerebrospinal fluid (CSF) fistula, and postoperative hemorrhage in the resection cavity in 1 patient. Only six patients (2.6%) deteriorated neurologically after surgery. Systemic complications occurred in 17 patients (7.4%) and included pulmonary embolism \( (n = 5) \), pneumothorax \( (n = 2) \), sepsis due to pneumonia in mechanically ventilated patients \( (n = 6) \), myocardial infarction with heart failure \( (n = 3) \), and status epilepticus \( (n = 1) \).

Recurrence
Local recurrence occurred in 41 or 17.9% patients, and distant new metastases occurred in 39 or 17% of all patients. In 23 patients or 10%, both local and distant recurrence occurred. In case of recurrence, reoperation
or FSRT were considered. Reoperation for recurrence was performed in five patients. These patients were not double counted in the study.

Significant factors for prolonged survival
Prognostic favorable factors for prolonged survival were KPS >70%, RPA Class I and II, age <65 years, female sex, DS-GPA Score of 2.5–3 and 3.5–4, and adjuvant WBRT. Patients with breast cancer metastases had the longest median survival time.

Comparison of RPA classification and DS-GPA classification
To evaluate the diagnostic power of DS-GPA and RPA class in respect of survival, two Cox regressions were modeled. RPA Classification was more accurate in predicting the outcome than the DS-GPA score. In both models the predictive power of two gradings is highly significant ($P < 0.005$), the RPA classification showed a better predictive power ($-2 \log \text{likelihood} = 1771.235$ and $\chi^2 = 16.807$).

DISCUSSION
In the past 25 years, several studies have analyzed prognostic factors which influence survival in patients operated for brain metastasis. Five large studies were performed in Germany, Italy, South Korea, and USA. An overview of the most important studies on the surgically treated brain metastases with comparison of prognostic parameters is provided in Table 2. The resources expended in the research and treatment of brain metastases have not been commensurate with the scope of the problem, in part due to an often nihilistic approach to the problem, given the relatively short survival of many patients with metastatic disease to the brain, the inability of regulators and pharmaceutical companies to come to grips with a “compartmental solution,” i.e. improving intracranial control without necessarily impacting survival, and the inability of most drugs to cross the blood–brain barrier in sufficient concentrations to have a genuine impact on intracranial metastases.

Indications
Our patients consisted of a selected group judged as not being suitable for radiotherapy alone. We decided for the resection of the tumor when it offered a significant mass reduction to reduce intracranial pressure and gain time for adjuvant treatments. An important indication was also an unknown primary tumor. The indication for resection of infratentorial metastasis was given to avoid occlusion of the fourth ventricle and hydrocephalus. Supramarginal resection was performed, which in a recent study of Pessina et al. showed to be safe and effective for selected patients with large brain metastasis. In patients with multiple metastasis, usually the supratentorial metastases with significant mass (>25 cm³) were resected or infratentorial metastases with edema and compression of the fourth ventricle. Six patients who were treated with SRS due to single metastasis experienced permanent growth after the treatment with neurological deficits due to edema and then underwent surgery. A recent study by Shimony et al. showed that resolution of tumor-associated edema in brain metastasis suitable for either surgery or SRS was significantly faster after surgical resection than after SRS.

Despite the advantages of SRS or radiotherapy as a local treatment, studies on surgical resection have demonstrated that surgery is even more beneficial for improving neurological status and survival. With more advances in surgical techniques, intraoperative imaging, and the risk of misdiagnosis without histological diagnosis, surgical resection is still a promising and reasonable treatment for brain metastases. In addition to improved survival, surgical resection leads to reduction of mass effects with symptom relief and decompression of the CSF pathways, especially in the posterior fossa, preventing occlusive hydrocephalus with life threatening complications. Extent of resection and its influence on MST remains controversial. While the study of Lee et al. showed prolonged MST in patients who underwent gross total resection regardless of the postoperative radiotherapy, as well as a higher complication rate in the group of patients who underwent subtotal resection, in the study of Schödel et al., extent of resection was not statistically significant. Pecuneal resection in comparison to en-bloc resection showed larger incidence of complications in the study of Patel et al. The recent study of D’Andrea et al. showed a correlation of surgery of the primary tumor to prolonged MST.

Median survival time
In our study, we dealt with two groups of patients, the group with single metastasis and the group with multiple metastases. So far in literature there are five major studies including patients both with single and multiple metastases evaluating outcome after surgery. Other studies include either patients with single metastasis or patients with multiple metastases.

Lee et al. reported a median survival in their surgical series of 19.3 months, 28.1 months in patients with no evidence of systemic disease, and 23.3 months in patients with stable disease. Pakc et al. reported a mean survival of 8.5 months after surgery plus WBRT versus 5.3 months after WBRT alone, whereas Schackert et al. reported a median OS of 6.5 months, including 9.4 months as longest time and 4.2 months as the shortest time not being affected by resection extent or histology.

MST was 8 months for the entire group, and 8 months for the group of single metastasis and 6 months for the group of multiple metastases. MST in this study was larger.
Table 2: Overview of studies which evaluated relevant prognostic factors in patients with surgically treated brain metastases with comparison of study design, number of patients, number of metastasis, median age, sex, preoperative performance status, MST, primary tumor, adjuvant radiotherapy, type and duration of follow up, use of any prognostic scores or RPA/DS-GPA Classification with overview of prognostic factors relevant for survival

| Author and year | Study design | Number of patients | Number of metastasis | Median age (yrs) | Sex | Preoperative performance status | Primary tumor | Adjuvant radiotherapy | Type and duration of follow up | Use of any prognostic scores or RPA/DS-GPA Classification | Prognostic factors relevant for survival |
|-----------------|--------------|--------------------|----------------------|------------------|-----|---------------------------------|---------------|----------------------|-----------------------------|---------------------------------|-------------------------------------|
| Patchell et al. 1990[40] | Randomized prospective | 48 | Single | 59 | 32 male 16 female | All KPS > 90% | 40 weeks | Not specified | WBRT | Follow up identical to length of survival | Adjuvant WBRT |
| Bindal et al. 1993[10] | Retrospective | 82 | Single and multiple | 52 | 27 male 29 female | Mean KPS 76-79 + SD | 10 months | multiple 14 months single | Melanoma Breast Lung Sarcoma Colon Renal Ovary Unknown | Follow up to the last follow up examination or death | Absence of systemic disease Removal of all lesions in selected patients with multiple metastases |
| Hazuka et al. 1993[20] | Retrospective | 46 | Single and multiple | 54 | 32 male 14 female | 84% of patients RTOG Class I and II (mild to moderate deficits) | 11 months | Lung Melanoma Genito urinary Breast Unknown | WBRT | Follow up identical to length of survival | RTOG Classification Number of metastasis RTOG Class I/II |
| Schackert et al. 2001[47] | Retrospective | 104 | Single and multiple | 61 in singles metastasis, 58 in multiple metastases | Not specified | KPS 70% average in single metastasis KSP 60% average in multiple metastases | 10 months | single metastasis 6 months multiple metastasis | Lung Breast Colon Kidney Melanoma Unknown | WBRT | Not specified | No Extent of extracerebral tumor burden Age < 70 years Number of metastasis Solitary metastasis Adjuvant WBRT in patients with single metastasis Preoperative KPS > 70%, post operative KPS > 80% Histology (breast cancer favorable, renal cell cancer and melanoma non-favorable) |
| Korinth et al. 2002[26] | Retrospective | 187 | Single and multiple | 58.5 | 99 male and 58 female patients | 75% KPS > 80 25% KPS < 80 | 9.8 months | Lung Gastrointestinal Renal cell cancer | WBRT | Follow up identical to length of survival | None |

Contd...
| Author and year | Study design | Number of patients | Number of metastasis | Median age (yrs) | Preoperative performance status | Primary tumor | Adjuvant radiotherapy | Type and duration of follow up | Use of any prognostic scores or RPA/DS-GPA Classification | Prognostic factors relevant for survival |
|----------------|--------------|--------------------|----------------------|------------------|---------------------------------|---------------|---------------------|-------------------------------|---------------------------------------------------------------|--------------------------------------|
| Paek et al. 2005[38] | Retro prospective, single-surgeon | 208 | Single and multiple | 103 male and 105 female patients | 92.3% of patients KPS > 70 | 8 months | Lung | WBRT | Not specified | RPA Class I and II |
| Tan et al. 2007[60] | Retro prospective | 49 | Single and multiple | 27 male and 22 female | 76.4% KPS > 70 | 16.23 months | Lung | WBRT | 1 year | RPA Class I and II |
| Schackert et al. 2013[46] | Retro prospective | 127 | Multiple | 79 male, 48 female | 43.3% KPS > or = 70% 56.7% KPS < 70% | 6.5 months | Lung | WBRT | Median follow up 29 months | RPA Class I vs. II vs. III |
| Lee et al. 2013[27] | Retro prospective | 157 | Single and multiple | 82 male, 75 female | Mean KPS 81.3 +/− SD | 19.3 months | Lung | WBRT | 17 years | RPA Class I and II |
| Schödel et al. 2013[41] | Retro prospective | 206 | Single and multiple | Female 84, male 122 | 9.7% RPA Class I, 77.7% RPA Class II, 12.6% RPA Class II | 6.3 months | Lung | WBRT | 6.1 months | RPA Class I vs. II vs. III |

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than MST in the study of Schödel et al. (6.3 months)\textsuperscript{48} and Mintz et al. (5.6 months)\textsuperscript{32} and was comparable to MST in the study of Pack et al.\textsuperscript{19} Other studies showed larger MST than in this study: 19.3 months in the study of Lee et al.,\textsuperscript{27} 16 months in studies of Schackert et al. and Tan et al.,\textsuperscript{46,47,60} 11 months in D’Andrea et al.,\textsuperscript{13} 5.8–10.6 months in Schackert et al.,\textsuperscript{46} 13.2 months in Smith et al.\textsuperscript{53} Thirty-eight percent of our patients had preoperatively a KPS <70%, which showed a strong correlation to unfavorable outcome, as shown in other studies. Ninety-four percent of these patients remained with KPS <70% after surgery. Our patients with single metastasis with KPS >70% had a significantly longer MST of 10 months. Preoperative KPS >70% and postoperative KPS >80% were found to be prognostic significant for longer MST in the study of Schackert et al.\textsuperscript{46} Table 2 shows the preoperative functional status of the patients in the previous studies. Only the study of Schackert et al., involving patients with multiple metastases, shows a patient cohort with larger percentage of patients with KPS <70 than our study. Korinth et al.,\textsuperscript{26} Pack et al.,\textsuperscript{38} Tan et al.,\textsuperscript{60} and Lee et al.\textsuperscript{27} all recognized preoperative

| Author and year | Study design | Number of patients | Number of metastases | Median age (yrs) | Preoperative performance status | MST (yrs) | Primary tumor | Adjuvant radiotherapy | Type and duration of follow up | Use of any prognostic scores or RPA/DS-GPA Classification | Prognostic factors relevant for survival |
|-----------------|--------------|--------------------|----------------------|------------------|-------------------------------|-----------|--------------|---------------------|-----------------------------|---------------------------------|----------------------------------|
| Smith et al. 2014\textsuperscript{53} | Retro prospective | 150 | Multiple 46.2 | 62.7% female | Not specified 13.2 | Urothel Prostate Other Lung Breast Melanoma Renal-cell Colon | 17 months No | | | | Primary breast histology favorable, primary colon histology unfavorable Female sex |
| D’ Andrea et al. 2017\textsuperscript{13} | Retro prospective | 71 | Single 67 meta stases (n = 70) and multiple (n = 1) | Not specified 11.08 | Lung Kidney Breast Gastrointestinal Melanoma | WBRT SRS Follow up to death or last known follow-up evaluation | RPA GPA | | | | Surgery of primary tumor Surgery + radio therapy + chemo therapy vs. surgery only |
| This study | Retro prospective | 229 | Single and multiple 149 patients (65.1%) single meta stasis 80 patients (34.9%) multiple meta stases | 59.7 | 62% of patients KPS > 70% and 38% of patients KPS < 70% | Lung 86 or 37.5% Breast 50 or 21.9% Gastrointestinal 30 or 13.1% Melanoma 24 or 10.5% Renal 22 carcinoma 15 or 6.5% CUP and others 22 or 10.5% | Adjuvant radiotherapy in 182 patients (79.4%); WBRT in 160 patients (69.9%), FSRT in 22 patients (9.6%) | 10.3 months | RPA DS-GPA Follow Up to end point (death of the patient) in 207/229 patients | Age < 65 years Female sex Pre operative and post operative KPS > 70% RPA Class I and II DS-GPA Score of 2.5-3 and 3.5-4 Adjuvant radiotherapy (WBRT or FSRT) |

Studies in bold include mixed patient cohorts with single and multiple metastases. KPS: Karnofsky Performance Score, MST: Median Survival Time, RPA: Recursive Partitioning Analysis, DS-GPA: Diagnosis-Specific Graded Prognostic Assessment, RTOG: Radiation Therapy Oncology Group, WBRT: whole brain radiation therapy, FSRT: fractionated stereotactic radiotherapy, SRS: stereotactic radiosurgery, CUP: carcinoma of unknown origin, TFG: tumor functional grade.
KPS >70 as a factor showing correlation to prolonged MST.

**Age and gender**

Age was very early recognized as an important factor in survival\cite{20} [Figure 2]. In our study, it was an important prognostic factor which influenced MST, unlike in the study on multiple metastases by Schackert et al.\cite{46} and the recent study of D’Andrea et al.\cite{13} Lee et al.\cite{27} recognized age <65 and Schackert et al.\cite{47} age <70 years as important prognostic factors related to favorable outcome. Gender was also an important prognostic factor. Correlation between female sex and increased survival was noted in previous studies and probably reflects the increased incidence of primary breast malignancy in females.\cite{53} Previous studies have reported excellent survival in breast cancer patients with intracranial metastasis, particularly those with a HER-2-positive phenotype.\cite{56} In our study, similar to the study of Smith et al.,\cite{27} primary breast histology was associated with longer MST compared to other tumor entities but it did not reach statistical significance.\cite{53}

**Recursive partitioning analysis**

Comparing the MST according to RPA classification, our results were highly significant. An MST of 11 months for Class I and II and an MST of 4 months for Class III is longer than the MST predicted in the original paper of Gaspar et al. (7.1 vs. 4.2 vs. 2.3 for Class I, II, and III, respectively). This study has a larger percentage of patients who preoperatively belonged to RPA Class III than the studies of Schackert et al. and Tan et al.\cite{46,60} The patients with RPA Class I and II had the same median survival time (11 months) [Figure 2]. The difference between Class I and Class II is made on the presence of extracranial metastases. Analogue to this, our study showed no impact of the presence of extracranial metastases on MST. This can be explained due to improved screening and treatment modalities which influence disease control for some primary tumors compared to the 1990s and 2000s, even in case of metastases in multiple regions. Paek et al.\cite{38} were the first to show that patients with RPA Class I have longer MST than the others. Our results are consistent with the findings of Lee et al.\cite{27} Tan et al.\cite{60} and Schödel et al.\cite{48} who showed that both RPA Class I and II patients have longer MST than the patients of Class III.

**Primary tumor and Diagnosis-Specific Graduated Prognostic Analysis**

Patients with breast cancer metastases had the longest median survival time of 8 months. This is significantly lower than the study of Smith et al. (22.9 months).\cite{53} This is probably because all patients with single brain metastasis in the study of Smith et al. received radiotherapy (stereotactic radiotherapy in this case) following surgery. In our study, the subgroup of patients with single breast cancer metastasis (n = 32), all of whom received postoperative radiotherapy, showed the largest MST of 11 months. Although there were differences in MST according to the diagnosis of primary tumor, these differences were not statistically significant. It is interesting to note that beside the original papers of Sperduto et al., which led to the establishment of GPA and DS-GPA Classification, only the study of Smith et al. evaluates the influence of diagnosis of primary tumor on survival.\cite{53,56,58,59} Other data from the literature are inconsistent. In the study of Schackert et al., the longest MST in a cohort of multiple metastases had patients with renal cell carcinoma.\cite{61} In contrast to this are findings of Patel et al., where diagnosis of renal cell carcinoma is correlated to higher complications rate and shorter MST.\cite{61} Korinth et al.\cite{40} showed that breast cancer is related to a favorable diagnosis of renal cell cancer and melanoma is associated with a nonfavorable outcome. Kondziolka et al.\cite{24} provided the possible explanation for this. Early clinical series, which primarily evaluated the impact of whole brain radiotherapy, combined all histologies together for many years, with the recognition that normal brain tolerance would set the dose limits, and thus a precedent was set to use the “one size fits all” approach. Second, it was easier to accrue patients to those studies by not excluding specific tumor types, and third the tumor diagnosis evolved from routine hematoxylin and eosin histologic classification, to the inclusion of special stains, and the more recent identification of receptors and genetic/molecular characteristics which segment single histologic entities into multiple different prognostic and treatment subgroups. For example, luminal A, luminal B, and triple negative breast cancers are different diseases in terms of the likelihood of developing brain metastases, responding to therapeutic interventions and survival.\cite{88} There are single studies evaluating the survival in patients with brain metastasis undergoing surgical resection in different primary tumors including lung cancer, renal cell cancer, sarcoma, hepatocellular carcinoma, gastrointestinal carcinomas, and breast cancer.\cite{15,18,19,33,66-70}

According to the DS-GPA Classification, patients with a score of 0–1 had a longer MST than predicted by Sperduto et al. (4 months vs. 3–5.4 for different primary tumors), score 1.5–2 with MST of 7 months (compared to 7.7 in breast cancer, 7.3 in renal carcinoma, 5.5 in lung cancer, 4.7 melanoma, and 4.4 for GI cancers in the original paper of Sperduto et al.), score 2.5–3 had a MST of 9 (compared to 9.4 for lung cancer, 8.8 melanoma, 15.1 breast cancer, 11.3 renal cell carcinoma, 6.9 GI cancer) and with DS-GPA score of 3.5–4 MST of 10 months (less than predicted in all groups of primary tumors). As explained by Kondziolka et al., an important prognostic variable was left out in the previous trials due to not considering the primary tumor in the prognostic
assessment. What is also curious is the relative paucity of melanoma cases, one of the most common primary cancers to spread to the brain. In our study, 10.5% of cases had melanoma as primary tumor.

When compared to DS-GPA Score, RPA Classification showed a better predictive power, although both scores had a highly significant predictive power. This is not to be misunderstood with importance of primary tumor diagnosis, which is not being taken into consideration in RPA classes. Prospective randomized trials are needed to be done to assess new prognostic scores which combine the parameters from RPA classification and DS-GPA score.

Prognostic indices have been utilized in different malignancies with the aim to improve the understanding of patients' prognosis and aid in the clinical and therapeutic decision making. Furthermore, prognostic scores play a crucial role in patient selection, stratification and randomization in clinical trials. They also play an important role in balancing the cost of treatment and providing realistic expectations to the patients' and the caregivers. Multiple studies, albeit retrospective in nature, have elucidated prognostic factors and recommended prognostic scoring systems for brain metastases. Gaspar et al. in 1997 evaluated 1,200 patients from three RTOG trials who were treated with WBRT for brain metastases. Overall, KPS, age, control of primary and the status of extracranial disease were found to impact survival. Using RPA, three classes were formulated. Inherent deficiency of RPA index is that it is best for patients treated with WBRT showing consistent survival within the same class, across different studies but the same may not be true for patients treated with other modalities such as surgery and SRS. Agboola et al. were first to show that RPA Classification has prognostic value in patients treated surgically, whereas Class I showed correlation to favorable outcome. Although Pack et al. postulated that RPA Class III and number of metastases >4 are exclusion criteria in regard to surgery as a valid treatment option, a recent study by Schödel et al. relativizes this parameter by showing that the functional improvement rate was equally distributed throughout the RPA classes, indicating a significant benefit of neurological function and quality of life even in patients belonging to the worst prognostic group. Arita et al. related risk of early death after surgery (with 6 months) to patients who belong to Class III. RPA Class I and II were associated with prolonged MST in studies of Tan et al., Schödel et al., and Lee et al. [Table 2].

In 2007, a new scoring system called the GPA was proposed. The GPA incorporated four factors: age, KPS, extra cranial metastases, and number of metastases. The primary tumor type was not considered in any of the previous prognostic indices, until Sperduto et al. evaluated 4,259 patients from 11 different institutions. Age, KPS, number of brain metastases, and sites of extracranial metastases strongly predicted survival in lung (non small cell and small cell) cancer. Age, KPS, and subtype were the prognostic factors that impacted survival in breast cancer. Only age and KPS were significant factors predicting survival in melanoma and renal cell cancer patients. Among GI cancer patients, only KPS predicted survival. Genetic subtypes of breast cancer had significant effect in prognosis of patients with brain metastases. The basal subtype (ER/PR negative and human epidermal growth factor receptor 2 (HER2) HER2 negative) patients had the shortest survival whereas the luminal B subtype (ER/PR positive and HER2 positive) patients had the best survival. To our knowledge, there has not been a study yet which validated the DS-GPA score in a group of surgically treated patients with brain metastases.

A considerable variation in survival prediction was noted in the study by Kondziolka et al., supporting a need for a better prognostic tool or index. Radiation oncologists and neurosurgeons overestimated the survival while medical/ neuro-oncologists underestimated the survival. Most prognostic scores have some inherent limitations. RPA does not include the number of brain metastases as an important prognostic factor. The DS-GPA was formulated for brain metastases from different primary malignancies but did not consider the role of mutations or imaging characteristics. Another limitation of prognostic indices is that all the factors are derived based on survival and there are no scores that address endpoints other than survival. In recent times, numerous trials have used time to neurologic progression or decline as primary endpoint.

**Single vs. multiple metastases**

The number of metastases was not a significant factor which influenced prolonged median survival time. Smith et al. showed that the 1-year survival for patients with multiple intracranial metastases treated with resection followed with stereotactic radiosurgery is similar to established outcomes in patients with single brain metastasis. In study by Paek et al., there was no difference in MST in patients with single and multiple metastases. Hazuka et al. and Schackert et al. showed that the number of metastasis is relevant for survival, whereas patients with single metastasis who received postoperative radiotherapy had a longer MST. Removal of all lesions in selected patients with multiple metastases showed a correlation to prolonged MST in the study of Bindal et al. The number of metastasis was an important prognostic factor in the study on treatment of multiple metastases of Schackert et al., but only when patients with 2–3 metastases were compared to the ones with 4 or more metastases.
The importance of the actual number of metastases as a significant factor for prognosis was disputed in a recent review article. According to Kondziolka et al., this bias in literature is due to fact that the surgical resection was most often used in patients with one metastasis and that number of metastasis was wrongly used as a reasonable estimate of tumor burden. Studies evaluating radiosurgery in patients with multiple metastases postulated that the total tumor volume and not the number of brain tumors play a key role. In the study by Schackert et al., the number of cerebral lesions influenced the MST, but this difference was only significant for more than four lesions in the cohort. Kondziolka et al. question the whole concept of micro-metastases which can be seen on high-resolution imaging in patients with single metastasis. In the 2010 brain metastases guidelines, the authors concluded that while both single dose SRS and WBRT were effective for treating patients with brain metastases, single dose radiosurgery alone appeared to be superior to WBRT alone for patients with up to three metastases in terms of a survival advantage. If deadly micro-metastases create a diffuse disease scenario, then WBRT populations should be associated with distinct survival advantages. However, in no large study does the addition of WBRT to radiosurgery improve survival.

**Neurological outcome**

Surgical resection causes significant neurofunctional improvement in most patients with brain metastasis independent from RPA classification. Overview of studies which evaluated complications, operative morbidity and mortality as well as neurological outcome is provided in Table 3.

Only 6 patients (2.6%) deteriorated neurologically after surgery. Korinth et al. and D’Andrea et al. report that there were no cases of neurological deterioration in their cohorts. In the study of Tan et al., no patient who was neurologically intact preoperatively deteriorated after surgery, and in most of the other studies, the rate of neurological deterioration following the operation is higher than in our patient group. From 125 patients which had a neurological deficit preoperatively, 98 patients or 78.2% improved after surgery, 2 worsened, and 25 remained unchanged. This is comparable to results of D’Andrea et al., where in a

| Author and year | Number of patients | Preoperative performance status | Surgical complications | Systemic complications | 30-days mortality | Neurological outcome |
|-----------------|--------------------|---------------------------------|------------------------|------------------------|------------------|---------------------|
| Patchell et al. 1990 | 48 | All KPS 90%+ | 17% | Not specified | 4% | Not specified |
| Bindal et al. 1993 | 82 | Mean KPS 76-79 ± SD | 9 patients (11%) | Not specified | 3 patients (3.6%) | 13% and 6% neurological deterioration assigned to different groups |
| Hazuka et al. 1993 | 46 | 84% of patients RTOG Class I and II (mild to moderate deficits) | 4 patients (8.9%) | 4 patients (8.9%) | None | Not specified |
| Arita et al. 2014 | 264 | 70% of patients KPS > 70 | 20 cases (7.6%) | Not specified | 4 patients (1.5%) | 8 patients (3%) with neurological deterioration |
| Schackert et al. 2001 | 104 | KPS 70% average in patients with single metastasis KPS 60% average in patients with multiple metastases | 3 patients (2.9%) | 1 patient (0.96%) | Not specified |
| Korinth et al. 2002 | 187 | 75% KPS > 80 25% KPS < 80 | 19 patients (10.2%) | Not specified | None | No deterioration |
| Tan et al. 2007 | 49 | 76.4% KPS > 70 | 2 patients (3.6%) | 6 patients (12.24%) | None | 2 patients (3.6%) with increased long-term deficit |
| Paek et al. 2005 | 208 | 92.3% of patients KPS > 70 | 13 patients (6%) | 21 patients (13.9%) | 4 patients (1.9%) | 18 patients (8.65%) with neurological deterioration |
| Schackert et al. 2013 | 127 | 43.3% KPS > or = 70% 56.7% KPS <70% | Not specified | Not specified | 7 patients (5.5%) | Not specified |
| Lee et al. 2013 | 157 | Mean KPS 81.3 ± SD | 7 patients (4.5%) | Not specified | 2 patients (1.3%) | Not specified |
| Schödel et al. 2013 | 206 | 9.7% RPA Class I, 77.7% RPA Class II, 12.6% RPA Class II | 34 patients (16.6%) | Not specified | None | 6.3% of patients with new neurological deficits |
| Patel et al. 2015 | 1033 | 83% KPS > 70 | 154 patients (15%) | 13 patients (1.2%) | 50 patients (4.84%) | 104 patients (10%) with one or more neurological deficits |
| This study | 229 | 62% of patients KPS > 70% 38% of patients KPS <70% | 20 patients (8.7%) | 17 patients (7.4%) | 18 patients (7.9%) | 6 patients (2.6%) with neurological deterioration |
A retrospective study of 71 surgically treated patients with brain metastasis, 52 patients or 73.2% improved and 19 or 26.7% remained unchanged. As previously described, postoperative temporary or permanent impairment of motor function was not related to the type of primary tumor. However, as expected, postoperative temporary and permanent impairment of motor function was related to tumor location. Korinth et al. published the only study which evaluated location of the metastasis to prognosis and postulated that involvement of frontal and parietal lobes was related to favorable and involvement of temporal lobes to unfavorable outcome. Schödel et al. showed that increased ICP and motor impairment such as hemiparesis are specifically amendable to surgical treatment, whereas aphasia and visual deficits are less beneficially influenced. While we observed the same effect with increased ICP, more patients in our group recovered from aphasia than from motor impairment.

13.1% of patients were asymptomatic. Although routine brain screening is not common, oncologists tend to obtain MRI on any sign of neurological symptoms. In the future, the inclusion of increasing numbers of asymptomatic brain metastases from screening may lead to a lead time bias for survival outcomes.

**Radiotherapy**

Our study confirmed the importance of adjuvant radiotherapy after surgical resection of brain metastases. Postoperative radiotherapy was performed in 79.4% of patients and showed significant influence on MST compared to patients which did not receive radiotherapy (8 months vs. 5 months) [Figure 8]. This effect of radiotherapy on overall survival was shown in previous studies. Historicall, the standard treatment for intracranial metastases has been resection followed by fractionated WBRT.

Two randomized clinical trials have demonstrated that surgical resection is superior to WBRT only, and that WBRT after resection significantly reduces the brain specific recurrence rate. This is in contrast to a report by Mintz et al., which failed to detect a significant beneficial effect of surgical resection. However, the results of this study are controversial because more than 45% of the patients followed in this trial had uncontrolled systemic disease and 40% presented with a KPS of 50 or less. Lee et al. found no influence of the adjuvant radiotherapy on MST.

When used as a primary treatment for solitary metastasis, radiosurgery has been associated with local tumor control rates of 75–94% and less morbidity than WBRT. Radiosurgery has also been shown to reduce local tumor recurrence following gross total resection of a single brain metastasis. Surgery followed by radiotherapy to the resection cavity and synchronous lesions showed to be an effective treatment protocol for patients with intracranial metastasis and will probably completely replace WBRT in the time to come. Longer survival time after radiotherapy was shown in two prospective studies with patients with SCLC in all other entities there are only retrospective data so far. Although WBRT suppresses micro-metastatic lesions outside the field of SRS, it has not been shown to improve mortality. Furthermore, the latest studies show the same MST after surgical excision followed by WBRT compared to radiosurgical treatment of one to three brain lesions. SRS plus WBRT did not show a survival benefit over WBRT alone; however, performance status and local control were significantly better in the SRS plus WBRT group. SRS has shown to be the preferred treatment for patients younger than 50 years without WBRT.

In our study, only 15 patients or 7.28% underwent postoperative FSRT immediately following the operation. These patients had an MST of 15 months, although due to small sample and bias due to the fact that all these patients had a KPS 100% no comparison to the WBRT group is possible. SRS can lead to excellent tumor control and survival rates comparable to surgical evacuation, but it does not primarily reduce mass effects and can induce regressive changes such as intratumoral hemorrhages, per focal edema, and radionecrosis.

This is a valid treatment option for patients with small, deep seated, or multiple tumors located in surgically inaccessible areas and bears specific limitations especially in tumors larger than 3 cm in diameter. However, in patients medically suited for surgical intervention, with tumors larger than 2 cm in diameter causing significant mass effects and neurological deficits, surgical evacuation should be considered as a beneficial treatment strategy for each individual patient independent of rigid prognostic indices.

There are several questions on the issue that the patients who received postoperative radiotherapy had longer MST than the patients who did not receive the treatment, which due to the retrospective character of our study cannot be answered. Do these patients live longer...
because they develop less new metastases in the brain or because the operated and irradiated metastasis showed no recurrence or did the patients who received radiotherapy had controlled disease with less extra cranial metastases where the brain metastasis was not the immediate cause of death, remains to be evaluated in large prospective studies in the future.

Complications

Compared to other studies, we could show a low complication rate. Both neurological deterioration as well as local and systemic complications are lower than in the study of Paek et al., Schackert et al., Patel et al., and Bindal et al. An overview of studies which evaluated complications, operative morbidity, and mortality, as well as neurological outcome is provided in Table 3. From 17 patients who had systemic complications, eight died due to these complications. Among 20 patients with surgical complications, only 1 patient died due to this surgical complication.

Eighteen patients or 7.9% died in the period of 30 days after the surgery, which is higher than in the series of Bindal et al., Hazuka et al., Arita et al., Schackert et al., Paek et al., and Patel et al. possibly because more than half of them (10) had a KPS <70%. As postulated by Arita et al., risk factors for early death (in the original paper defined early death as death 6 months after the operation) were lack of systemic therapy after surgery and uncontrolled extracranial malignancies. Patients who cannot undergo chemotherapy (e.g., due to multidrug resistance to systemic therapy) are at high risk of early death after surgery. Postoperative chemotherapy had no significant influence on MST in our study. This is consistent with the previous studies. D'Andrea et al. showed no significant impact of chemotherapy alone on MST, although the patients who received all three therapy modalities (surgery + radiotherapy + chemotherapy) had a longer overall survival than the patients who received surgery alone. Common neurological causes of death described are leptomeningeal metastases, progression of brain metastases after radiotherapy, and brainstem infarction. As in previous studies, systemic complications were more often the cause of death in the early postoperative period than neurological complications.

The shortcoming of the study is its retrospective design. Because of our limited sample size, our study may be too underpowered to detect differences between subgroups. Despite these limitations, this study is, to our knowledge, the first single-institution analysis of survival following resection of brain metastasis which is reevaluating and comparing RPA Classes and DS-GPA Score. Our findings show the importance of surgery, as well as the importance of adjuvant radiotherapy in assessing the prognosis after surgery, but also indicate the shortcomings of the DS-GPA Score, as the RPA Classification showed a better predictive power. Future prospective randomized studies are needed to establish the efficacy of the existing treatments and to lead to improvement of estimation of survival of each patient and in addition to it to optimize individual therapy and increase survival.

CONCLUSION

Prognostic favorable factors for prolonged survival were KPS >70%, RPA Class I and II, age <65 years, female sex, DS-GPA Score of 2.5–3 and 3.5–4 and adjuvant radiotherapy (WBRT or FSRT). Patients with breast cancer metastases had a longer MST compared to other primary tumors, although these differences were not statistically significant. Prospective randomized trials are needed to be done to assess new prognostic scores which combine the parameters from the RPA Classification and the DS-GPA Score.

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Conflicts of interest
There are no conflicts of interest.

REFERENCES

1. Agboola O, Benoit B, Cross P, Da Silva V, Esche B, Lesiuk H, et al. Prognostic factors derived from recursive partition analysis (RPA) of Radiation Therapy Oncology Group (RTOG) brain metastases trials applied to surgically resected and irradiated brain metastatic cases. Int J Radiat Oncol Biol Phys 1998;42:155-9.
2. Al-Shamy G, Sawaya R. Management of brain metastases: The indispensable role of surgery. J Neurooncol 2009;92:275-82.
3. Antoni D, Clavier JB, Pop M, Benoit C, Lefebvre F, Noël G. An institutional retrospective analysis of 93 patients with brain metastases from breast cancer: Treatment outcomes, diagnosis-specific prognostic factors. Int J Mol Sci 2012;13:16489-99.
4. Aoyama H, Tago M, Kato N, Toyoda T, Kenjiro M, Hirota S, et al. Neurocognitive function of patients with brain metastasis who received either whole brain radiotherapy plus stereotactic radiosurgery or radiosurgery alone. Int J Radiat Oncol Biol Phys 2007;68:1388-95.
5. Arita H, Narita Y, Miyakita Y, Ohno M, Sumi M, Shibui S. Risk factors for early death after surgery in patients with brain metastases: Reevaluation of the indications for and role of surgery. J Neurooncol 2014;116:145-52.
6. Auperin A, Arriagada R, Pignon JP, Le Péchoux C, Gregor A, Stephens RJ, et al. Prophylactic cranial irradiation for patients with small-cell lung cancer in complete remission. Prophylactic Cranial Irradiation Overview Collaborative Group. N Engl J Med 1999;341:476-84.
7. Barnholtz-Sloan JS, Yu C, Sloan AE, Vengoechea J, Wang M, Dignam J, et al. A nomogram for individualized estimation of survival among patients with brain metastasis. Neuro Oncol 2012;14:910-8.
8. Bhatnagar AK, Flickinger JC, Kondziolka D, Lunsford LD. Stereotactic radiosurgery for four or more intracranial metastases. Int J Radiat Oncol Biol Phys 2006;64:898-903.
9. Bhatnagar AK, Kondziolka D, Lunsford LD, Flickinger JC. Recursive partitioning analysis of prognostic factors for patients with four or more intracranial metastases treated with radiosurgery. Technol Cancer Res Treat 2007;6:153-60.
10. Bindal RK, Sawaya R, Leavens ME, Lee JJ. Surgical treatment of multiple brain metastases. J Neurosurg 1993;79:210-6.
11. Borgerit B, Gelber R, Kramer S, Brady LW, Chang CH, Davis LW, et al.
The palliation of brain metastases: Final results of the first two studies by the Radiation Therapy Oncology Group. Int J Radiat Oncol Biol Phys 1980;6:1-9.

12. Chao JH, Phillips R, Nickson JJ. Roentgen-ray therapy of cerebral metastases. Cancer 1954;7:682-9.

13. D’Andrea G, Palombi L, Mininni G, Pesce A, Marchetti P. Brain Metastases: Surgical Treatment and Overall Survival. World Neurosurg 2017;97:169-77.

14. Elliott RE, Rush S, Morsi A, Mehta N, Spriet J, Narayana A, et al. Neurological complications and symptom resolution following Gamma Knife surgery for brain metastases 2 cm or smaller in relation to eloquent cortices. J Neurosurg 2010;113(Suppl):53-64.

15. Esmaeilzadeh M, Malesara A, Faridari A, Hafezi M, Hong B, Esmaeiling-Shirvani H, et al. Brain metastasis from gastrointestinal cancers: A systematic review. Int J Clin Pract 2014;68:890-9.

16. Gaspar LE, Scott C, Murray K, Curran W. Validation of the RTOG recursive partitioning analysis (RPA) classification for brain metastases. Int J Radiat Oncol Biol Phys 2000;47:1001-6.

17. Gavrilovic IT, Posner JB. Brain metastases: Epidemiology and pathophysiology. J Neurooncol 2005;75:5-14.

18. Han MS, Moon KS, Lee KH, Cho SB, Lim SH, Jang WY, et al. Brain metastasis from hepatocellular carcinoma: The role of surgery as a prognostic factor. BMC Cancer 2013;13:567.

19. Hara Y, Sakurai K, Hori K, Fujisawa A, Ono Y, Nagaesthesia S, et al. [Evaluation of the Cases Given Primary Tumor Resection after Systemic Therapy for Metastatic Breast Cancer]. Kan To Kagaku Ryoho 2015;42:1506-8.

20. Hazuka MB, Burleson WD, Stroud DN, Leonard CE, Lillehei KO, Kinzie J. Multiple brain metastases are associated with poor survival in patients treated with surgery and radiotherapy. J Clin Oncol 1993;11:369-73.

21. Jagannathan J, Yen CP, Ray DK, Schlesinger D, Song D, Pouratian N, et al. Gamma Knife radiosurgery to the surgical cavity following resection of brain metastases. J Neurosurg 2009;111:431-8.

22. Kocher M, Soffietti R, Abacioglu U, Vilia S, Fauchon F, Baumert BG, et al. Adjunctive whole-brain radiotherapy versus observation after radiosurgery or surgical resection of one to three cerebral metastases: Results of the EORTC 22952-26001 study. J Clin Oncol 2011;29:134-41.

23. Kocher M, Witaig A, Pirioh MD, Treuer H, Seegenschmiedt H, Ruge M, et al. Stereotactic radiosurgery for treatment of brain metastases. A report of the DEGRO Working Group on Stereotactic Radiotherapy. Strahlenther Onkol 2014;190:521-32.

24. Kondziolka D, Kalkanis SN, Mehta MP, Ahluwalia M, Loeffler JS, et al. It is time to reevaluate the management of patients with brain metastases. Neurosurgery 2014;75:1-9.

25. Kondziolka D, Parry PV, Lunsford LD, Kano H, Flickinger JC, Rakfal S, et al. Prognostic indices for brain metastases—usefulness and challenges. Radiat Oncol 2009;4:10.

26. Korinth MC, Delonge C, Hütter BO, Gilsbach JM. Prognostic factors, and outcome. Acta Neurochir (Wien) 2013;155:379-87.

27. Lee CH, Kim DW, Kim JW, Han JH, Kim YH, Park CK, et al. Prophylactic cranial irradiation in extensive small-cell lung cancer. N Engl J Med 1990;322:494-500.

28. Medline P, Schödel P, Schebesch KM, Brawanski A, Proescholdt MA. Surgical resection of brain metastases-impact on neurological outcome. Int J Mol Sci 2013;14:8708-18.

29. Miyazaki C, Mittal I, Weingart J,elmet I, Roos M, Lack B, et al. Prognostic factors influencing survival after treatment of the brain. J Neurosurg 2012;114:460-9.

30. Patchell RA, Tibbs PA, Wong W, Dempsey RJ, Mohiuddin M, Kryscio R, et al. Postoperative radiotherapy in the treatment of single brain metastases to the brain: A randomized trial. JAMA 1998;280:485-9.

31. Patchell RA, Tibbs PA, Walsh JW, Dempsey RJ, Maruyama Y, Kryscio R, et al. A randomized trial of surgery in the treatment of single metastases to the brain. N Engl J Med 1990;322:494-500.

32. Patan A, Koki S, Hizlibag M, Rao YF, Fox BD, Sawaya R. Gamma Knife radiosurgery to the surgical cavity following resection of Cerebral Metastases Leads to Faster Resolution of Peritumoral Edema than Stereotactic Radiosurgery: A Volumetric Analysis. Ann Surg Oncol 2010;17:2246-55.

33. Patil CG, Pricola K, Sarmiento JM, Garg SK, Bryant A, Black KL. Whole brain radiation therapy (WBRT) alone versus WBRT and radiosurgery for the treatment of brain metastases. Cochrane Database Syst Rev 2012;CD006121.

34. Pessina F, Navarria P, Cozzi L, Ascolee AM, Maggi G, Rossi M, et al. Role of Surgical Resection in Patients with Single Large Brain Metastases: Feasibility, Morbidity, and Local Control Evaluation. World Neurosurg 2016;94:6-12.

35. Redmond AJ, Diluna ML, Hebert R, Molterino JA, Desai R, Knisely JP, et al. Gamma Knife surgery for the treatment of melanoma metastases: The effect of intratumoral hemorrhage on survival. J Neurosurg 2008;109(Suppl):99-105.

36. Sahgal A, Aoyama H, Kocher M, Neupane B, Collette T, Tago M, et al. Phase 3 trials of stereotactic radiosurgery with or without whole-brain radiation therapy for 1 or 4 brain metastases: Individual patient data meta-analysis. Int J Radiat Oncol Biol Phys 2015;91:710-7.

37. Schackert G, Lindner C, Petschke S, Leimert M, Kirsch M. Retrospective study of 127 surgically treated patients with multiple brain metastases: Indication, prognostic factors, and outcome. Acta Neurochir (Wien) 2013;155:379-87.

38. Schackert G, Steinknetz A, Meier U, Sobottka SB. Surgical management of single and multiple brain metastases: Results of a retrospective study. Onkologie 2001;24:246-55.

39. Schödel P, Schödel P, Schebesch KM, Brawanski A, Proescholdt MA. Surgical resection of brain metastases-impact on neurological outcome. Int J Mol Sci 2013;14:8708-18.
55. Sperduto PW, Berkey B, Gaspar LE, Mehta M, Curran W. A new prognostic index and comparison to three other indices for patients with brain metastases: An analysis of 1,960 patients in the RTOG database. Int J Radiat Oncol Biol Phys 2008;70:510-4.

56. Sperduto PW, Chao ST, Sneed PK, Luo X, Suh J, Roberge D, et al. Diagnosis-specific prognostic factors, indexes, and treatment outcomes for patients with newly diagnosed brain metastases: A multi-institutional analysis of 4,259 patients. Int J Radiat Oncol Biol Phys 2010;77:655-61.

57. Sperduto PW, Kased N, Roberge D, Chao ST, Shanley R, Luo X, et al. The effect of tumor subtype on the time from primary diagnosis to development of brain metastases and survival in patients with breast cancer. J Neurooncol 2013;112:467-72.

58. Sperduto PW, Kased N, Roberge D, Xu Z, Shanley R, Luo X, et al. Summary report on the graded prognostic assessment: An accurate and facile diagnosis-specific tool to estimate survival for patients with brain metastases. J Clin Oncol 2012;30:419-25.

59. Sperduto PW, Shanley R, Luo X, Andrews D, Werner-Wasik M, Valicenti R, et al. Secondary analysis of RTOG 9508, a phase 3 randomized trial of whole-brain radiation therapy versus WBRT plus stereotactic radiosurgery in patients with 1-3 brain metastases; poststratified by the graded prognostic assessment (GPA). Int J Radiat Oncol Biol Phys 2014;90:526-31.

60. Tan TC, Black PM. Image-guided craniotomy for cerebral metastases: Techniques and outcomes. Neurosurgery 2007;61 (1 Suppl):349-56; discussion 356-347.

61. Tsao M, Xu W, Sahgal A. A meta-analysis evaluating stereotactic radiosurgery, whole-brain radiotherapy, or both for patients presenting with a limited number of brain metastases. Cancer 2012;118:2486-93.

62. Vecht CJ, Haaxma-Reiche H, Noordijk EM, Padberg GW, Voormolen JH, Hoeckstra FH, et al. Treatment of single brain metastasis: Radiotherapy alone or combined with neurosurgery? Ann Neurrol 1993;33:583-90.

63. Venur VA, Ahluwalia MS. Prognostic scores for brain metastasis patients: Use in clinical practice and trial design. Chin Clin Oncol 2015;4:18.

64. Walker AE, Robins M, Weinfeld FD. Epidemiology of brain tumors: The national survey of intracranial neoplasms. Neurology 1985;35:219-26.

65. Weidle UH, Niewöhner J, Tiefenthaler G. The Blood-Brain Barrier Challenge for the Treatment of Brain Cancer, Secondary Brain Metastases, and Neurological Diseases. Cancer Genomics Proteomics 2015;12:167-77.

66. Wroński M. [Surgical treatment of brain metastases from non-microcellular lung cancer]. Neurol Neurochir Pol 1992;26:837-44.

67. Wroński M, Arbit E, Burt M, Galicich JH. Survival after surgical treatment of brain metastases from lung cancer: A follow-up study of 231 patients treated between 1976 and 1991. J Neurosurg 1995;83:605-16.

68. Wroński M, Arbit E, Burt M, Perino G, Galicich JH, Brennan MF. Resection of brain metastases from sarcoma. Ann Surg Oncol 1995;2:392-9.

69. Wroński M, Arbit E, Russo P, Galicich JH. Surgical resection of brain metastases from renal cell carcinoma in 50 patients. Urology 1996;47:187-93.

70. Wroński M, Lederman G. A randomized trial to assess the efficacy of surgery in addition to radiotherapy in patients with a single cerebral metastasis. Cancer 1997;80:1002-4.