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Original Article

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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Key Words: Brain metastasis, Diagnosis-Specific Graded Prognostic Assessment, Recursive Partitioning Analysis

INTRODUCTION

Almost 25% of all patients with oncological diseases present with cerebral metastases.[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%).[11,12,51,56,64]

Surgery and radiosurgery are established treatment strategies for patients with single brain metastasis, followed by radiation therapy.[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.[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.[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.[2] 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.[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.[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.[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 the 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

Contd...

Table 1: Contd...

Characteristic	Number of patients
DS-GPA Classes postoperative	
0-1.4	48
1.5-2	67
2.5-3	71
3.5-4	43

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].

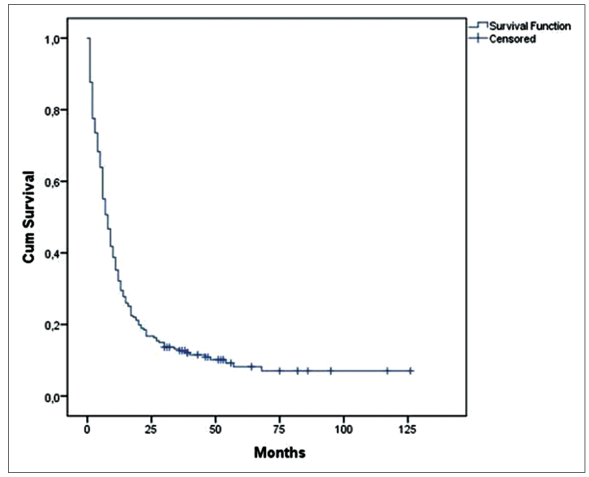

Figure 1: Kaplan–Meier curve with median survival time (MST) for the whole group

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,

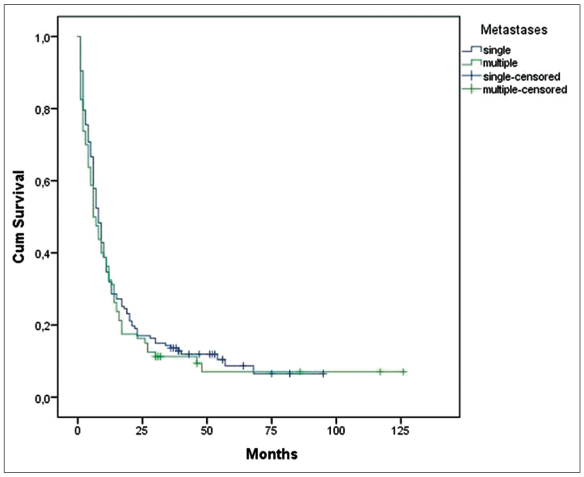

Figure 2: Kaplan–Meier curves with median survival time (MST) for single and multiple metastases

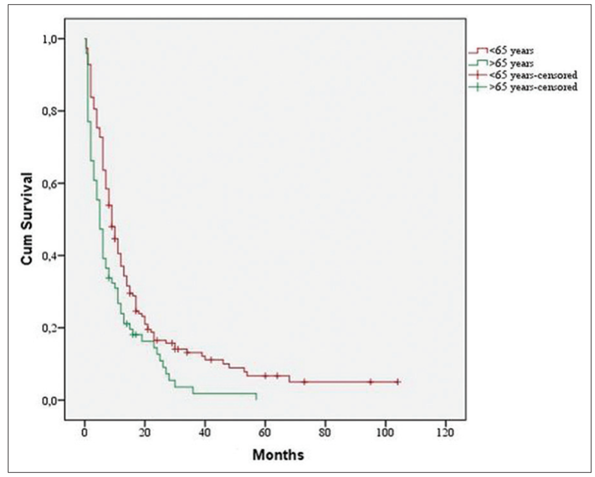

Figure 3: Kaplan–Meier curves for age

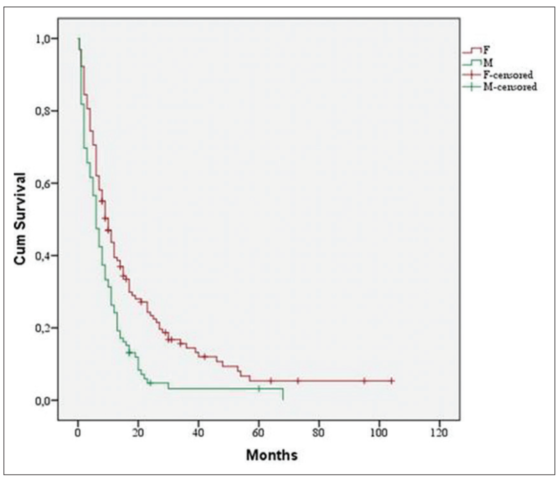

Figure 4: Kaplan–Meier curves for sex

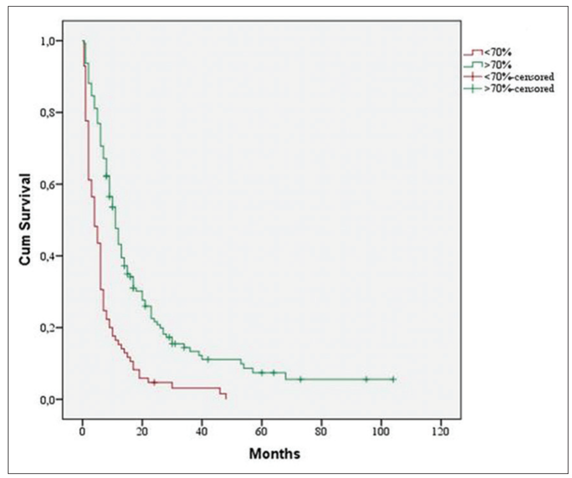

Figure 5: Kaplan–Meier curves for postoperative KSP Score

$P < 0.001$) [Figure 6]. 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 ($n = 1$).

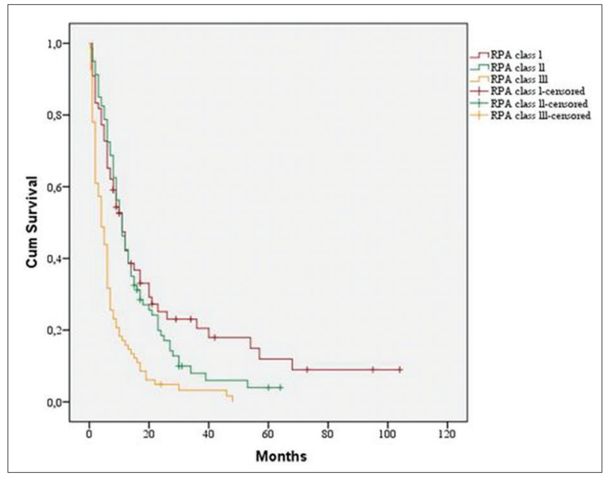

Figure 6: Kaplan–Meier curves for postoperative RPA Classes

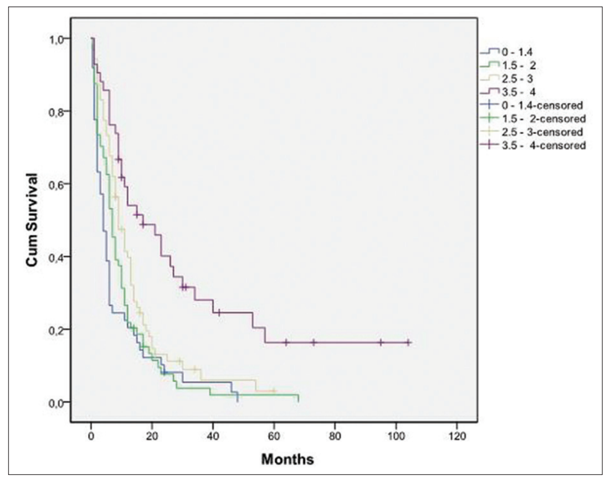

Figure 7: Kaplan–Meier curves for the postoperative DS-GPA Score

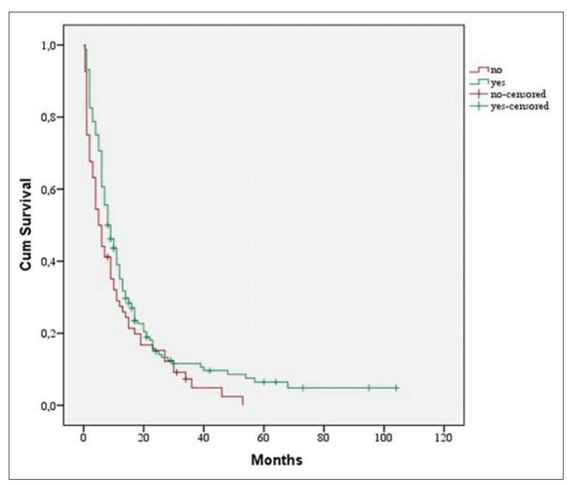

Figure 8: Kaplan–Meier curve for the postoperative radiotherapy

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 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.[26,31,32,39,41,46,47,60] Five large studies were performed in Germany, Italy, South Korea, and USA.[13,27,41,46,48] 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.[24]

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.[43] In patients with multiple metastasis, usually the supratentorial metastases with significant mass (>25 cm^3) 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.[50]

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.[34] 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.[27] 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.[34] 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,[27] in the study of Schödel *et al*., extent of resection was not statistically significant.[48] Piecemeal resection in comparison to *en-bloc* resection showed larger incidence of complications in the study of Patel *et al*.[41] The recent study of D'Andrea *et al*. showed a correlation of surgery of the primary tumor to prolonged MST.[13]

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.[27,38,47,48,60] Other studies include either patients with single metastasis[32,41,70] or patients with multiple metastases.[10,20,46]

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.[27] Paek *et al*. reported a mean survival of 8.5 months after surgery plus WBRT versus 5.3 months after WBRT alone,[38] whereas Schackert *et al*.[46] 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 meta stasis	Median age (yrs)	Sex	Preoperative performance status	MST	Primary tumor	Adjuvant radio therapy	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]	Rand omized pros pective	48	Single	59	32 male 16 female	All KPS >90%	40 weeks	Not specified	WBRT	Follow up identical to length of survival	No	Adjuvant WBRT
Bindal et al. **1993**[10]	Retro spective	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	WBRT	Follow up to the last follow up examination or death	No	Absence of systemic disease Removal of all lesions in selected patients with multiple metastases
Hazuka et al. **1993**[20]	Retro spective	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 Classi fication	Number of metastasis RTOG Class I/II
Schackert et al. **2001**[47]	Retro spective	104	**Single and multiple**	61 in singles meta stasis, 58 in multiple meta stases	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%
Korinth et al. **2002**[26]	Retro spective	187	**Single and multiple**	58.5	99 male and 58 female patients	75% KPS >80 25% KPS <80	9.8 months	Lung Gastroin testinal Renal cell cancer	WBRT	Follow up identical to length of survival	None	Histology (breast cancer favorable, renal cell cancer and melanoma non‑favorable)

Contd...

Table 2: Contd...

Author and year	Study design	Number of patients	Number of meta stasis	Median age (yrs)	Sex	Preoperative performance status	MST	Primary tumor	Adjuvant radio therapy	Type and duration of follow up	Use of any prognostic scores or RPA/DS-GPA Classification	Prognostic factors relevant for survival
								CUP Breast cancer Malignant melanoma				Location (frontal and parietal lobe favorable) Duration of symptoms (longer than 60 days favorable) KPS <70 unfavourable
Paek et al. **2005**[38]	Retro spective, single-surgeon	208	**Single and multiple**	59	103 male and 105 female patients	92.3% of patients KPS >70	8 months	Lung Breast Melanoma Colon Kidney Other Unknown	WBRT	Not specified	RPA	High KPS RPA Class I Adjuvant WBRT Adjuvant chemo therapy
Tan et al. **2007**[60]	Retro spective	49	**Single and multiple**	58	27 male 22 female	76.4% KPS >70	16.23 months	Lung Melanoma Gastro intestinal Breast Kidney Other Unknown	WBRT 80%, SRS 20%	1 year	RPA	RPA Class I and II
Schackert *et al*. 2013[46]	Retro spective	127	Multiple	67	79 male, 48 female	43.3% KPS > or =70% 56.7% KPS < 70%	6.5 months	Lung Melanoma Gastro intestinal Breast Renal CUP Other	WBRT	Median follow up 29 months	RPA	KPS >70 Complete resection of all lesions Number of lesions 2-4 vs 4 Adjuvant WBRT
Lee et al. **2013**[27]	Retro spective	157	**Single and multiple**	53.7	82 male, 75 female	Mean KPS 81.3 +- SD	19.3	Lung Breast Genito urinary Gastro intestinal Melanoma Kidney CUP Others	WBRT 69.4%, SRS 10.8%, 19.7% none	17 years	RPA	Gross total resection RPA Class I and II KPS >70 Age <65 Stable extracranial cancer
Schödel et al. **2013**[48]	Retro spective	206	**Single and multiple**	61.1	Female 84, male 122	9.7% RPA Class I, 77.7% RPA Class II, 12.6% RPA Class II	6.3 months	Lung Melanoma Breast Colon Renal CUP	WBRT 64.6%, SRS 18.5%	6.1 months	RPA	RPA Class I vs. II vs. III

Contd...

Table 2: Contd...

Author and year	Study design	Number of patients	Number of meta stasis	Median age (yrs)	Sex	Preoperative performance status	MST	Primary tumor	Adjuvant radio therapy	Type and duration of follow up	Use of any prognostic scores or RPA/DS-GPA Classification	Prognostic factors relevant for survival
								Urothel Prostate Other				
Smith *et al*. 2014.[53]	Retro spective	150	Multiple	46.2	62.7% female	Not specified	13.2	Lung Breast Melanoma Renal-cell Colon	SRS	17 months	No	Primary breast histology favorable, primary colon histology unfavorable Female sex
D' Andrea *et al*. 2017[13]	Retro spective	71	Single meta stasis (*n*=70) and multiple (*n*=1)	67	44 men, 72 women	Not specified	11.08	Lung Kidney Breast Gastroin testinal 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 spective	229	**Single and multiple** 149 patients (65.1%) single meta stasis 80 patients (34.9%) multiple meta stases	59.7	114 male (49.8%) and 115 female (50.1%) patients	62% of patients KPS >70% 38% of patients KPS <70%	8 months	Lung 86 or 37.5% Breast 50 or 21.9% Gastroin testinal 30 or 13.1% Melanoma 24 or 10.5% Renal carcinoma 15 or 6.5% CUP and others 22 or 10.5%	Adjuvant radio therapy in 182 patients (79.4%); WBRT in 160 patients (69.9%), FSRT in 22 patients (9.6%)	10.3 months Follow Up to end point (death of the patient) in 207/229 patients	RPA DS-GPA	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

than MST in the study of Schödel *et al*. (6.3 months)[48] and Mintz *et al*. (5.6 months)[32] and was comparable to MST in the study of Paek *et al*.[38] Other studies showed larger MST than in this study: 19.3 months in the study of Lee *et al*.,[27] 16 months in studies of Schackert *et al*. and Tan *et al*.,[46,47,60] 11 months in D'Andrea *et al*.,[13] 5.8–10.6 months in Schackert *et al*.,[46] 13.2 months in Smith *et al*.[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*.[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*.,[26] Paek *et al*.,[38] Tan *et al*.,[60] and Lee *et al*.[27] all recognized preoperative

KPS >70 as a factor showing correlation to prolonged MST.

Age and gender

Age was very early recognized as an important factor in survival[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.*[46] and the recent study of D'Andrea *et al.*[13] Lee at al.[27] recognized age <65 and Schackert *et al.*[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.[53] Previous studies have reported excellent survival in breast cancer patients with intracranial metastasis, particularly those with a HER-2–positive phenotype.[30] In our study, similar to the study of Smith *et al.*, primary breast histology was associated with longer MST compared to other tumor entities but it did not reach statistical significance.[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.*[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 extraranial 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.*[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.*,[27] Tan *et al.*,[60] and Schödel *et al.*[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).[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.[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.[46] 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.[41] Korinth *et al.*[26] 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.*[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.[18] 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.[15,18,19,31,66-70]

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. 3–3.4 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.*,[24] 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.[24] 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 asses 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 the clinical and therapeutic decision making.[36] Furthermore, prognostic scores play a crucial role in patient selection, stratification and randomization in clinical trials.[63] They also play an important role in balancing the cost of treatment and providing realistic expectations to the patients' and the caregivers.[54] Multiple studies, albeit retrospective in nature, have elucidated prognostic factors and recommended prognostic scoring systems for brain metastases.[63] 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.[16] 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.[63] 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.[1] Although Paek *et al*. postulated that RPA Class III and number of metastases >4 are exclusion criteria in regard to surgery as a valid treatment option,[38] 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.[48] Arita *et al*. related risk of early death after surgery (with 6 months) to patients who belong to Class III.[5] RPA Class I and II were associated with prolonged MST in studies of Tan *et al*.,[60] Schödel *et al*.,[48] and Lee *et al*.[27] [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[55] 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.[56,63] Age, KPS, number of brain metastases, and sites of extracranial metastases strongly predicted survival in lung (nonsmall 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.[3,57,63] 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*.,[25] 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.[63] 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.[63]

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.[53] In study by Paek *et al*., there was no difference in MST in patients with single and multiple metastases.[38]

Hazuka *et al*.[20] and Schackert *et al*.[47] 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*.[10] The number of metastasis was an important prognostic factor in the study on treatment of multiple metastases of Schackert *et al*.[46] 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.[24] According to Kondziolka *et al.*,[24] 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.[8,9] 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.[46] Kondziolka *et al.* question the whole concept of micro-metastases which can be seen on high-resolution imaging in patients with single metastasis.[24] 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.[28] 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.[48] 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.[13,26] In the study of Tan *et al.*, no patient who was neurologically intact preoperatively deteriorated after surgery,[60] and in most of the other studies, the rate of neurological deterioration following the operation is higher than in our patient group.[10,41,46] 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

Table 3: Overview of the studies on surgically treated brain metastases with comparison of neurological outcome and complication rate

Author and year	Number of patients	Preoperative performance status	Surgical complications	Systemic complications	30-days mortality	Neurological outcome
Patchell *et al*. 1990[40]	48	All KPS 90%+	17%	Not specified	4%	Not specified
Bindal *et al*. 1993[10]	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[20]	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[5]	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[47]	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	Not specified
Korinth *et al*. 2002[26]	187	75% KPS > 80 25% KPS < 80	19 patients (10.2%)	Not specified	None	No deterioration
Tan *et al*. 2007[60]	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[38]	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[46]	127	43.3% KPS > or = 70% 56.7% KPS <70%	Not specified	Not specified	7 patients (5.5%)	Not specified
Lee *et al*. 2013[27]	157	Mean KPS 81.3 +- SD	7 patients (4.5%)	Not specified	2 patients (1.3%)	Not specified
Schödel *et al*. 2013[48]	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[41]	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

retrospective study of 71 surgically treated patients with brain metastasis, 52 patients or 73.2% improved and 19 or 26.7% remained unchanged.[13] 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.[37] 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.[26] 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.[48] 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.[24]

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.[10,46] Historically, the standard treatment for intracranial metastases has been resection followed by fractionated WBRT.[29]

Two randomized clinical trials have demonstrated that surgical resection is superior to WBRT only,[40,62] and that WBRT after resection significantly reduces the brain specific recurrence rate.[39,40] This is in contrast to a report by Mintz *et al*., which failed to detect a significant beneficial effect of surgical resection.[32] 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.[27]

When used as a primary treatment for solitary metastasis, radiosurgery has been associated with local tumor control rates of 73–94% and less morbidity than WBRT. Radiosurgery has also been shown to reduce local tumor recurrence following gross total resection of a single brain metastasis.[21,29] Surgery followed by radiotherapy to the resection cavity and synchronous lesions showed to be an effective treatment protocol for patients with intracranial metastasis[53] 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[6,52] 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.[22,33,61] Furthermore, the latest studies show the same MST after surgical excision followed by WBRT compared to radiosurgical treatment of one to three brain lesions.[22] 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.[42] SRS has shown to be the preferred treatment for patients younger than 50 years without WBRT.[42,45]

In recent years, surgery and FSRT or radiosurgery alone largely replaced WBRT.[22,23] Current studies provide no solid proof regarding which group of patients will profit from WBRT; the assumption is that these patients despite good control of extracranial disease do not have a sufficient control in the brain and would die due to the cerebral progress.[22,23,45] The development of the so called "small molecules" which cross the blood–brain barrier and achieve the local tumor control in the therapy of breast cancer and melanoma metastasis[65] also contributed to abandoning the WBRT for certain tumor entities. Neurotoxicity in the form of neurocognitive decline is a further argument against WBRT.[4]

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,[48,49] but it does not primarily reduce mass effects and can induce regressive changes such as intratumoral hemorrhages, per focal edema, and radionecrosis.[14,44] 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.[48]

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*.[10,38,41,46] 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*.[5,38,41,46,47] possibly because more than half of them (10) had a KPS <70%. As postulated by Arita *et al*.,[5] 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.[5] 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.[13] 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.[5]

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 asses 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.

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