Aus der Klinik für Neurochirurgie der Heinrich-Heine-Universität Düsseldorf
Direktor: Univ. Prof. Dr. Hans-Jakob Steiger

Current neurosurgical concepts and outcome predictors of cerebral metastases resection

Dissertation

zur Erlangung des Grades eines Doktors der Medizin der Medizinischen Fakultät der Heinrich-Heine-Universität Düsseldorf

vorgelegt von

Christopher Munoz-Bendix

2019

Als Inauguraldissertation gedruckt mit der Genehmigung
der Medizinischen Fakultät der Heinrich-Heine-Universität Düsseldorf

Dekan: Univ.-Prof. Dr. med. Nikolaj Klöcker
Referent: Prof. Dr. med. Detlef Kindgen-Milles
Koreferent: Prof. Dr. med. Nadine Lübke

Teile dieser Arbeit wurden veröffentlicht:

- Munoz-Bendix C, Rapp M, Mijderwijk HJ, von Sass C, Dibue-Adjei M, Cornelius JF, Steiger HJ, Turowski B, Sabel M, Kamp MA (2019) **Risk factors for in-brain local and distant recurrence in elderly patients after resection of cerebral metastases** Sci Rep; 9 (1):7431

- Kamp MA, Munoz-Bendix C, Mijderwijk HJ, Turowski B, Dibue-Adjei M, Cornelius JF, Steiger HJ, Rapp M, Sabel M (2019) **Is the 5-ALA fluorescence of cerebral metastases a prognostic factor of local recurrence and overall survival?** J Neurooncol; 141 (3): 547-553

- Kamp MA, Fischer I, Dibue-Adjei M, Munoz-Bendix C, Cornelius JF, Steiger HJ, Slotty PJ, Turowski B, Rapp M, Sabel M (2018) **Predictors for a further local in-brain progression after re-craniotomy of locally recurrent cerebral metastases** Neurosurg Rev; 41(3):813-823

Current neurosurgical concepts and outcome predictors of cerebral metastases resection
Christopher Munoz-Bendix

ZUSAMMENFASSUNG

Herausfordernde Paradigmen und Überschreiten der Grenzen definieren Innovation. Innovation selbst hängt vom Wissen ab. Trotz vieler etablierter Therapiemöglichkeiten für Hirnmetastasen bietet die chirurgische Resektion eine enorme Entlastung der Krankheitslast. Selbstverständlich bleibt die Rolle der Neurochirurgie ein wesentlicher Bestandteil einer interdisziplinären Arbeit. Trotz neurochirurgischer Behandlung erleidet ein erschreckend hoher Anteil an Patienten trotzdem eine lokale Progression. Insbesondere wird Alter über 65 Jahren oftmals als prognostisch ungünstiger Faktor angesehen. Diese Dissertation analysiert daher das chirurgische Ergebnis von älteren Patienten über 64 Jahren gemessen am progressions-freien und Gesamtüberleben. Als ein weiterer potentieller prognostischer Marker wurde die 5-Aminolävulinsäure-basierte Fluoreszenz (5-ALA) von zerebralen Metastasen untersucht. Im Rezidivfall haben multimodal vorbehandelte Patienten oft eingeschränkte Therapieoptionen, so dass oftmals nur noch die Operation als Behandlungsmöglichkeit bleibt. Daher wurde die Prognose von Patienten mit chirurgischer Therapie einer Rezidivmetastase bestimmt.

Die vorliegende retrospektive Arbeit zeigte, dass in unserer Patientenpopulation am UKD die lokale Progressionsrate bei Patienten > 65 Jahren nach Resektion einer zerebralen Metastase über 25% lag, dass der Nachweis von Resttumor im frühen postoperativen MRT der einzige Risikofaktor für ein Lokalrezidiv war und dass das mediane Überleben nach Metastasenresektion mit 13 Monaten vergleichbar mit bisher publizierten Serien jüngerer Patienten war. In der gesamten Patientenpopulation ohne Alterslimit war zwar die 5-ALA-Fluoreszenz von zerebralen Metastasen ein günstiger prognostischer Marker, hatte aber keinen Einfluss auf das Ausmaß der Resektion. Nach erneuter Resektion eines Lokalrezidivs konnte eine vollständige Metastasenresektion – gemessen am führen postoperativen MRT in ca. 30% der Fälle besprochen. Eine definitive Tumorkontrolle konnte nach weiterer Therapie aber in über 90% erreicht werden.

Die Prognose von Patienten mit einzelnen zerebralen Metastasen hat sich in den letzten Jahren zwar verbessert, allerdings ist die lokale Progression ein immer noch vollständig gelöstes Problem. Mit multimodalen Therapieansätzen und mehrfachen Operation kann allerdings schlussendlich in über 90% eine lokale Kontrolle erzielt werden. Die Identifikation von prognostischen Faktoren hilft in der Einschätzung und Therapie von zerebralen Metastasen. Unserer Arbeit zeigt, dass die 5-Aminolävulinsäure-basierte Fluoreszenz von zerebralen Metastasen zwar keinen Einfluss auf den Operationserfolg hat, aber ein unabhängiger prognostischer Marker ist. Alter kann per se nicht als ungünstiger prognostischer Marker angesehen werden.

Diese These versucht, unsere Wahrnehmung dieser Pathologie in eine objektive Realität zu verbessern.

Current neurosurgical concepts and outcome predictors of cerebral metastases resection

Christopher Munoz-Bendix

SUMMARY

Challenging paradigms and pushing the limits defines innovation. Innovation itself depends on knowledge. Despite many established therapeutic options for cerebral metastases, surgical resection offers a tremendous relief in the burden of disease. Needless to say, the role of neurosurgery still remains a crucial part of an interdisciplinary work. However, a high number of patients have a recurrence after surgical resection of a cerebral metastasis. Particularly in neuro-oncology, age above 65 years is still defined as a negative prognostic factor. This thesis focuses on surgical outcome in patients above 65 years of age after resection of cerebral metastases, as well as progression-free- and overall-survival. Additionally, the role of 5-aminolevulinic acid as a prognostic factor was analyzed. Furthermore, patients with recurrent disease after multimodal therapy and relatively reduced therapeutic options, that may only rely on another surgical resection were studied. The prognosis of this subpopulation after a second operation was evaluated.

Our retrospective analysis shows a local recurrence rate of about 25% after metastasectomy in patients above 65 years of age. The only risk factor accountable for local in-brain recurrence was tumor-remnant in early postoperative MRI. Mean overall survival was 13 months and comparable with recent studies from younger patients. Without an age-classification in cerebral metastases surgery, was 5-aminolevulinic acid a positive prognostic factor, however it showed no fluorescence-guided resection benefit. Gross-total resection after a second metastasectomy was achieved in about 30% of the patients according to an early postoperative MRI, and a definitive tumor-control was attained in over 90% of the patients.

Although the prognosis in patients with a single cerebral metastasis has been slightly improved, recurrence still remains a challenge. Multimodal therapy and multiple operations may attain a tumor-control in over 90% of the patients. Moreover, identification of newer prognostic factors will help in the assessment and therapy of cerebral metastases. Age per se is not a negative prognostic factor.

This thesis tries to enhance our perception of this pathology into an objective reality.

Abkürzungen/ Abbreviations

CNS	central nervous system
LM	leptomeningeal metastases
BM	brain metastases
BBB	blood-brain barrier
CSF	cerebrospinal fluid
CT	computer tomography (from the head, unless otherwise specified)
MRI	magnetic resonance imaging (from the head, unless otherwise specified)
MRS	magnetic resonance spectroscopy (from the head, unless otherwise specified)
fMRI	functional magnetic resonance imaging (from the head, unless otherwise specified)
DTI	diffusion tension imaging
FDG-PET	fluorodeoxyglucose-positron emission tomography (from the head, unless otherwise specified)
SPECT	single photon emission computer tomography (from the head, unless otherwise specified) mg: milligrams
NSCL	non-small-cell lung carcinoma
SCL	small-cell lung carcinoma
CALLA	common acute lymphoblastic leukemia antigen
CDX2	caudal-type homeobox transcription factor 2
CEA	carcinoembryonic antigen
CGA	chromogranin A
AFP	alpha-fetoprotein
CK	cytokeratin
GCDFP-15	gross cystic disease fluid protein 15
Hep Par-1	hepatocyte paraffin 1 marker
MART-1	melanoma antigen recognized by T-cells-1
MFTP	microphthalmia transcription factor protein
NCAM	neural cell adhesion molecule
PAP	prostatic acid phosphatase
PSA	prostate specific antigen
RCC	renal cell carcinoma marker
SYN	synaptophysin
TTF-1	thyroid transcription factor 1
WT1	Wilm's tumor 1 transcription factor
SRS	stereotactic radiosurgery
WBR	whole-brain radiation therapy
KPS	Karnofsky performance scale/status
RPA	recursive partitioning analysis for the Radiation Therapy Oncology Group
GPA	graded prognostic assessment
DS-GPA	disease-specific graded prognostic assessment
GA	geriatric assessment

Table of Contents

List of Figures

List of Tables

Preface

Cancer still represents one of the leading causes of death in the world. [1] Nonetheless, the prognosis has changed over the years because of the advances of therapeutic strategies, surgical and non-surgical, and especially considering the early and higher quality of detection methods. The clinical course and prognosis of each patient depends on many factors e.g. age, location of the tumor, its histological type and subtype, benign or malignant neoplasia, as well as loco-regional or distant spread of the disease i.e. metastases.

Incidence of primary tumors is well defined in men and women. The most common cancer in men is prostatic, followed by lung and colon (including rectum). In women breast cancer is the most significant, also followed by lung and colon. [2] Possible risk factors for the development of neoplasias involve environmental factors, age, acquired predisposing condition, genetic predisposition and its interaction with the environment.

All malignant neoplasias are capable of metastasize, however, the frequency of each is different. Few inherent characteristics of the tumor, such as lack of differentiation, aggressive local invasion, rapid growth and size could probably dictate the likelihood of the tumor to metastasize. Exceptions do occur. [3] Prevailing sites for metastases involve bone, lung, liver and the brain. A metastatic disease implies a great reduction in the probability of cure. In almost 30% of the patients, a metastasis will be present at the time of diagnosis of a primary neoplasia. [4-6,3,7-9]

Brain metastases represent the most frequent intracranial neoplasia, and as a result of improved detection and efficacy in controlling the extra-cerebral or extra-axial disease, the incidence of brain neoplasias may be increasing. It is well described, that surgery is essential for the proper treatment of brain metastases along with an adjuvant radio-oncological therapy.[10-12] Despite an adequate treatment, surgical and non-surgical, many patients still present with a local recurrence of the resected metastasis. Data on the incidence and risk factors for an in-brain recurrence are lacking. Furthermore, due to the advances in treatments of primary tumor and their increased efficacy, no information is available regarding risk factors that alter the survival rate or even data on survival rate alone in this subgroup of patients. More important, no data is available regarding patients with an in-brain local recurrence.

Additionally, age is still thought of as a determinant factor for treatment and prognosis in this pathology. [13]

There are still many controversies and unresolved issues regarding the optimal line of treatment regarding cerebral metastases.

Three publications from the field of neuro-oncology for the treatment of cerebral metastases are summarized in this thesis. These publications represent original research from the author and his co-workers.

This thesis will provide a brief review of the current literature regarding cerebral metastases, followed by a shortened and revised version of the original publications. The original articles are annexed within this thesis.

1. Introduction and Background

1.1 Definition

Metastasis is defined as the dissemination of neoplastic cells of a primary tumor to another location that is not directly next to or connected with the primary neoplasia. As benign neoplasias do not metastasize, every metastatic disease is generally considered distinctly malignant. [3]

Central nervous system (CNS) metastatic disease results from the spread of tumors cells originating outside the CNS to brain parenchyma, spinal cord, dura, leptomeninges, skull base, cranial nerves, peripheral nerves and dural sinuses. [14,15] For the purposes of this study, only metastases in brain parenchyma, dura, leptomeninges, skull base and dural sinuses will be included.

Leptomeningeal metastases (LM), also known as carcinomatous meningitis or neoplastic meningitis, refers to a desolating complication of an advanced cancer. Even though most remain undiagnosed or asymptomatic [16-22], it occurs in up to 5% of all metastatic diseases. [23,24] Its survival, in spite of every available or possible therapy, averages three to four months. [25]

1.2 Epidemiology

In order to understand the natural course of brain metastases (BM) or secondary brain tumors, a previous analysis of possible primary tumors has to be performed. Table 1 shows the incidence of primary tumors, as well as the estimated incidence of metastases to the brain, dura or leptomeninges.

Table 1.

Primary Tumor	Men %	Women %	Mortality Primary Tumor Men %	Mortality Primary Tumor Women %	Incidence of Brain Metastases %
Melanoma (skin)	5[1]	4[1]	N/A	N/A	7[2]
Oropharynx	4[1]	N/A	N/A	N/A	0.4[3]
Lung	14[1]	13[1]	28[1]	26[1]	16-20[2]
Breast	N/A	29[1]	N/A	15[1]	5[2]
Liver	3[1]	N/A	5[1]	3[1]	0.9[4]
Kidney	5[1]	3[1]	3[1]	N/A	7-10[2]
Colon & Rectum	8[1]	8[1]	8[1]	9[1]	1-2[2]
Urinary Bladder	7[1]	N/A	4[1]	N/A	1[5]

Prostate	26[1]	N/A	9[1]	N/A	0.7-5[6]
Leukemia	4[1]	3[1]	5[1]	4[1]	*10[7]
Non-Hodgkin Lymphoma	5[1]	4[1]	4[1]	3[1]	7[7]
Uterus	N/A	7[1]	N/A	4[1]	1.1[8]
Thyroid	N/A	6[1]	N/A	N/A	1[9]
Pancreas	N/A	3[1]	7[1]	7[1]	<1[10]
Others	20[1]	21[1]	28[1]	30[1]	N/A

Table 1. Shows the estimated incidence and mortality for primary tumors according to sex, as well as incidence of brain metastases from a primary neoplasia.
N/A: no data/not applicable; *Leptomeningeal spread
1: [26]; 2: [27,28]; 3: [29,30]; 4: [31]; 5: [32]; 6: [33,34]; 7: [35]; 8: [36]; 9: [37]; 10: [38]

In descending order, the most common origin of metastasizing neoplasias to the brain are as follows: lung, breast, skin, kidney and gastrointestinal tract. [39,40] As previously stated, prostatic cancer represents the prevailing cancer in men, however they rarely metastasize to the brain. [33,41,42] Although a proper distinction between the incidence of a primary tumor and their BM has to be made, the primary tumor histological type dictates generally the frequency and pattern of BM. [43] (See Table 2) A precise incidence of BM from all primary neoplasias is not known. Current literature presents many limitations and biases and represents mostly clinical-series or autopsy-series. Only a few population-based epidemiologic studies regarding BM are reported in the literature and are relatively old. Incidence rates in these studies range from 2.8-14.3 per 100.000 habitants. [28,44-50,27] Furthermore, cancer registries may also lack information regarding BM. As a result, only estimations can be made, although a statistically significant trend of increasing incidence of BM has been reported. [28] Some other factors that might explain this increase are the aging patient population, as well as the longer survival rates of patients with cancer, and obviously an increase in the incidence of primary tumor per se. [43]

Table 2.

Primary Tumor Localization	Incidence of Primary Tumor (%)	Cases of BM (%)
Lung	14	30-60
Breast	29	10-30
Melanoma	4	5-21
Others	53	<5

Table 2. Shows the distribution of all cases (as a percentage) of BM according to primary tumors and their incidence.
[51-72,26]

BM can occur at any age, but predominantly in adults between the fifth to seventh decade of life. Nevertheless, there is some distribution according to age group. Until the age of 15 years, the most

significant cause of BM is considered to be hematopoietic. Between 15 to 21 years of age, BM are commonly produced by germ-cell tumors. After the second decade of life, the incidence remains constant as previously stated. [73,74,51,75-78,52,7,79,80]

BM are not gender selective with a probable exception in melanoma patients, where a male predominance exists. [81,82,51] Interestingly, melanoma represents the most capable primary tumor to metastasize to the CNS. [83,63,84] This is possibly a result of their shared embryological origin, differentiated function and same signaling molecules of both melanocytes and central/peripheral nervous tissue. [85]

LM most commonly arise in patients with breast cancer (12-35%), followed by lung (10-26%), skin (5-25%) and gastrointestinal malignancies (4-14%), as well as neoplasias of unknown origin (1-7%). They have a tendency of coinciding with BM in up to 80% of the patients. [86,24,35,23,87-91] It has also been proposed, that surgical resection of BM, especially piece meal resection or incomplete resection, might have an influence on the development of distant BM and LM as a result of neoplastic cell spreading. [92-95,40,96]

1.3 Physiopathology

1.3.1 Basic molecular biology

Parenchyma and reactive stroma are the two key components present in every tumor, they classify and even dictate their biologic behavior. [3,97-99] Parenchyma is composed of neoplastic cells, whereas reactive stroma has multiple components: various cells originating from the immune system, blood vessels and connective tissue. [100,3,101,102,98,99] In general, malignant neoplasias are characterized by anaplasia or lack of cell differentiation, although other forms of morphological attributes may be present, such as: pleomorphism, abnormal cell nucleus, rate of mitoses, loss of polarity and necrosis.[3] As soon as metaplasia or dysplasia ensues and the basement membrane is penetrated, it becomes an invasive neoplasia.

As previously mentioned, there are a series of factors playing a crucial role in the cancer risk. Some pathological states, such as chronic inflammation, precursor lesions or immunodeficiency could also predispose the development of primary neoplasias. [3,97,99]

Malignant neoplasias do not differentiate well from the normal surrounding tissue and do not present a homogenous, well-defined plane. Some malignant tumors develop a pseudo-capsule, which histologically shows an infiltrating pattern to the contiguous tissue i.e. rupture or breach of the margin by malignant cells. [3]

Carcinogenesis begins with a mutation or initial damage to the genetic components possibly caused by inheritance, environmental factors or spontaneous changes. Furthermore, a clonal expansion of these damaged cells ensues. These neoplastic-associated mutations activate proto-oncogenes, down-regulate or alter tumor suppressor genes, as well as apoptosis-regulating genes and DNA-repair-genes. As a result, a genomic instability also referred to as "mutator phenotype" occurs and represents the first step to malignancy. Malignant neoplasias also evolve and can also change their behavior following therapy. Moreover, epigenetic aberrations i.e. DNA methylation and histone modifications may dictate the differentiation of normal or neoplastic cells. Epigenetic alterations might be reversible and are currently being investigated as a goal-directed therapy. [3,103-105,97,99]

It is important to mention that chromosomal abnormalities clearly lead to genetic changes and some of these adjustments are greatly associated with specific cancers. [97,99] Table 3 synthetizes the accepted cellular development or change distinctive of malignant neoplasia.

Table 3.

Action	Characteristic
Growth Signals: self-sustaining (Proto-oncogenes, Oncogenes and Oncoproteins)	• Proto-oncogenes present multiple actions causing self-sustaining abilities: growth factors, growth receptors, signal transducers, transcription factors, cell-cycle constituents • Promotion of limitless cell growth without any signals • Oncoproteins linked to accelerators of cell replication and DNA
Growth Inhibition: unresponsive (tumor suppressor genes)	• Alteration or suppression of tumor suppressor genes functionality • Normal cell cycle progression, DNA repair, senescence/quiescence and apoptosis compromised • Overexpression of growth factors
Altered Cellular Metabolism (Warburg effect)	• Biochemical alteration in glucose pathways • Cell autophagy

Apoptosis	• Mitochondrial pathway i.e. intrinsic apoptotic pathway inactivated • Extrinsic pathway might be altered
Limitless Replication	• Cell senescence avoided • Elusion of mitotic crisis • Self-regeneration of cancer stem cells
Angiogenesis	• Overexpression of inducing signals triggered by hypoxia • Loss of inhibiting factors
Invasion and Metastasis	• Interaction with extracellular matrix • Selected degradation of extracellular matrix • Coupling with extracellular matrix components • Cancer cell dissociation and invasion after degrading basement membrane
Evasion Immune Response	• Immunoediting i.e. alteration of tumor cell immunogenic characteristics • Oncogenic viruses' capacity of production of tumor antigens • Overexpression of oncofetal antigens/proteins • Modification of cell membrane • Diminished or loss of MHC-molecules expression • Expression of immunosuppressive factors • Regulatory T-cell development causing immunoevasion

Table 3. Describes the cellular hallmarks of cancer and their characteristics.
[103,104,3,105,97,106,99]

After creating a favorable and suitable environment for development on the primary organ, malignant neoplasia usually continues its path.

1.3.2 Spreading and predisposing localization

Gavrilovic et al. [107] proposed a series of steps, how BM develop. At the primary organ, as mentioned before, the cell of origin undergoes an alternate malignant transformation involving genetic change, growth, angiogenesis and invasion. After completing this initial development, it continues the process with transportation. An intravasation into the blood or lymph vessels occurs entering the circulation until it is detained in a small capillary bed, where the neoplastic cell extravasates. Then a period of dormancy ensues, promoting angiogenesis and growth.

The hematogenous route is the preferred way of spreading by most neoplasias. As a result, the anatomical distribution of most BM will follow the distribution of the greater artery i.e. middle cerebral artery in the brain. [108] Additionally, the distribution of blood flow to the brain also explains the localization of BM (hemispheres 80%, cerebellar 15%, brainstem 5%). [109,107] For years it has been taught that the interface between the grey and white matter represents a predisposed location for BM because of the characteristic reduced diameter of the arteries at this junction, where neoplastic cells get trapped. [108-110] This anatomical or mechanical hypothesis is partially discouraged, as this does not happen the same way in every organ. Based on this, the seed and soil hypothesis proposed by Paget [111], postulated that neoplastic cells seek (seed) or find specific hosts (soil or receptors) and continue the process, which serve as an alternate route of spreading.

Neurotropic factors could be responsible for the passage through the blood-brain barrier (BBB) and the direct interaction with neural structures. At this site, the preexisting endothelial cells promote angiogenesis and proliferation of the neoplastic cells supported by tumor cell vascular endothelial growth factor. [112-114]

Other mechanisms of neoplastic cell distribution other than arterial include: (1) spread via Batson's plexus, (2) patent foramen ovale, and (3) centripetal growth. [110,115-117,7,39,60,118,119]

Primary neoplasias present different tendencies in producing single or multiple BM depending on their provenance and histopathological features. The three most common metastatic neoplasias (i.e. lung, breast and skin) have a tendency of producing multiple metastases. On the other hand, renal and gastrointestinal BM are in more than 50% of the cases single BM. [108] Patients presenting a miliary pattern of BM (e.g. miliary metastases or carcinomatous encephalitis) most commonly have a lung neoplasia as a primary tumor. [120] Interestingly, the most frequent type of metastases to the choroid plexus arises, for still unknown reasons, from a renal origin. Furthermore, BM from renal or dermatological origin, as well as choriocarcinoma and to a lesser extent pulmonary origin are the most vascularized metastases and represent, in some cases, a surgical challenge due to the bleeding provoked. A reactive astrocytosis may also be seen by these BM. [108,121,122] Posterior fossa BM seem to arise mostly from pelvic or abdominal primary tumors, as well as breast tumors. [109,123]

1.3.3 CNS barriers

There are three different barriers that control the passage of substances between the blood, neural tissue and fluid spaces: (1) BBB formed by the continuous cerebrovascular lining of the endothelial cells between blood and interstitial fluid, (2) the epithelium of the choroid plexus between ventricular cerebrospinal fluid (CSF) and circulating blood, and (3) the arachnoid epithelium between subarachnoid CSF and circulating blood. (See Figure 1) [124]

The BBB is the largest area of exchange between blood and the brain and therefore, controls most of the interaction. [125] It represents a highly selective and specialized neurovascular unit, which protects all of its contents from the circulating noxa in the blood. [126,43,127]

Different cells form the neuroprotective barrier and produce a special microenvironment, so that only selected substances can cross. These cells are capillary endothelial cells and their basement membrane, neuroglial membrane, pericytes, neurons and the projections of the astrocytes from the neuroaxial side of the membrane, known as glial end feet. [128,127,43]

The specialized microenvironment known as neurovascular unit, transports different substances in diverse ways by electrochemical and concentration forces: (1) simple and (2) facilitated diffusion, (3) via aqueous channels or aquaporins, and (4) via protein carriers through active transport. [43,127,126,129-131] The BBB differs from other barriers in the body by having tighter junctions and having a predisposition for lipid-soluble molecules. [43,128] These junctions form a fascia occludentes with one another, decreasing the paracellular transport. [127,132,133] Endothelial cells in the BBB have rather few pinocytotic vesicles producing an almost exclusive receptor-mediated transport. [127,130]

Figure 1.

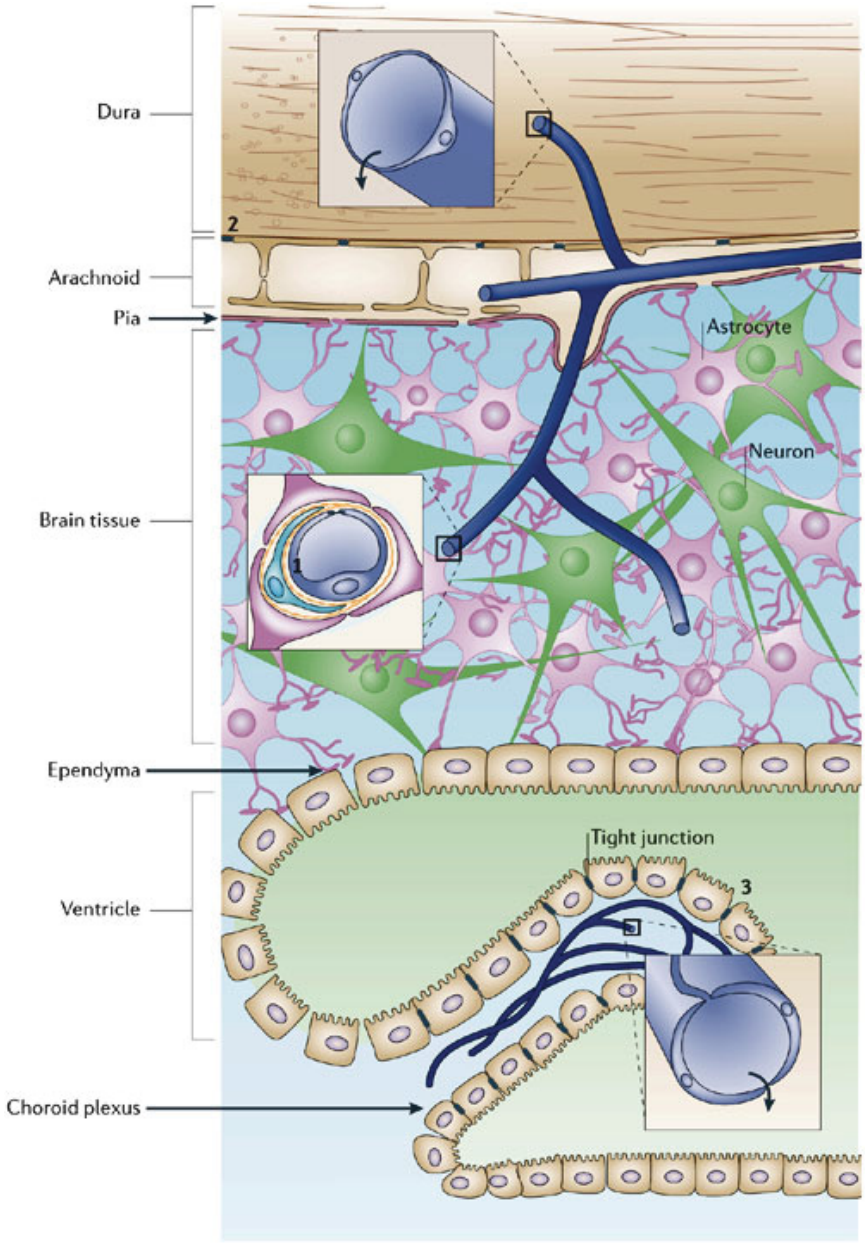

Figure 1: Shows the three different CNS barrier-sites: (1) BBB or functional neurovascular unit, (2) arachnoid epithelium, and (3) choroid plexus epithelium.
Adapted and with permission from [124].

Several chemical substances in the circulating plasma or produced by cells can cause a dysfunction or modification of the BBB. Pathological states can also disrupt the BBB. Table 4 shows the most common substances and pathological states that alter the BBB.

Table 4.

Agents	Pathology
• Glutamate, Serotonin, Bradykinin, Histamin • Adenosine Diphosphate, Adenosine Triphosphate, Adenosine Monophospate, Glutamate • Adenosine, Platelet-Activating Factor, Thrombin • Phospholipase A2, Arachidonic Acid, Prostagladins, Leukotrienes • Free Radicals, Nitric Oxide, Endothelin-1 • Interleukins: IL-1alpha, IL-1beta, IL-6 • Tumor Necrosis Factor alpha, Macrophage-Inhibitory Proteins 1 and 2 • Steroids, Cyclic Adenosine Monophosphate, Adrenomeduline, Noradrenergic Agents • Glial-derived Neurotrophic Factor • Basic Fibroblastic Growth Factor • Polyunsaturated Fatty Acids • Transforming Growth Factor-Beta • Compliment Derived Polypeptide: C3a-desArg	• Stroke • Trauma • Infectious or Inflammatory Diseases • Multiple Sclerosis • HIV • Alzheimer's Disease • Parkinson's Disease • Pain • Epilepsy • Brain Tumors including metastases

Table 4. Shows the most common substances and pathological states that alter the blood-brain-barrier (BBB).
Modified and adapted from [43,124,134-137]

1.4 Clinical Presentation

Most of the patients with a BM develop symptoms as tumor mass grows causing subsequent shifting or disruption of neighboring parenchyma. Peritumoral edema might also ensue creating even more disruption. As a result, most of the signs and symptoms tend to be sub-acute or chronically progressive. Symptoms might also occur acutely as a result of intratumoral hemorrhage, non-communicating hydrocephalus or emboli, resulting in a stroke-like symptoms. [138]

Signs and symptoms in patients with LM occur rather acutely and might be present as multiple manifestations, specific and/or unspecific, as every part of the nervous axis could be involved. [139,21,19,73,22]

There are specific and unspecific manifestations. These can also be classified according to the localization of the metastases, as well as the initiation of the symptoms.

Regarding parenchymal BM, headache is the most common symptom affecting around 50% of these patients and is usually worse in the morning or even awakens patients from their sleep. Cephalalgia can progressively become more critical and commonly associated with nausea, vomiting and drowsiness, as a sign of increased intracranial pressure. Focal neurological deficits prevail in almost 40% of the patients. Altered mental status, cerebellar signs and seizures are present in approximately 30%, 20% and 16%, respectively. [140,141,138] Interestingly, papilledema presents in only 10% of the patients. [14]

Patients with skull base metastases normally develop symptoms as the tumor grows and disrupts the surrounding structures. Cranial neuropathy, also known as craniofacial pain, is the most common presenting symptom in patients with a skull base metastasis (28%). According to the location affected, specific clinical syndromes may ensue. The most prevalent in descending order are sellar and parasellar syndromes (29%), middle fossa syndromes (6%) and jugular foramen syndromes (3.5%). [142-144]

With regard to dural metastases, the most usual symptoms are headache, cranial neuropathies, visual disturbances, altered mental status and seizures, as a consequence of compression or invasion of inherent structures, elevation of the intracranial pressure or traction of the dura itself. [145,146]

Spinal cord metastases are a rarity and cause a paresis in almost 90% of the patients. Not uncommon symptoms also include back pain, radicular pain, sensory deficits and sphincter dysfunction, as well as incomplete spinal cord syndromes. [147,148]

Clinical features of LM are varied, usually multifocal and depend on the affected anatomic location. Headache, altered mental status, nausea, vomiting or cerebellar signs are frequently seen with cerebral involvement. Cranial nerve affection normally is associated with visual deficits, hypoacusis, dysgeusia, dysphagia, hoarseness and facial paresis. Spinal cord affliction presents with motor or sensory deficits, pain and sphincter disturbances. [149,150]

Clinical characteristics and their involvement in the patients' ability to perform his daily/common activities have been proposed as predictors on prognosis, which will be discussed later on.

1.5 Diagnosis

After completing a thorough history and physical examination of the patient, complimentary diagnostic testing has to be attained. Initially, radiological imaging is to be performed, as it will detect or diagnose an intracranial tumor. It will also aid on how to proceed with the pathology at hand, and secondarily, it will help with the post-interventional evaluation and/or subsequent follow-up evaluations. Although radiological imaging allows a highly accurate detection and clarification of diagnosis, an ultimate diagnosis is achieved only after examining a tissue sample e.g. after surgical therapy and histopathological testing.

Nowadays, whole-body scans are performed in some centers on patients with a newly diagnosed systemic neoplasia, although no neurologic symptoms are present. As a result, a BM will be present in almost 30% of the patients at the time of diagnosis of a primary neoplasia, as previously stated. [4-6,3,7-9] Clinical diagnosis of a BM could be challenging in about 10% of the cases, as they remain asymptomatic. [140] However, BM may also be the featuring presentation in approximately 10% of the patients. [151,110] Nonetheless, the central nervous system should be newly screened, if a patient with a primary neoplasia presents with new neurological signs and/or symptoms.

Current imaging modalities for the detection, diagnosis and clarification of BM involve contrast-enhanced computer tomography (CT), gadolinium-enhanced magnetic resonance imaging (MRI), magnetic resonance spectroscopy (MRS), functional MRI (fMRI), diffusion tension imaging (DTI) for tractography, single-photon emission computer tomography (SPECT) and fluorodeoxyglucose-positron emission tomography (FDG-PET). [43,152] Of these, gadolinium-enhanced MRI remains the imaging modality of choice for the detection and characterization of a BM. [153,154,152,155,156] However, clinical status, timing of presenting symptoms and the necessity to make an immediate treatment decision are all factors that determine which imaging modality is to be chosen. Non-enhanced CT will rule out moderate to severe complications such as hemorrhage, hydrocephalus or herniation [156,157] and plays a critical role in unstable patients or in those with an acute onset of symptoms.

If a patient presents a contraindication for an MRI, a contrast-enhanced CT will be the imaging of choice. Generally, metastatic disease is shown as a well-circumscribed enhancing lesion associated

with moderate to severe peritumoral edema at the grey-white matter junction. In some cases, multifocality exists. [157,107-110] However, imaging morphology of BM in non-enhanced CT ultimately depends on the histological origin. [158]

Cha [156] describes the limitations of contrast-enhanced CT: (1) subtle intraparenchymal changes (infiltrative and non-enhancing tumor) are not shown because of the poor soft-tissue contrast uptake; (2) a three-dimensional representation of the tumor, especially concerning resolution, multiplanes and physiology-based techniques are suboptimal; and (3) it involves the use of ionizing radiation and iodinated enhancement agent. These issues are of no concern with the use of gadolinium-enhanced MRI, in fact, are opposite.
Although the history of a patient usually involves a primary neoplasia, some intracranial tumors are radiologically difficult to differentiate and subsequent imaging-tests will be needed in order to reinforce or discard the diagnosis. There are several entities that could mimic BM radiologically. These include primary brain tumors, lymphoma of the CNS, abscesses, encephalitis, hemorrhagic stroke, progressive multifocal leukoencephalopathy, demyelinating disease and radiation necrosis. [15,14] In some instances, its nature remains unclear until the tissue examination has been completed.

1.5.1 Gadolinium-enhanced MRI and physiology-based imaging

As previously stated, MRI remains the imaging of choice for the detection, diagnosis and further differentiation of a brain tumor. [153,154,152,155,156] Although different protocols are being employed, the most standardized protocol for this pathology uses pre- and post-gadolinium-enhanced T1-weighted sequences, T2-weighted sequence and Fluid Attenuated Inverse Recovery (FLAIR) sequence. [15,14,156,157]

Early postoperative MRI (within 72hr following surgical resection of brain tumors) has also been established as part of the protocol in some of the neuro-oncological centers across Europe to assess the degree of surgical resection. [159-163] Furthermore, detection of partial or incomplete surgical resection of a BM in early postoperative MRI has been associated with a high incidence of local recurrence [159] and therefore augmenting its importance. [162]

One of the main distinguishing diagnostic advantages of gadolinium-enhanced MRI T1-sequence is to show the typical BBB disruption of BM and should always be analyzed in conjunction with

the non-enhanced T1-sequence in order to discard other possible differential diagnoses. Once the BBB disruption has been delimited it is safe to assume an inflammatory reaction of the brain, manifested as profound vasogenic edema and mostly apparent in the T2-sequence. [156,157]

When evaluating a newly diagnosed neoplasia of the CNS, utmost care has to be taken to diagnose/search for a diffuse or multifocal pathology, as well as the leptomeningeal space. Considering the previously stated CNS barriers and spreading hypothesis, the hematogenous route could easily produce a distribution of neoplastic cells within the subarachnoid space and into the leptomeningeal space, and then transported through the CSF to the entirety of the CNS. [15,164,73,14] Most of the radiological features of LM are manifested in the ventricular system and peripheral CNS. Findings include: nodular patterns of leptomeningeal growth, thickening of the leptomeninges, ependymal-cells, tentorium, cortical and basal cisterns enhanced with gadolinium, and hydrocephalus. [157,14,164,139,165] However, almost 50% of the patients with LM present no radiological characteristics for a LM. [139] In order to confirm the spread of malignant cells through the leptomeningeal space, a lumbar punction with cytopathological analysis has to be performed. [73,23,162]

1.5.2 Further diagnostic testing?

Nowadays, there are many additional imaging diagnostic tools, yet their usefulness in BM remains unclear and may only aid in the characterization of a brain tumor. [156] MRS, SPECT and FDG-PET represent molecular imaging tools, which detect all major brain metabolites and correlate their biochemistry accordingly to many CNS pathologies. [166] Basically, this procedure differentiates biochemical markers in a region of interest, evaluating the type of tissue at hand. [156] Their most important roles are to differentiate between recurrence and treatment effect, as well as to analyze the response of the neoplasia to therapy. [167-169] As a result, their utility as an initial diagnostic tool remains uncertain and it is not part of the basic work-up for BM.

fMRI exemplifies an important characterization of brain activation. [170] Preoperative knowledge about the functional surroundings of a brain neoplasia may represent an important development in order to achieve a complete resection of the tumor without causing any surgical damage. [171] This non-invasive diagnostic tool, combined with DTI for tractography, characterizes, localizes and differentiates specific functions of the brain, as well as the important fiber tracts surrounding the neoplasia. [170,172] Although they might serve as convenient and useful instruments, fMRI and

DTI still deal with some patient-dependent, as well as, tool-dependent limitations. Patient compliance continues to play a key role in performing these tests, but also technical or tool-dependent difficulties are still being optimized in order to produce the best results possible. [172,170,173-183] In addition, intraoperative anatomical variations due to brain shifting could further reduce the accuracy of the preoperative diagnostic fMRI or DTI. [184,185] Knowledge of the functional anatomy is fundamental and its correlation with intraoperative physiological monitoring is by far a more reliable diagnostic and therapeutic tool.

1.5.3 Unknown primary tumors

By definition, BM are secondary brain neoplasias and might be diagnosed as a synchronous, metachronous or even as a first presentation of a systemic pathology. Almost 80% of the patients have a metachronous presentation. [7] Regarding a first presentation, a thorough history and physical examination have to be performed, as well as a CT scan of the thorax, abdomen and pelvis to localize the primary tumor, determine the extent of disease and define a therapeutic plan.

Nowadays, PET scan also plays a characteristic role as a staging tool [186,187], but it has not been able to demonstrate to be superior to CT scans [188,189] and should only be recommended if CT scans showed negative results. [162] In some cases, mammography, bone scan or even serum markers could also be useful to determine a primary tumor. Despite all possible diagnostic tools, histopathological and immunohistochemical testing, a primary tumor remains unknown in up to 20% of the patients in autopsy series[190].

1.5.4 Histology

“In no area of surgical pathology, possibly even in all diagnostic histopathology, does the pathologist play a more important and crucial role than in the diagnosis of tumors”. [191]

Although BM usually maintain the features of the primary tumor, some may present as poorly differentiated metastases, consequently further diagnostic studies have to be performed and, in some cases, the primary tumor site still remains unknown.

In order to make a proper classification, a sub-classification i.e. an immunoprofile from each tumor has to be confirmed. (See Table 5) This profiling has a special importance in patients with an unknown primary tumor.

Table 5.

Tumor	+	± or + in a subset	-
Non-Small-Cell Lung Carcinoma (NSLC)	CK7, TTF-1*		CK20
Small-Cell-Lung Carcinoma (SCL)	TTF-1*, CGA, SYN, CD56 (NCAM)	CKs	CK7, CK20
Breast Carcinoma	CK7	ER*,PR*, HER2, GCDFP-15, S-100, mammaglobin	CK20
Prostatic Carcinoma	PSA, PAP		CK7, CK20
Renal Cell Carcinoma	CD10 (CALLA), RCC		CK7
Melanoma	S-100, HMB-45, Melan-A (MART-1), MTFP*, tyrosinase		
Gastroesophageal Carcinoma		CDX2*, CK7, CK20, CEA	
Colorectal Carcinoma	CK20, CDX2*, CEA		CK7
Ovarian Carcinoma	WT1*	CK7, CK20, CA125	
Endometrial Carcinoma	CK7, CA125 (MUC16)	Mammaglobin	CK20
Hepatocellular Carcinoma	Hep Par-1, AFP, CEA, CD10, CD13**		CK7
Thyroid Carcinoma	TTF-1*, thyroglobulin		CK20
Squamous Cell Carcinoma	CK5/6, p63*	TTF-1* (only in lung)	CK7, CK20

Table 5. Shows metastatic epithelial/epitheloid malignancies and their common immunoprofiles.
* Nuclear Staining. ** Canalicular pattern of staining
CALLA, common acute lympphoblastic leukemia antigen; CDX2, caudal-type homeobox transcription factor 2; CEA, carcinoembryonic antigen; CGA, chromogranin A; AFP, alphafetoprotein; CK, cytokeratin; GCDFP-15, gross cystic disease fluid protein 15; Hep Par-1, hepatocyte paraffin 1 marker; MART-1, melanoma antigen recognized by T-cells-1; MFTP, microphthalmia transcription factor protein; NCAM, neural cell adhesion molecule; PAP, prostatic acid phosphatase; PSA, prostate specific antigen; RCC, renal cell carcinoma marker; SYN, synaptophysin; TTF-1, thyroid transcription factor 1; WT1, Wilm's tumor 1 transcription factor.
Adapted with permission from [108]

Histological and immunohistochemical characteristics are correlated with the chemo-radiosensitivity of a secondary neoplasia and could anticipate the response to the treatment options. The histological type and subtype could also represent an indicator on the survival/prognosis of each patient. Table 6 shows a list of tumors and their sensitivity to radiotherapy and chemotherapy.

Table 6.

Radiosensitive	Chemosensitive
High • Small-Cell Lung Carcinoma (SCLC) • Germ-cell tumor • Choriocarcinoma • Lymphoma	• SCLC • Lymphoma • Germ-cell tumors • Breast cancer
Intermediate • Non-Small-Cell Lung Carcinoma (NSLC) • Breast cancer • Colon cancer	*Targeted Therapies* • NSLC • Breast cancer • Melanoma
Minimal • Renal cell carcinoma • Melanoma • Sarcoma	

Table 6. Shows the sensitivity of some tumors regarding radiotherapy or chemotherapy. [43,192,193]

1.6 Therapy

BM require an interdisciplinary approach and as Chamberlain [110] precisely describes it, treatment is a continuum. Regardless of whether the patient is treated conservatively (i.e. medically), surgically, with radiation therapy or combined, each patient has to be individualized. Not every brain neoplasia is treated surgically, so that all therapy modalities are presented here. It is important to mention that less than 30% of the patients with a brain tumor will die as a direct consequence of the CNS pathology, but rather from the sequelae of systemic disease. [110,194]

1.6.1 Medical

Initial treatment is symptomatic and the ultimate therapy should be planned according to the history, physical examination and diagnostic testing. Each patient needs to be individualized and treated accordingly [110], even more crucial, the patient's wishes for each therapy or therapy in general, has to be taken into account.

As previously mentioned, most of BM cause a moderate to severe peritumoral vasogenic edema, explaining most of the patient's symptoms. Once diagnosed, initiation of steroids remains the mainstay of medical therapy. [110,195-197,14,15] Dexamethasone is the steroid of choice. Its rapid onset of action, administration and less side effects make this drug preferential. [197,110,195,15] Vecht et. al. [197] showed that a higher dosage does not necessarily mean better results. A dosage of 4 milligrams (mg) dexamethasone per day was as effective as 16mg per day in patients with no imminent signs of brain herniation and consequently the secondary effects were less. [197] So far, no evidence-based data about the dose-response relationship has been determined. [110] The quality of life might be reduced due to the side effects of dexamethasone, usually occurring after prolonged administration (longer than 3 weeks of therapy). [197,110]

Antiepileptic therapy should only be administered in patients with seizures and not as a prophylactic measure. [198,199,15,162]

1.6.2 Chemotherapy

Most chemotherapeutics against systemic cancers are non-lipid-soluble with a large molecular weight making the passage through the BBB almost impossible. Although BM cause a disruption of the BBB, the use of steroids theoretically restitutes the BBB adding to the impossibility of passage of these molecules. Furthermore, patients taking medication which influence the hepatic P450 system (via enzyme induction or inhibition) have to be closely monitored since the bioavailability of these drugs and/or the chemotherapeutics can be greatly altered. [110,200,14] Table 7 shows a partial list of inhibitors and inducers of the hepatic cytochrome P450 i.e. mixed-function oxidases.

Table 7.

Inducers	**Inhibitors**
• Barbiturates	• Amiodarone
• Benzo(a)pyrene (tobacco smoke)	• Azole Antifungi
• Carbamazepine	• Chloramphenicol
• Corticosteroids	• Cimetidine
• Efavirenz	• Clarithromycin
• Ethanol	• Cyclosporine
• Isoniazid	• Diltiazem

• Omeprazole • Phenytoin • Pioglitazone • Primidone • Rifampin	• Eryhromycin • Fluoroquinolones • Grape fruit juice • HIV protease inhibitors • Isoniazid • Macrolides • Metronidazole • Omeprazole • Quinine • Selective Serotonin Reuptake Inhibitors • Tacrolimus • Zafirlukast • Zileuton

Table 7. Partial list of inducing/inhibiting agents of the mixed-function oxidases system i.e. hepatic cytochrome P450.[201]

Needless to say, intrinsic tumor sensibility to the chemotherapeutic medication represents an additional factor, as the optimal systemic therapy usually differs from the chemotherapy passing through the BBB, resulting in skepticism in the role of chemotherapy in the treatment of BM. Therefore, chemotherapy for BM is usually limited to patients in whom radiotherapy was refractory or where salvage-therapy is needed, as well as an initial treatment for chemosensitive tumors (see Table 6), and is not considered a standard therapeutic approach for every BM. [110,13,162] Nevertheless, if the need for intrathecal chemotherapy as a salvage therapy arises, certain medications with unclear effect are available. [14]

Newly targeted therapies, such as epidermal growth factor receptor (Erlotinib and Genfitinib) or anaplastic lymphoma kinase (crizotinib), both tyrosine kinase inhibitors, appear to have some activity against BM, but their use is still controversial and usually combined with radiotherapy. [202-212,13] As for Bevacizumab and Temozolomide, which have shown some activity against primary brain tumors, the results for BM in combination with radiotherapy are also uncertain. [213,214,13] The use of intracavitary carmustine wafers remains also controversial, although some results suggest an improvement in local control. [215]

1.6.3 Radiotherapy

Radiation therapy, its variants and their indications have been evolving over the past decades. Nowadays, radiation therapy is either used as an adjuvant therapy after surgical resection or as primary approach as stereotactic radiosurgery (SRS). Whole brain radiation therapy (WBR) alone is performed only in specific indications. In order to understand the current radiation therapy approach and its indications, a short review will be given.

Goal of every conservative oncological treatment has been to alleviate symptoms, reduce tumor-mass, prolong the survival, and most important preserving or improving the quality of life. Radiation therapy is not the exception. Most of the reported literature since the 1950's describe a decrement in the symptoms i.e. symptom alleviation after radiation therapy. [216-219] Unfortunately, not all primary tumors including their secondary brain counterparts are radiosensitive and thus represent a difficulty in tumor mass reduction. [220,221] As for survival, none of the radiation therapies alone have shown an increase in the survival rate. However, when applied as an adjuvant therapy, it impacted positively on it. [222,223]

1.6.3.1 Whole Brain Radiation Therapy Alone

Since the 1920's, when the first descriptions of WBR or roentgen-ray therapy for the brain was introduced [221,224], this type of radiotherapy as a mono-therapy remains the only treatment for many patients with BM. [110] The main reasons and/or indications for a WBR alone are patients with multiple foci (>3) where distant metastases could also play a role, and salvage therapy. [116,117,28,225,226,10,227-235,13] Although it alleviates most symptomatic patients, it has been shown to be detrimental to the quality of life because of multiple adverse reactions, especially the affection of neurocognitive function. [93,236] Because of the different radiosensitive characteristics of each tumor, response is highly irregular and not satisfying. As a monotherapy, the probability for long-term local control has been reported between 0-14%. [222,235] It has also failed to show a significant raise in the overall survival rates. [237,238]

1.6.3.2 Stereotactic Radiosurgery

SRS represents a comfortable and alternative type of radiation therapy. It accesses regions, where resection of BM would be impossible without damaging non-affected brain structures. Additionally, it can be performed as an ambulatory procedure. [13]

Solitary BM with a diameter of less than 3 centimeters or volume up to 15 milliliters without any symptoms or mass effect are the ideal indication for this type of treatment. Nonetheless, SRS is also used in patients with ≤3 BM, if those are non-resectable, as well as for local recurrence cases. Combination of two radiation modalities, SRS plus WBR, has also been proposed, in order to achieve a greater local and distant control. [116,117,28,225,226,10,227-235,13,239-241] Some reports indicate a better local and distant control, but unfortunately no difference in the overall survival or less adverse effects. [231] Use of SRS for radio-resistant tumors i.e. melanoma, renal cell carcinoma and sarcoma remains controversial. [227,234,242] The most common arguments against this type of radiation are perifocal symptomatic radio-necrosis and lack of distant control of the disease. [13,243,244]

Tendency towards SRS following surgery into the resection cavity has begun. At the moment many trials are ongoing and will clarify the possible radiation options for most therapeutic paradigms.

1.6.4 Surgery

Without an immunohistological diagnosis, the initiation of an empirical therapy for BM is not adequate and might result in an important reduction in the quality of life, as well as an incorrect treatment for the patient. On the other hand, surgery alone for the treatment of BM, either biopsy or complete removal, should not automatically be considered as an optimal treatment option, as the local recurrence and risk of neurological death from a BM significantly rises. [10] It is essential that the extracranial disease be controlled, in order to achieve a benefit from surgery. [162]

In every neuro-oncological surgery, the primary goal remains surgical removal of the pathology without infringing any damage. Current indications for surgery are summarized in Table 8.

Table 8.

Indications
• Symptomatic BM (also applies for multifocality) • No history of systemic disease or controlled systemic disease • Unclear diagnosis • Mass effect (also applies for multifocality) • Intratumoral hemorrhage • Posterior fossa tumor • Recurrence

Table 8. Describes the current indications for surgical therapy for brain metastases (BM). [228,227,10,140,245,246,215,247-250,226,222,110]

1.6.4.1 Surgical technique

According to each patient, every surgery has to be orderly planned. Additional tools such as navigation, intraoperative neurophysiological monitoring, ultrasonography, use of aminolevulinic acid (5-ALA), fluorescein, indocyanine green, ultrasonic aspirator, amongst others, have to be considered. Although in many cases experimental, application of these different devices has augmented the precision in localizing the neoplasia, has reduced the craniotomy size, has optimized operating time and has achieved complete removal of the pathology. It even allows supramarginal resections without damaging the surrounding structures. Nonetheless, they represent only supplementary accessories.

Two techniques have been utilized to resect BM: en bloc and piece-meal resection. Most surgeries attempt an en bloc resection, as it has been suggested as a factor for decreasing the incidence of local recurrence, distant recurrence, LM and complication rate, as well as increased survival. [251,252,40,96,162] The philosophy behind this technique advocates lesser tumor violation, therefore theoretically no neoplastic cell is able to spread through the CSF or vascular system. This technique achieves a complete tumor resection. On the other hand, piece-meal fashion might lead to an incomplete removal of the tumor, and more important spreading of neoplastic cells in the CNS because of the nature of the resection.

Some studies have shown an infiltration of secondary neoplasias into the surrounding tissue [253-255], also suggesting a possible “incomplete” removal with en bloc resection or even proposing a

more aggressive approach with a supramarginal resection of BM, in order to avoid a tumor-remnant.

Nowadays, the use of ultrasonic aspiration devices is becoming more common. The way this system works is the following: the tissue to be removed, vibrates, accelerates and decelerates within the tip and gets fragmented; cavitates, and as the tip continues to work, it produces localized pressure waves causing vapor pockets at a cellular level with high water content originating a rupture and suctioning of the tissue. [256] Fragmented debris not suctioned by the device could also represent a possible spreading of neoplastic cells, but no evidence-based data is available at the moment. Combination of an en bloc resection with the use of an ultrasonic aspiration device to achieve a supramarginal resection might represent a more precise surgical option, if the area operated upon allows it without infringing any damage. For piece-meal resection, the use of such ultrasonic aspiration devices should be standard in order to remove as much BM as possible, without leaving remnants behind. As a result of a peace-meal resection, a higher incidence of neoplastic cell spreading (i.e. LM) should be expected. This would also apply for cystic BM, if the cyst ruptures during the operation.

1.6.4.2 Number of metastases

Currently, elective treatment with SRS and surgery are reserved for patients with ≤3 BM. In acute settings, each therapy has its indications. Resection of multiple BM has also been proposed, when patients have an indication for surgery and meet the prognostic criteria mentioned later on. [249,250,257] Complication rates remain unaltered, whilst the survival benefit increases significantly. [250,258]

SRS for ≥4 BM has also been proposed [259], but as mentioned before, a greater local and distant control might be achieved with a combination of WBR and SRS. Adverse effects, especially with WBR, need to be previously discussed. [116,117,28,225,226,10,227-235,13,239-241]

1.6.4.3 Local control after surgery and recurrent disease

As mentioned before, intracranial disease can only be treated if extracranial pathology is absent or controlled. Surgery as a monotherapy is not an option. Surgical resection of BM without adjuvant therapy would raise the probability of death from neurological causes. [260,246,261,262] Herein lies the importance of local control after surgical resection.

Multiple studies have demonstrated that although surgical resection with concomitant adjuvant radiotherapy represents a better local and distant in-brain control, it has not yet showed a significant improvement in the overall survival. [223,222,247,10] Still, surgery alone in almost every case is no rational option. Nowadays, rigorous guidelines for each type of therapy are set in order to achieve the best evidence-based treatment possible and optimal local and systemic control. [162]

Despite the fact that recurrent disease represents a deterioration in the prognosis for patients with BM if left untreated, choice of treatment for recurrent disease remains controversial. [249] Additional surgery for recurrent BM offers an improvement in quality of life, as well as prolongation of survival. [249] Surgery continues to be an alternative for patients treated with SRS, if a recurrence ensues. Some studies report a better prognosis in patients who underwent surgery after having had a recurrence following SRS. [263] Apparently, time-to-recurrence plays a significant role as a prognostic factor. The bigger the interval, the better the median overall survival. [249,264] Other suggested factors which would potentially contraindicate surgery are: presence of active extracranial disease at time of recurrence, Karnofsky performance status scale (KPS) equal or less than 70, less than 4-6 months interval between first surgery and recurrence, age above 40 years, and primary tumor type (breast cancer and melanoma), as well as postoperative tumor remnant in MRI after the first surgical therapy. [264,265,249,159,162,246] Unfortunately, most patients with recurrent disease will have at least one or two of these characteristics.

Palliative interventions with radiotherapy (WBR and SRS) or chemotherapy, as a salvage therapy, could also be an alternative. As mentioned before, adverse reactions, incompliance, contraindications or unclear benefit have to be accounted for and each patient must be individualized.

1.6.4.4 Surgical palliative interventions

The implantation of a device, such as an Ommaya or Rickham Reservoir, or CSF derivation procedures should always be considered as a surgical option. In some instances, intrathecal administration of adjuvant therapy is indicated. In those cases, an Ommaya or Rickham Reservoir plays a significant role. Furthermore, some unresectable BM could compromise the CSF dynamics causing a secondary hydrocephalus and consequently, the necessity for derivation of CSF. Both of

these surgical alternatives are usually considered as palliative interventions. [194,14] As mentioned before, every case should be individually assessed.

1.6.5 Prognostic factors

According to the current literature, most of the surgical procedures are performed after careful selection of patients depending on different factors. However, if the established criteria are strictly followed, the number of possible surgical candidates with BM is significantly reduced to about one third. [266] For this reason, most patients can only rely on non-surgical treatment with a suboptimal survival rate.

Currently there are many tools aiming to assess the prognosis in patients with BM. The most commonly utilized are the recursive partitioning analysis (RPA), also known as the Radiation Therapy Oncology Group recursive partitioning analysis, and the graded prognostic assessment (GPA) with its disease-specific variant (DS-GPA). Both assessment tools use several factors to predict a prognosis. [267,268,260] RPA classifies patients into classes I, II and III and depending the class so is the median survival in descending order. [260] GPA and its variant DS-GPA gives patients a specific score according to the factor evaluated. A higher score means a greater median survival. [267,268] Tables 8 and 9 give an insight of both evaluation instruments. One of the key factors to be evaluated in both assessment tools is the KPS or a simplified form of the KPS. First described in 1948 [269], KPS remains the cornerstone for evaluation and prognosis in cancer patients (see Table 10). In both tools, age still represents a limitation when it comes to prognostic grading with ages over 60-65 set as a cut-off point for worsening of prognosis (see Tables 9 & 10). [260,13,270,267,162]

Table 9.

Class	Prognostic Factors	Median Survival (months)
I	KPS ≥70 Age <65 years No other metastases Controlled primary neoplasia	7.1
II	All others	4.2
III	KPS <70	2.3

Table 9. Describes the RPA classes, its factors and accordingly, their median survival in months.
KPS: Karnofsky performance scale/status
Adapted from [260]

Table 10.

Factor	Points 0	Points 0.5	Points 1		GPA Score	Median Survival (months)
Age	>60	50-59	<50		0-1	2.6
KPS	<70	70-80	90-100		1.5-2.5	3.8
Number of BM	>3	2-3	1		3	6.9
Extracranial metastases	Present	-	Absent		3.5-4	11

Table 10. Depicts the GPA scoring according to the prognostic factors and how the score reflects median survival.
KPS: Karnofsky performance scale/status; GPA: graded prognostic assessment; BM: brain metastases
Adapted from [267]

Table 11.

Criteria	Score	Definition
Normal, no complaints, no evidence of disease	**100**	No special care is needed. Able to carry on normal activity and to work.
Able to carry on normal activity, minor signs or symptoms of disease	**90**	
Normal activity with effort, some signs or symptoms of disease	**80**	
Cares for self, unable to carry on normal activity or to do active work	**70**	Unable to work, able to live at home, care for most personal needs. A varying amount of assistance is needed.
Requires occasional assistance, but is able to care for most of his needs	**60**	
Requires considerable assistance and frequent medical care	**50**	
Disabled, requires special care and assistance	**40**	Unable to care for self. Requires equivalent of institutional or hospital care. Disease may be progressing rapidly.
Severely disabled, hospitalization is indicated although death not imminent	**30**	
Very sick, hospitalization necessary, active supportive treatment necessary	**20**	
Moribund, fatal processes progressing rapidly	**10**	
Death	**0**	

Table 11. Describes an adaptation of the original Karnofsky performance status scale (KPS) initially described as “performance status”.
Adapted from [269]

It is quintessential to have a primary tumor control. Absence or controlled extracranial pathology would represent a better prognostic factor, better loco-regional control of the disease, as well as prolongation of survival. [267,260,13,270,15,162]

Nowadays, morbidity and mortality associated with neurosurgical removal of a BM has considerably progressed. Clinical improvement has been shown in up to 84% of the patients after surgery [250], as well as an increase in the KPS of about 33-59%. [269,271,194] Data suggest an estimated 30-day mortality rate after surgical removal of a BM to range about 1.9-5%. [271,272]

1.6.6 Age-dependent treatment?

Life expectancy and declining birth rates in Western societies are causing a demographic shift towards old age. [273] Inevitably, ageing precipitates biological and psychological changes, diseases and different conditions. Ortman et. al. [274] expect that in the year 2050 20% of the population in USA will be over 65 years of age. Most cancers, not necessarily BM, appear in patients above 65 years, yet this subgroup is mostly excluded from clinical trials and remain undertreated. [275] More attention has to be paid to this subgroup. Unfortunately, when a patient over 65 years of age is diagnosed with cancer, stratification occurs in order to predict or assess their prognosis. Advanced age remains a negative prognostic factor for cancer patients and automatically disqualifies patients for some types of treatment without any evidence of its benefit or deleterious effect.

Geriatric assessment (GA) has been proposed in order to give a full evaluation of this subgroup of patients. Its components include functional status (physiological reserve), comorbidities and medications, cognition, nutritional and psychological status, social support and advanced care planning. GA might represent more valuable prognostic information, early identification and treatment of conditions that might have otherwise been unrecognized, and simplifying the individual approach for each patient above 65 years of age. [276-280] Regrettably most often it is not being considered during the decision-making process for cancer, even less so for BM. Rothenbacher et.al. [281] showed that active involvement in the decision-making process was preferentially performed in patients under 60 years with higher KPS. Patients above the age of 60 preferred a more collaborative/conjoined or passive role. However, patients' age should not be an automatic disqualification for oncologic surgery, as the impact of treatment on the quality of life is substantial after individualization. [275] Nowadays, operations can be performed safely in elderly patients without severe comorbidities. To our knowledge, there is no significant data that rigorously contraindicates an operation because of the patients' age. [275] Yet again, this subgroup is mostly excluded from clinical trials so that evidence-based data is non-existent.

2. Objectives

Brain metastases (BM) are the most frequent brain tumor. Recurrence rate after treatment is about 40-60%. Age is still thought of as a determinant factor for treatment and prognosis in this pathology. Increasing rates and longer-term observations have resulted in newly found issues and consequently, in confrontation with further concerns. To the best of our knowledge, no studies have analyzed the risk factors for local in-brain recurrence after surgical resection of brain metastases, especially in patients above 65 years. Additionally, the increasing expected lifespan, early and superior diagnostic modalities, as well as improved conservative treatments result in a higher demand in prognostic tools and surgical optimization, even a second or third surgery.

The publications summarized in the present thesis identify and address some of the current nuances in cerebral metastases surgery, namely:

1. Establish the risk factors for local in-brain recurrence after surgical resection of brain metastases in patients above 65 years of age
2. Analyze complications after surgery of brain metastases in elderly patients
3. Determine the impact of protoporphyrin IX-fluorescence on the local progression-free and overall survival
4. Identify the risk factors of further local in-brain progression after re-craniotomy for locally progressive cerebral metastases
5. Question treatment and prognostic paradigms

These concerns are addressed by three different retrospective analysis focusing on the following:

1. risk factors for in-brain local progression in elderly patients after resection of cerebral metastases
2. implication of 5-ALA fluorescence of cerebral metastases on local recurrence and overall survival
3. predictors for a further local in-brain progression after re-craniotomy of locally recurrent cerebral metastases

The first publication summarized represents a first authorship. The second publication also represents a first authorship, but with equally contribution/distribution. The third publication is co-authored.

3. Original publications

3.1 Risk factors for in-brain local progression in elderly patients after resection of cerebral metastases

www.nature.com/scientificreports

SCIENTIFIC REPORTS

OPEN

Risk factors for in-brain local progression in elderly patients after resection of cerebral metastases

Received: 15 January 2019
Accepted: 2 May 2019
Published online: 15 May 2019

Christopher Munoz-Bendix[1], Marion Rapp[1], Hendrik-Jan Mijderwijk[1], Christiane von Sass[1], Maxine Dibué-Adjei[1], Jan Frederick Cornelius[1], Hans-Jakob Steiger[1], Bernd Turowski[2], Michael Sabel[1] & Marcel A. Kamp[1]

Intracranial metastases are the most frequent brain tumor with recurrence rates after treatment of around 40–60%. Age is still considered a determinant of treatment and prognosis in this pathology. Recent studies analyzing the impact of metastasectomy in elderly patients focused on reporting perioperative mortality and morbidity rates but not on the evaluation of oncological outcome parameters. Aim of this study is to determine risk factors for in-brain local recurrence after brain surgery in this sub-population. From October 2009 until September 2016 all patients aged 65 years and above with histopathologically confirmed metastasis after surgical resection were retrospectively studied. Clinical, radiological and perioperative information was collected and statistically analysed. Follow-up consisted of clinical and radiological assessment every 3-months following surgery. 78 patients were included, of these 50% were female (39 patients). Median age was 71 years (66–83). Early postoperative-MRI verified a complete surgical resection in 41 patients (52.6%) and showed a tumor-remnant in 15 patients (19.2%). In 22 patients the MRI result was inconclusive (28.2%). None of the patients experienced severe complications due to surgery. The median postoperative NIHSS was adequate 1 ± 1.4 (0–6), nonetheless, insignificantly improved in comparison to the preoperative NIHSS ($p = 0.16$). A total of 20 patients (25.6%) presented local recurrence. The only statistically significant factor for development of local in-brain recurrence after resection of cerebral metastases in patients above 65 years of age was a tumor-remnant in the early postoperative MRI ($p = 0.00005$). Median overall survival was 13 months. Local in-brain recurrence after surgical resection of a cerebral metastasis in patients above 65 years of age was 25.6%. In our analysis, tumor-remnant in early postoperative MRI is the only risk factor for local in-brain recurrence. Oncological parameters in the present cohort do not seem to differ from recent phase III studies with non-geriatric patients. Nevertheless, controlled studies on the impact of metastasectomy in elderly patients delivering high quality reliable data are required.

Although the exact incidence of cerebral metastases from solid cancers is unknown, intracerebral metastases are the most frequent brain tumors with a 3–5 times higher incidence than newly diagnosed primary malignant brain tumors each year[1,2]. Incidence of cerebral metastases was considered to increase from 2.8–11.1 per 100,000 population in the years before 1990 to an incidence of 7–14.3 per 100,000 population in more recent studies[1]. Cumulative incidence of cerebral metastases may be age-related as the highest cumulative incidence is observed in patients with primary breast cancer at the age between 20 and 39 years, in lung cancer patients at the fifth decade and in malignant melanoma patients at the sixth decade of life[3]. Cumulative incidence is considered to be lowest for all primary cancers in the age group above 70 years, with exception of melanoma[3].

Despite the presumably lower incidence of cerebral metastases in elderly patients, incidence in this subgroup increases due to the high number of elderly patients, general increase of occurrence of cerebral metastases, improved diagnosis of brain metastases and better treatment of the primary cancer. Moreover, age above 60 years was one major risk factor for impaired overall survival (OS) in an early prospective randomized study comparing combined treatment of surgery and adjuvant whole-brain radiation therapy (WBRT) with an exclusive WBRT[4]. A recent individual patient data meta-analysis of 3 randomized trials of stereotactic radiosurgery (SRS) with or

[1]Department of Neurosurgery, Heinrich Heine University Hospital, Dusseldorf, Germany. [2]Institute for Diagnostic and Interventional Radiology, Heinrich Heine University Hospital, Dusseldorf, Germany. Correspondence and requests for materials should be addressed to C.M.-B. (email: christopher.munoz@med.uni-duesseldorf.de)

without WBRT for 1 to 4 cerebral metastases suggested that age might be a factor influencing the efficiency of an adjuvant WBRT following SRS. For patients <50 years of age, SRS alone favoured survival and an additional WBRT did not impact the distant in-brain progression rate. Adjuvant WBRT significantly decreased the risk of new cerebral metastases without affecting the OS in patients aged >50 years[5]. Some recent retrospective studies reported age as a risk factor for a reduced survival[6]. Age is therefore still considered to be a determinant of treatment and prognosis in this pathology in recent guidelines[7].

The Dutch prospective and randomized study (surgery and WBRT vs. WBRT alone) identified age as a major determinant for OS[4,8]. However, patients included in this study were recruited between 1985 and 1991, a preoperative MRI to diagnose single intracerebral metastases was not mandatory and histological confirmation of the presumed metastasis was not necessarily required prior to treatment. Since the end of the 1980s, advancements in pre- and postoperative diagnosis and surgical techniques have been made[9–19]. Recent studies analyzing the impact of metastasectomy in elderly patients focused on reporting perioperative mortality and morbidity rates but not on evaluation of oncological outcome parameters.

Aim of the present retrospective study was therefore to analyze the progression-free and overall survival, rate of local in-brain progression and complications after surgery of brain metastases in elderly patients over the age of 65.

Methods and Materials

Study design, inclusion and exclusion criteria. This study represents a clinical and radiological retrospective analysis of a consecutive series of patients treated for intracranial metastases at a large European tertiary care centre. This study involved the review of clinical records as part of medical care. We retrospectively studied and analysed medical records and their corresponding radiological diagnostic tests of every patient presenting with histologically confirmed brain metastases from October 2009 until September 2016.

Inclusion criteria were: (1) histological diagnosis of an intracranial secondary tumor, (2) operated only at our institution, (3) between October 2009 and September 2016, (4) pre- and postoperative MRI (pre- and post gadolinium-enhanced T1-weighted sequences, T2-weighted sequences and Fluid Attenuated Inverse Recovery (FLAIR)), (5) clinical and radiological follow-up at our institution, (6) age older than 65 years.

Exclusion criteria included: (1) other tumor than cerebral metastases (primary brain tumor, small cell lung cancer, neuroendocrine or sarcoma metastases and lymphoma) (2) prior surgical treatment at a different institution, (3) exclusively palliative or no neuro-oncological treatment, (4) previous treatment with the following: biopsy, stereotactic biopsy, radiotherapy and/or SRS, and (5) preoperative diagnosis of leptomeningeal carcinomatosis (LC).

Surgery. All patients included in this study received surgical treatment for one cerebral metastases, although patients with more than one metastasis were also considered for surgery. Indication for surgical treatment of one cerebral metastasis in patients with 2 or more cerebral metastases was (1) symptomatic lesions, (2) mass effects (3) no history of systemic disease or unclear diagnosis, (4) intratumoral hemorrhage, and (5) large posterior fossa tumors.

Intraoperative frozen sections were obtained in all patients. After the histological diagnosis of a cerebral metastasis by frozen section, standard white-light assisted – and if possible – *en bloc* circumferential resection was performed. Surgery integrated the intraoperative use of ultrasound (ProSound alpha7, Hitachi Aloka Medical America Inc., U.S.A.), neuro-navigation (Brainlab Navigation System, Brainlab AG, München, Germany) and awake surgery using an asleep-awake-asleep protocol as described before for patients with eloquent located cerebral metastases[11]. An eloquent brain region was defined as a cortical or subcortical brain area where we expect intraoperative stimulation to elicit changes in neurologic conditions (particularly regarding speech, movement and tactile sensation) or to elicit a response in electrophysiological recordings in corresponding areas[11,20]. Adjuvant therapy was individually decided upon in every case after histological diagnosis in an interdisciplinary tumour board. Recommendations for adjuvant radiation depended on various parameters such as number of cerebral lesions, degree of resection, Karnofsky Performance Scale (KPS) and the patient preference.

Data collection, follow-up and definition of outcome measures. Additionally, pre- and postoperative clinical characteristics of the patients, preoperative performance scale, localization, number of metastases, characteristics and classification of the tumor, treatment and incidence of each primary tumor, extent of surgical resection, fluorescence of the tumor, use of intraoperative monitoring, perioperative complications, periodically follow-up visits, recurrence, time to recurrence, loco-regional or distant metastases, neoadjuvant/adjuvant/palliative therapy, survival, cause and date of death (if applicable) were collected from charts and electronic records and analyzed.

Pre-, postoperative and follow up clinical assessments were standardized using the National Health Institute of Stroke Scale (NIHSS). Degree of surgical resection was verified by early postoperative 1.5T-MRI as described before[16]. A senior neurosurgeon and neurological radiologist performed the radiological analysis. After surgery, patients were followed-up including a contrast-enhanced MRI every 3 months.

Local in-brain-progression/recurrence was defined according to the RANO criteria[21], as an increase by 20% from the initial longest diameter of the target lesion with an absolute 5 mm growth, as measured in contrast-enhanced T1, T2 and diffusion sequences. Radiological postoperative evaluation of the resection cavity was defined as inconclusive when characteristics such as postoperative blood residues, pronounced vessels, reactive tissue, suboptimal image quality were present[16]. Distant in-brain-progression was defined as appearance of new metastasis distant to the site of the resected metastasis (distance to the resection cavity of at least 2 cm). Dural inclusion of cerebral metastasis and leptomeningeal carcinomatosis (LC) were interpreted as different radiological entities. Dural inclusion explicitly represented radiological or intraoperatively verified contact of the dura

with the brain metastases (BM) with no additional radiological signs of LC. LC was diagnosed by cranial MRI showing a diffuse enhancement of meninges or by lumbar puncture and confirmation of malignant tumour cells in the cerebrospinal fluid (CSF). Time to in-brain-progression was defined as time between surgery and diagnosis of the in-brain-tumour progression. The overall survival was considered as time span between surgery and death.

Statistical analysis. Follow-up ended in April 2018 and the database was finalized shortly thereafter. All statistical analyses were performed with SPSS software (Version 22.0, -IBM-, USA). Data is presented as the median and standard deviation. Descriptive statistics including mean and standard error of mean were calculated for all continuous variables. The Chi-Square-test was used in nominal variables to identify significant differences. Contingency tables were performed according to the number of possible answers. As multiple statistical testing was performed, the significance level according to Šidák's and Bonferroni's correction: Šidák's and Bonferroni-correction revealed an adjusted p-value of 0.0051 or 0.005, respectively.

Ethical statement. Data acquisition, radiological interpretation, as well as an analysis of both, were approved by the institutional research ethics board (Medical Faculty, Heinrich-Heine- University, Nr. 5713). For every patient treated at our institution with any brain pathology we obtained an informed consent allowing a retrospective analysis of the data, as well as the inclusion of the pathological specimen in an institutional tumor-bank.

Results

Patient's characteristics. A total of 78 patients aged 65 or above were included; of these 50% were female (39 patients). The median age was 71 years (66–83). In our series, 50 patients (64.1%) presented a single metastasis, 18 patients (23.1%) had two or three cerebral metastases and 10 patients (12.8%) presented more than three metastases. All patients were required to be in good clinical condition to be eligible for surgery. Every patient had a preoperative Karnofsky Performance Scale (KPS) of 70 or more. The median preoperative KPS was 90 ± 9.8 and the median pre-operative NIHSS was 1 ± 1.9 (0–10).

The most common primary tumor type was non-small cell lung carcinoma (NSCLC) in 35 patients (44.9%). Adenocarcinoma was the most frequent histological diagnosis and was present in 58 patients (74.4%). Epidemiological features of the present patient population are summarized in Table 1.

Treatment. Surgery was performed as an en-bloc resection in 40 patients (51.2%) and as piece-meal resection in 38 patients (48.7%). Early postoperative-MRI verified a complete removal in 41 patients (52.6%) and showed a tumor-remnant in 15 patients (19.2%). In 22 patients the MRI result was inconclusive (28.2%).

No patient experienced a severe complication due to surgery, such as surgery-associated death or cardio-pulmonary complications. The median post-operative NIHSS was 1 ± 1.4 (0–6). The median post-operative NIHSS was 1 ± 1.4 (0–6). Therefore, median post-operative NIHSS was not significantly improved in comparison to the pre-operative NIHSS ($p = 0.16$; Fig. 1) The NIHSS improved after surgery in 28 patients (35.9%), decreased in 9 patients (11.6%) and was unchanged in 41 patients (52.6%).

As local adjuvant treatment, almost half of the patients received whole brain radiation therapy (37 patients, 47.4%) and in 15 patients no adjuvant therapy was performed (summarized in Table 1).

Local in-brain progression and overall survival. A total of 20 patients above 65 years of age (25.6%) presented a local recurrence with a median time-to-local recurrence of 3 ± 2.9 months (0–10 months). 23 patients (26.9%) developed distant metastases and 13 patients (16.7%) carcinomatous meningitis. (See Table 2).

According to statistical correlation, the only factor statistically significant for the development of local in-brain recurrence after resection of cerebral metastases in patients above 65 years of age was a tumor-remnant in the early postoperative MRI ($p = 0.00005$). In our series no other risk factors such as sex, localization, number of metastases, preoperative KPS and NIHSS, postoperative NIHSS, primary tumor site, histology, type of surgical resection and type of adjuvant radiation, could be identified (each $p > 0.05$).

A total of 8 patients (10.3% on May 22nd 2018) were still alive at the end of the study and continued with the scheduled follow-up visits. Two of these 8 patients suffered from local recurrence. The median OS was 13 months. Kaplan Meier estimates for OS and local in-brain progression are shown in Fig. 2.

Discussion

The main results of our analysis are as follows: (1) the local in-brain recurrence after surgical resection of a BM in patients above 65 years of age is 25.6% with a median time to occurrence of three months; (2) in patients above 65 years of age tumor-remnant in an early postoperative MRI was the only risk factor for local in-brain recurrence and (3) the median overall survival was 13 months in the present series.

Most studies analyzing the impact of cerebral metastasis resection focus on reporting perioperative morbidity and mortality rates but omit oncological outcome parameters such as (local) in-brain progression and survival. Median overall survival was 13 months after metastasectomy in the present retrospective series of elderly patients aged 65 years and over. It ranged between 2.8 and 18 months in recent prospective randomized and controlled phase III trials including surgery as treatment of cerebral metastases (e.g. 11.6 and 12.2 months in the NCCTG N107C/CEC·3 trial by Brown *et al.*, 2017; 17 and 18 months in the study by Mahajan *et al.* 2017; 2.8 months in the trial by Roos *et al.*, 2011, 10.7 and 10.9 months in the EORTC 22952–26001 study by Kocher and coworkers, 2011, respectively). Although results from retrospective studies have limited comparability to those derived from prospective randomized and controlled phase III trials, median survival in the present analysis seems to be comparable to those in recent phase III studies. However, overall survival was related to the treatment of cerebral metastases only in early phase III trials from the 1990s (Patchell *et al.*, 1990; Vecht *et al.*, 1993) but not in more recent phase III trials (e.g. Kocher *et al.*, 2011; Brown *et al.*, 2017; Mahajan *et al.*, 2017). Occurrence of single

	No. patients	%	Local In-Brain Recurrence p-value	Distant In-Brain Recurrence p-value
Gender				
Male	39	50		
Female	39	50		
Age				
median age (years)	71			
range (years)	66–83			
Number of Metastases			0.8665*	N/A
1	50	64.1		
2/3	18	23.1		
>3	10	12.8		
Primary site			0.4228*	0.7897*
NSCLC	35	44.8		
Malignant melanoma	9	11.5		
Breast Cancer	8	10.3		
Renal Cancer	6	7.7		
Gastrointestinal Cancer	10	12.8		
Urogenital Cancer	4	5.1		
Other	6	7.7		
Histology			0.4853*	0.2139*
Adenocarcinoma	58	74.4		
Malignant melanoma	9	11.5		
Clear cell carcinoma	4	5,1		
Others	7	9.0		
Localization				
Supratentorial	59	75.6		
Infratentorial	11	14.1		
Both	8	10.3		
Surgical technique			0.5675*	0.7929*
En bloc resection	40	51.3		
Peace-meal resection	38	48.7		
Use of intraoperative neurophysiological monitoring				
yes	40	51.3		
no	38	48.7		
Degree of surgical resection on MRI		0.00005*	0.3471*	
complete	41	52.5		
incomplete	15	19.2		
questionable	22	28.2		
Adjuvant radiation therapy				
Whole-brain radiation therapy	37	47.4		
stereotactic radiosurgery	14	18		
local fractionated radiation	10	12.8		
WBRT & SRS	2	2.6		
no radiation	15	19.2		
	78			
Local in-brain progression				
yes	20	25.6		
no	58	74.4		
Distant in-brain progression				
yes	21	26.9		
no	57	73.1		
Leptomeningeal carcinosis				
yes	13	16.7		
no	65	83.3		

Table 1. Epidemiological data. *Chi Square Test.

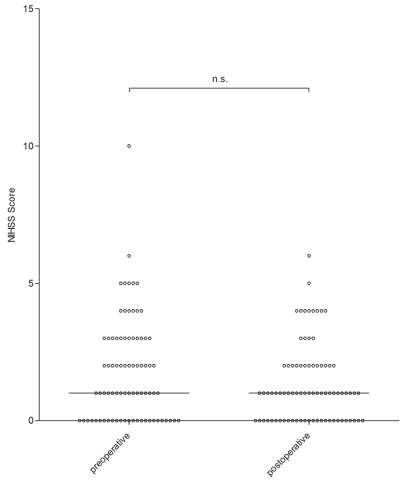

Figure 1. Pre- and postoperative NIHSS. shows the pre- and postoperative NIHS Scores which were not significantly different.

	No. of Patients	Mean (SD)*	min/max*
Overall Survival-Follow-Up - No. (%)			
	26 (30.2)	12 (14)	0/74
Progression Free Survival - No. (%)			
	26 (30.2)	9 (14)	0/74
Local Recurrence - No. (%)			
No	65 (30.5)		
Yes	21 (9.8)		
Time-to-Local Recurrence - No. (%)			
	21 (9.8)	6 (5)	0/22
Distant Recurrence - No. (%)			
No	63 (29.6)		
Yes	23 (10.8)		
Time-to-Distant Recurrence - No. (%)			
	23 (10.8)	7 (7)	0/35
Carcinomatous Meningitis - No. (%)			
No	72 (33.8)		
Yes	14 (6.6)		
Time-To-Carcinomatous Meningitis - No. (%)			
	14 (6.6)	8 (10)	0/46

Table 2. Recurrence rates. *Months.

cerebral metastasis and the choice of their treatment modalities may therefore be insufficient to predict survival of patients – even in elderly patients. In contrast, treatment of cerebral metastases is well known to influence the local and distant in-brain progression as well as patients' quality of life. In the present study, local recurrence rate was 25.6%, the distant development rate was 26.9%. These rates are congruent with our previous results and the recurrence rates reported in prospective randomized and controlled phase III trials. Therefore, elderly patients have comparable in-brain progression and overall survival as reported from previous oncologic patient cohorts. After thorough analysis, tumor-remnant in the early postoperative MRI as described in[16] was the only statistically significant risk factor for local recurrence. Relevance of early postoperative MRI in oncological patients has already been defined[16,22]. Although many factors (e.g. surgical technique, number of metastases, local control) have been proposed as the cause of local recurrence and distant development or carcinomatous meningitis[22–27], we could not establish another association or correlation in patients above 65 years of age.

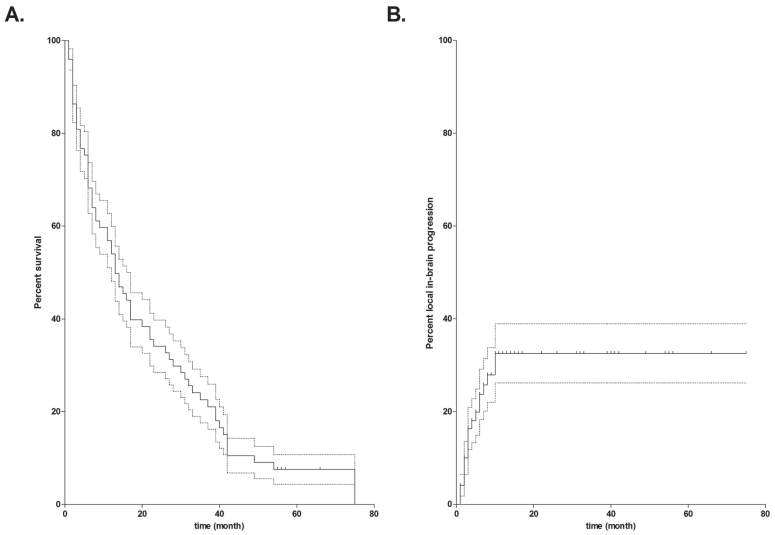

Figure 2. Progression-free and overall survival. shows the Kaplan Meier estimates for overall survival (**A**) and progression free (**B**) with its 95%-confidence intervals (dotted lines) over time in patients above 65 years after surgical resection of cerebral metastases.

In the present population, we observed no severe complication and no case fatalities within the first 30 days after surgery. The pre- and postoperative NIHSS, as well as KPS and follow-up visits showed no immediate or mediate deteriorations or complications. The median pre- and postoperative NIHSS was 1 without significant differences suggesting no new neurological deficits due to metastasectomy and a favorable overall surgical outcome. Perioperative morbidity and mortality were considered to be elevated in elderly patients in some neurosurgical but non-oncological series [e.g.[28]]. However, this may only partially be true for geriatric patients with cerebral metastases. Within a retrospective analysis of a United States inpatient sample, 4.907 patients aged 64 years and above were identified who underwent brain metastases resection. This study concluded that surgical resection of brain metastases among the elderly up to the ninth decade of life is feasible but that age above 80 years and comorbidities were important prognostic factors for inpatient outcome[29]. In a retrospective observational cohort-comparison study of patients with brain metastases, complication rate was 5.7% in the geriatric cohort with 174 patients aged 70 years and over[30]. Several further studies reported low complication rates after surgery of elderly patients with malignant brain tumors[31–34].

Limitations. Our study presents a single center experience with a reasonable number of patients, with a homogenous diagnostic and therapeutic approach allowing comparison. However, our study presents some limitations: (1) 78 geriatric patients suffering from cerebral metastases within a period of 7 years were included. This is based on a very dense net of exclusion criteria. Therefore, this cohort might not be representative for all geriatric patients. However, the present cohort is heterogeneous in terms of different primary sites and adjuvant therapies. Furthermore, a subgroup analysis for patients with urgent or acute surgery for BM was not performed. Due to the acute setting, proper planning and supplementary accessories might have been impossible to accomplish and thus have resulted in a higher probability of tumor-remnant or an increased risk of complications. (2) Extent of surgical resection was analysed by an early postoperative-MRI. In the current literature, only few retrospective studies analysed the impact of this method in diagnosing residual tumor tissue[16,35]. A definite conclusion regarding the resection degree was not possible in 28.2% for several reasons, e.g. residual tumor tissue could not reliably be differentiated from dilated vessels in the wall of the resection cavity, poor image quality (e.g. due to patient motion), blood in the resection. The early postoperative MRI revealed an incomplete surgical resection is in 19.2%. The comparatively high rate of incompletely and questionably completely resected metastases is in line with previous non-geriatric series[16]. (3) A median time-to-local recurrence of 3 ± 2.9 months (0–10 months) is fairly low. Time-to-local in brain-progression was therefore lower as in the recent phase III trials (e.g. 7.6 months and not reached in the recent phase III trial by Mahajan *et al.*)[36]. The reason for the comparatively low time-to-local in-brain progression remains unclear. One explanation might be the high rate of incomplete surgical resection or patients without any adjuvant radiation therapy (19.2% each) and the significant correlation between verification of tumor remnants on an early MRI and a later local in-brain progression. We are not aware of any studies directly analyzing a potential correlation between local recurrence and death. Several recent phase III studies addressed the local control and/or the overall survival after treatment of 1–4 cerebral metastases. Except the study by

El Gantery and coworkers (2014), none of the studies observed an effect of the therapy modality on the overall survival but nearly all studies showed a significant effect on the local control[9,12,29,30,37]. (4) Current prognostic indicators were not performed or analyzed in our population. A comparative analysis between our data and known literature cannot be performed. (5) Moreover, preoperative evaluation of the geriatric population should be required in order to increase quality of care, identify unknown entities, reduce complications and improve outcome[38]. There are many tools to preoperatively assess geriatric patients. Although there are still some discrepancies[39] and new innovative tools are being studied[40], the most common and thorough tool utilized to identify those patients with higher risk for worse outcome or a greater benefit from surgical treatment is the comprehensive geriatric assessment (CGA)[41]. Interestingly, most of the tools (if not all) use the KPS described in 1948 as a base[42]. Still, a unified guideline for this subgroup of patients has yet to be established. In our study, we did not perform any geriatric assessment. Nonetheless, the pre- and postoperative NIHSS, as well as KPS and follow-up visits showed no immediate or mediate deteriorations or complications, and more importantly, they represent an adequate parameter. However designed for other reasons and purposes[37,43,44], the NIHSS seems a feasible tool. (5) The influence of comorbidities, multi-organ metastatic disease, current medication and other elective or palliative surgeries was not taken into account. (7) Controlled or absent systemic neoplastic disease was assumed according to the clinical status and routine blood work. No evidence was established to prove that fact. (8) Another subgroup analysis of patients, in whom a palliative intervention therapy was performed, was also not analyzed separately. How this affects the course of disease, the type of therapy received additionally or the influence on overall survival remains unknown. (9) Patients' adherence, compliance, complications or changes altogether regarding adjuvant therapy were not analyzed. (10) Preoperative elaborate analysis of geriatric patients was not performed.

Conclusion

Local in-brain recurrence after surgical resection of a BM in patients above 65 years of age was 25.6%. Tumor-remnant in early postoperative MRI is the only risk factor for local in-brain recurrence. Mean overall survival was 13 months. Oncological parameters in the present cohort seem not to differ from recent phase III studies with non-geriatric patients. As reliable data are lacking, controlled studies analyzing the impact of metastasectomy in elderly patients are required.

Disclosure of potential conflicts of interest. Prof. Sabel and PD Dr. Rapp work as consultants for Johnson & Johnson Company and Integra Company. Dr. Dibué-Adjei is an employee of LivaNova PLC, manufacturer of vagus nerve stimulators. All other authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

References

1. Kong, X.-T., Alexandru, D. & Bota, D. A. Epidemiology of Central Nervous System Metastases. In: Hayat MA (ed) Brain Metastases from Primary Tumors. Epidemiology, Biology, and Therapy, vol 1. Academic Press, pp. 11–23 (2014).
2. Sawaya, R. Considerations in the diagnosis and management of brain metastases. *Oncology (Williston Park)* **15**, 1144–1154, 1157–1148; discussion 1158, 1163–1145 (2001).
3. Barnholtz-Sloan, J. S. *et al.* Incidence proportions of brain metastases in patients diagnosed (1973 to 2001) in the Metropolitan Detroit Cancer Surveillance System. *J Clin Oncol* **22**, 2865–2872, https://doi.org/10.1200/JCO.2004.12.149 (2004).
4. Noordijk, E. M. *et al.* The choice of treatment of single brain metastasis should be based on extracranial tumor activity and age. *Int J Radiat Oncol Biol Phys* **29**, 711–717 (1994).
5. Sahgal, A. *et al.* Phase 3 trials of stereotactic radiosurgery with or without whole-brain radiation therapy for 1 to 4 brain metastases: individual patient data meta-analysis. *Int J Radiat Oncol Biol Phys* **91**, 710–717, https://doi.org/10.1016/j.ijrobp.2014.10.024 (2015).
6. Stark, A. M., Stohring, C., Hedderich, J., Held-Feindt, J. & Mehdorn, H. M. Surgical treatment for brain metastases: Prognostic factors and survival in 309 patients with regard to patient age. *Journal of clinical neuroscience: official journal of the Neurosurgical Society of Australasia* **18**, 34–38, https://doi.org/10.1016/j.jocn.2010.03.046 (2011).
7. Soffietti, R. *et al.* Diagnosis and treatment of brain metastases from solid tumors: guidelines from the European Association of Neuro-Oncology (EANO). *Neuro Oncol* **19**, 162–174, https://doi.org/10.1093/neuonc/now241 (2017).
8. Vecht, C. J. *et al.* Treatment of single brain metastasis: radiotherapy alone or combined with neurosurgery? *Ann Neurol* **33**, 583–590, https://doi.org/10.1002/ana.410330605 (1993).
9. Chacko, A. G., Kumar, N. K., Chacko, G., Athyal, R. & Rajshekhar, V. Intraoperative ultrasound in determining the extent of resection of parenchymal brain tumours–a comparative study with computed tomography and histopathology. *Acta Neurochir (Wien)* **145**, 743–748; discussion 748, https://doi.org/10.1007/s00701-003-0009-2 (2003).
10. Coburger, J. *et al.* Tumor detection with 5-aminolevulinic acid fluorescence and Gd-DTPA-enhanced intraoperative MRI at the border of contrast-enhancing lesions: a prospective study based on histopathological assessment. *Neurosurgical focus* **36**, E3, https://doi.org/10.3171/2013.11.FOCUS13463 (2014).
11. Kamp, M. A. *et al.* Proof of principle: supramarginal resection of cerebral metastases in eloquent brain areas. *Acta Neurochir (Wien)* **154**, 1981–1986, https://doi.org/10.1007/s00701-012-1463-5 (2012).
12. Kamp, M. A. *et al.* The tumour is not enough or is it? Problems and new concepts in the surgery of cerebral metastases. *Ecancermedicalscience* **7**, 306, https://doi.org/10.3332/ecancer.2013.306 (2013).
13. Kamp, M. A. *et al.* 5-ALA fluorescence of cerebral metastases and its impact for the local-in-brain progression. *Oncotarget*, https://doi.org/10.18632/oncotarget.11488 (2016)
14. Kamp, M. A. *et al.* Predictors for a further local in-brain progression after re-craniotomy of locally recurrent cerebral metastases. *Neurosurgical review*, https://doi.org/10.1007/s10143-017-0931-z (2017).
15. Kamp, M. A. *et al.* 5-aminolevulinic acid (5-ALA)-induced fluorescence in intracerebral metastases: a retrospective study. Acta Neurochir (Wien) **154**, 223–228; discussion 228, https://doi.org/10.1007/s00701-011-1200-5 (2012).
16. Kamp, M. A. *et al.* Early postoperative magnet resonance tomography after resection of cerebral metastases. *Acta Neurochir (Wien)* **157**, 1573–1580, https://doi.org/10.1007/s00701-015-2479-4 (2015).
17. Kamp, M. A. *et al.* Incidence of local in-brain progression after supramarginal resection of cerebral metastases. Acta Neurochir (Wien) **157**, 905–910; discussion 910–901, https://doi.org/10.1007/s00701-015-2405-9 (2015).

18. Krieg, S. M. *et al.* Reliability of intraoperative neurophysiological monitoring using motor evoked potentials during resection of metastases in motor-eloquent brain regions: clinical article. *Journal of neurosurgery* **118**, 1269–1278, https://doi.org/10.3171/2013.2.JNS121752 (2013).
19. Unsgaard, G. *et al.* Intra-operative 3D ultrasound in neurosurgery. *Acta Neurochir (Wien)* **148**, 235–253; discussion 253, https://doi.org/10.1007/s00701-005-0688-y (2006).
20. Duffau, H. *et al.* Usefulness of intraoperative electrical subcortical mapping during surgery for low-grade gliomas located within eloquent brain regions: functional results in a consecutive series of 103 patients. *Journal of neurosurgery* **98**, 764–778, https://doi.org/10.3171/jns.2003.98.4.0764 (2003).
21. Lin, N. U. *et al*. Response Assessment in Neuro-Oncology g Response assessment criteria for brain metastases: proposal from the RANO group. *Lancet Oncol* **16**, e270–278, https://doi.org/10.1016/S1470-2045(15)70057-4 (2015).
22. Soffietti, R. *et al*. Diagnosis and treatment of brain metastases from solid tumors: guidelines from the European Association of Neuro-Oncology (EANO). *Neuro-Oncology* **19**, 162–174, https://doi.org/10.1093/neuonc/now241 (2017).
23. Patel, A. J. *et al.* Factors influencing the risk of local recurrence after resection of a single brain metastasis. *J Neurosurg* **113**, 181–189, https://doi.org/10.3171/2009.11.JNS09659 (2010).
24. Patel, A. J. *et al*. Impact of surgical methodology on the complication rate and functional outcome of patients with a single brain metastasis. *J Neurosurg* **122**, 1132–1143, https://doi.org/10.3171/2014.9.JNS13939 (2015).
25. Suki, D. *et al*. Comparative risk of leptomeningeal disease after resection or stereotactic radiosurgery for solid tumor metastasis to the posterior fossa. *J Neurosurg* **108**, 248–257, https://doi.org/10.3171/JNS/2008/108/2/0248 (2008).
26. Suki, D. *et al*. Comparative risk of leptomeningeal dissemination of cancer after surgery or stereotactic radiosurgery for a single supratentorial solid tumor metastasis. *Neurosurgery* **64**, 664–674; discussion 674–666, https://doi.org/10.1227/01.NEU.0000341535.53720.3E (2009).
27. Vogelbaum, M. A. & Suh, J. H. Resectable brain metastases. *Journal of clinical oncology: official journal of the American Society of Clinical Oncology* **24**, 1289–1294, https://doi.org/10.1200/JCO.2005.04.6235 (2006).
28. Munoz-Bendix, C. *et al*. Outcome following surgical treatment of chronic subdural hematoma in the oldest-old population. *Neurosurgical review* **40**, 461–468, https://doi.org/10.1007/s10143-016-0803-y (2017).
29. Grossman, R. *et al*. Predictors of inpatient death and complications among postoperative elderly patients with metastatic brain tumors. *Ann Surg Oncol* **18**, 521–528, https://doi.org/10.1245/s10434-010-1299-2 (2011).
30. Frati, A. *et al.* Surgical Treatment of the Septuagenarian Patients Suffering From Brain Metastases: A Large Retrospective Observational Analytic Cohort-Comparison Study. *World neurosurgery* **114**, e565–e572, https://doi.org/10.1016/j.wneu.2018.03.034 (2018).
31. Brandes, A. A. & Monfardini, S. The treatment of elderly patients with high-grade gliomas. *Semin Oncol* **30**, 58–62 (2003).
32. Mukerji, N. *et al*. Treating high grade gliomas in the elderly: the end of ageism? *J Neurooncol* **86**, 329–336, https://doi.org/10.1007/s11060-007-9476-2 (2008).
33. Pirracchio, R. *et al*. One-year outcome after neurosurgery for intracranial tumor in elderly patients. *Journal of neurosurgical anesthesiology* **22**, 342–346, https://doi.org/10.1097/ANA.0b013e3181e6daa2 (2010).
34. Rogne, S. G. *et al*. Intracranial tumor surgery in patients >70 years of age: is clinical practice worthwhile or futile? *Acta Neurol Scand* **120**, 288–294, https://doi.org/10.1111/j.1600-0404.2009.01157.x (2009).
35. Benveniste, R. J., Ferraro, N. & Tsimpas, A. Yield and utility of routine postoperative imaging after resection of brain metastases. *J Neurooncol* **118**, 363–367, https://doi.org/10.1007/s11060-014-1440-3 (2014).
36. Mahajan, A. *et al*. Post-operative stereotactic radiosurgery versus observation for completely resected brain metastases: a single-centre, randomised, controlled, phase 3 trial. *The lancet oncology* **18**, 1040–1048, https://doi.org/10.1016/S1470-2045(17)30414-X (2017).
37. Brott, T. *et al*. Measurements of acute cerebral infarction: a clinical examination scale. *Stroke; a journal of cerebral circulation* **20**, 864–870 (1989).
38. Tan, H. J., Saliba, D., Kwan, L., Moore, A. A. & Litwin, M. S. Burden of Geriatric Events Among Older Adults Undergoing Major Cancer Surgery. *Journal of clinical oncology: official journal of the American Society of Clinical Oncology* **34**, 1231–1238, https://doi.org/10.1200/JCO.2015.63.4592 (2016).
39. Extermann, M. *et al*. Task Force on CGAotISoGOUse of comprehensive geriatric assessment in older cancer patients: recommendations from the task force on CGA of the International Society of Geriatric Oncology (SIOG). *Crit Rev Oncol Hematol* **55**, 241–252, https://doi.org/10.1016/j.critrevonc.2005.06.003 (2005).
40. Min L. *et al*. Estimating Risk of Postsurgical General and Geriatric Complications Using the VESPA Preoperative Tool. *JAMA Surg*. https://doi.org/10.1001/jamasurg.2017.2635 (2017).
41. National Institutes of Health Consensus Development Conference Statement: geriatric assessment methods for clinical decision-making. *Journal of the American Geriatrics Society* **36**, 342–347 (1988).
42. Karnofsky, D. A. A. W. H., Craver, L. F. & Burchenal, J. H. The use of the nitrogen mustards in the palliative treatment of carcinoma. *Cancer* **1**, 634–656 (1948).
43. Appelros, P. & Terent, A. Characteristics of the National Institute of Health Stroke Scale: results from a population-based stroke cohort at baseline and after one year. *Cerebrovasc Dis* **17**, 21–27, https://doi.org/10.1159/000073894 (2004).
44. Kasner, S. E. Clinical interpretation and use of stroke scales. *Lancet neurology* **5**, 603–612, https://doi.org/10.1016/S1474-4422(06)70495-1 (2006).

Author Contributions

C.M.-B. and M.A.K. were involved in the conception and design of research approach, data acquisition, as well as drafting the manuscript. C.M.-B., M.A.K., M.R., H.-J.M., C.v.S., M.D.-A., J.F.C., H.-J.S., B.T. and M.S. participated in the analysis and interpretation of the data, revision of the manuscript and commented on the final version of the manuscript.

Additional Information

Competing Interests: Prof. Sabel and PD Dr. Rapp work as consultants for Johnson & Johnson Company and Integra Company. Dr. Dibué-Adjei is an employee of LivaNova PLC, manufacturer of vagus nerve stimulators. All other authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

Publisher's note: Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

3.2 Implication of 5-ALA fluorescence of cerebral metastases on local recurrence and overall survival

Journal of Neuro-Oncology
https://doi.org/10.1007/s11060-018-03066-y

CLINICAL STUDY

Is 5-ALA fluorescence of cerebral metastases a prognostic factor for local recurrence and overall survival?

Marcel A. Kamp[1] · Christopher Munoz-Bendix[1] · Hendrik-Jan Mijderwijk[1] · Bernd Turowski[2] · Maxine Dibué-Adjei[1] · Christiane von Saß[1] · Jan Frederick Cornelius[1] · Hans-Jakob Steiger[1] · Marion Rapp[1] · Michael Sabel[1]

Received: 7 June 2018 / Accepted: 28 November 2018

Abstract

Background 5-Aminolevulinic acid (5-ALA) fluorescence-guided resection technique was first introduced for malignant glioma. However, the impact of the 5-ALA fluorescence behaviour of cerebral metastases is still unclear. Aim of this study was to determine the impact of PpIX-fluorescence on the local progression-free and overall survival.

Materials and methods A secondary analysis was performed and included an updated follow-up of 136 patients comprised in two previous studies. Additionally, 82 new patients were included. All patients underwent surgical resection of cerebral metastasis and intraoperative estimation of 5-ALA-induced fluorescence. The 5-ALA fluorescence behaviour of cerebral metastases was correlated with the rate of local recurrences, the local progression-free and overall survival.

Results 218 patients suffering from cerebral metastatic spread fulfilled the inclusion criteria and were analysed: complete surgical resection could be achieved in 123/218 patients (56.4%). Dichotomised degree of surgical resection (complete vs. incomplete or questionable complete resection) was not related to dichotomized 5-ALA fluorescence of cerebral metastases ($p = 0.66$). 51 patients (23.4%) developed a local in-brain progression within or at the border of the resection cavity. Of these, 8 patients showed a PpIX-fluorescent metastasis. There was a trend towards a correlation between a higher local in-brain progression in PpIX-non-fluorescent metastases ($p = 0.03$). Median time to local in-brain progression was 4 ± 11 months. PpIX-fluorescent and PpIX-non-fluorescent metastases showed a significantly different progression-free survival ($p = 0.01$). PpIX-positive and –negative metastases showed a significantly different overall survival (20 and 14 months respectively; $p = 0.006$).

Conclusion The 5-ALA fluorescence behaviour was related to the local progression-free and the overall survival in the present retrospective series and might be considered a prognostic marker. Further studies are required to appreciate the oncological impact of the 5-ALA induced fluorescence behaviour of cerebral metastases.

Keywords 5-Aminolevulinic acid · Cerebral metastases · Recurrence · In-brain-progression · Overall survival

Introduction

Cerebral metastases are the most common intracerebral neoplasms with an increasing incidence which ranges between 2.8 and 14.3 per 100,000 population [16, 27]. Consequently, they show a 5 times higher incidence than malignant primary brain tumors [16, 27]. Overall survival of patients suffering from a single cerebral metastasis was not related to treatment modality in almost all recent phase III trials suggesting that the cancer patient's prognosis might not be related to the occurrence of a single cerebral metastasis suggesting that their prognosis does not seem to be related to occurrence of single cerebral metastases in cancer patients [3, 15, 18, 24]. However, treatment of cerebral metastases remains challenging, as treatment should ensure a long-lasting local control without affecting the quality of life. In particular, local control of cerebral metastases might be a problem as local in-brain progression rates were up to 50% in recent studies [15, 20, 36]. Incomplete and piecemeal-resections of

✉ Marcel A. Kamp
MarcelAlexander.Kamp@med.uni-duesseldorf.de

[1] Department of Neurosurgery, Medical Faculty, Heinrich-Heine-University, Düsseldorf, Moorenstraße 5, 40225 Düsseldorf, Germany

[2] Institute for Diagnostic and Interventional Radiology, Medical Faculty, Heinrich-Heine-University, Düsseldorf, Moorenstraße 5, 40225 Düsseldorf, Germany

Published online: 10 December 2018

cerebral metastases were considered as risk factors for local in-brain progression [5, 6, 8, 10–12, 21, 22, 32].

5-Aminolevulinic acid (5-ALA) fluorescence-guided resection technique was first introduced for malignant glioma. 5-ALA converts into protoporphyrin IX (PpIX) that selectively accumulates in vital malignant glioma cells and can be visualized under blue light. This technique is related to a more exhaustive surgical resection and subsequently an improved progression-free survival [29–31]. In contrast to malignant glioma, the more benign diffuse glioma shows no PpIX-fluorescence. Recently, PpIX-fluorescence in cerebral metastases was considered a favourable parameter for a long-lasting local tumor control after metastasectomy – independent of the degree of surgical resection [7]. Although no correlation was found in the later study between the PpIX-fluorescence in cerebral metastases and the overall survival, the relatively small study group might have skewed the results.

Aim of this study was to determine the impact of PpIX-fluorescence on the local progression-free and overall survival. A secondary analysis was performed and included an updated follow-up of 136 patients comprised in two previous studies [7, 9]. Additionally, 82 new patients were included.

Materials and methods

Ethical statement

Informed consent was obtained. The present analysis was performed in accordance with the Declaration of Helsinki and with the acceptance of the local Research Ethics Committee and institutional review board (internal study numbers: 3307 and 5269).

Study design, inclusion and exclusion criteria

A secondary analysis with an updated follow-up of 136 patients who had already been included in two previous studies [7, 9], as well as 82 new patients, was performed. All patients fulfilled the following criteria: (1) surgical resection of a cerebral metastasis, (2) histopathological confirmation of a carcinoma or malignant melanoma metastasis and (3) intraoperative documentation of the PpIX-fluorescence of at least one cerebral metastasis by the neurosurgeon. Exclusion criteria included: (1) other type of neoplasia, (2) patients with neuroendocrine small cell carcinoma, (3) leptomeningeal carcinomatosis.

Surgical and postoperative treatment

Surgery was performed as described before [7, 9, 10]. In summary, 5-ALA (Caesar & Loretz GmbH, Hilden, Germany) was administered 3 h prior to surgery in a dose of 20 mg per kilogram body weight as previously defined [9, 30]. Standard white-light assisted—and if feasible—en bloc circumferential resection was performed [9]. PpIX fluorescence was visualized by the surgical microscope (OPMI Pentero microscope with the FLOW 800 tool; Carl Zeiss Meditec, Oberkochen, Germany or Leica M530 OH6 microscope, Leica Microsystems GmbH, Wetzlar, Germany) and the dichotomized PpIX-fluorescence (fluorescent or non-fluorescent) was documented by the neurosurgeon. 5-ALA fluorescence was considered as "5-ALA fluorescent" if being strongly fluorescent or as non-fluorescent if being faintly or non-fluorescent.

After surgery, extent of surgical resection was documented by an early postoperative contrast-enhanced 1.5T-MRI within 72 h as described before [10]. Residual contrast-enhancing parts in the T1 sequences as well as T2 and diffusion sequences were examined for residual tumor [10]. A senior neurosurgeon and neurological radiologist carefully performed the radiological analysis. Recommendations for a further adjuvant treatment after metastasis resection were made by an interdisciplinary tumor board based on tumor type, degree of surgical resection and patients' neurological condition and wishes. Follow-up was performed every three months and consisted of clinical evaluation and radiological testing (i.e. contrast-enhanced MRI).

Definition of outcome parameters

A local tumour recurrence was defined according to RANO criteria for cerebral metastases [17]. Distant in-brain progression was defined as a new contrast enhancement on the follow-up MRI suspicious for cerebral metastases. Time to local or distant in-brain progression was defined as the period between surgery and diagnosis of tumor progression on MRI. Overall survival was defined as timespan between surgery and death.

The degree of surgical resection was determined on an early postoperative MRI within 72 h after surgery. For further analysis, the degree of surgical resection was dichotomised into complete vs. incomplete or questionable complete surgical resection.

Data management

Epidemiological data (age, gender), data regarding 5-ALA-fluorescence, primary site and histological entity of the tumour and postoperative and follow-up images were collected using an integrated medical-record system. Clinical and radiological follow-up ended on May 22nd 2018. All statistical analyses were performed with SPSS software (Version 25.0, IBM, USA) and the Graph Pad Prism 5 package

3.3.2 (GraphPad Software, Inc., La Jolla, USA). Continuous data are presented as median ± standard deviation.

For categorical data the Pearson χ^2 test was used to test the independence of variables. The χ^2 test was used in nominal variables to identify significant differences. Real-valued data were first tested for normality using the Shapiro–Wilk normality test. Kaplan–Meier survival curves were compared using the log-rank test, also known as the Mantel–Haenszel or Mantel–Cox test. As multiple statistical testing was performed, a significance level of $p < 0.013$ was considered significant according to the Šidák's correction. A trend towards significance was defined as p value above 0.013 but below 0.05.

Results

218 patients suffering from cerebral metastatic spread fulfilled the inclusion criteria and were analysed: 115 patients were female (52.8%) and 103 patients male (47.2%). Median age was 62 ± 11 years (range 26–87 years). Histologically, the vast majority of patients presented with adenocarcinoma (76.6%) and about half of the patients suffered from non-small cell lung cancer(110 pts: 50.5%). Clinical data are summarized in Table 1 and the fluorescence behaviour of the different histological subtypes and of metastases with different primary sites in Table 2.

A complete surgical resection could be achieved in 123/218 patients (56.4%). In 43 patients (19.7%), resection was incomplete and in 23.8% the degree of surgical resection was questionable. Dichotomised degree of surgical resection (complete vs. incomplete/questionable complete resection) was not related to dichotomized 5-ALA fluorescence of cerebral metastases ($\chi^2 = 0.19$; $p = 0.66$, Table 2). About half of the patients received adjuvant whole-brain radiation therapy (49.1%), 15% local stereotactic or fractionated irradiation and 20% no additional radiation therapy (Table 1).

51 patients (23.4%) developed a local in-brain progression within or at the border of the resection cavity. Of these, 8 patients showed a PpIX-fluorescent metastasis. There was a trend towards a correlation between a higher local in-brain progression in PpIX-non-fluorescent metastases ($\chi^2 = 4.9$; $p = 0.03$). Median time to local in-brain progression was 4 ± 11 months. PpIX-fluorescent and PpIX-non-fluorescent metastases showed a significantly divergent progression-free survival ($\chi^2 = 6$; $df = 1$; $p = 0.01$, 95% CI 0.26–0.86; log-rank test, Fig. 1).

General median overall survival was 14 months. PpIX-positive and –negative metastases showed a significantly different overall survival, 20 and 14 months respectively ($\chi^2 = 7.6$; $df = 1$; $p = 0.006$, 95% CI 0.44–0.86; log-rank test; Fig. 1).

Table 1 Summary of clinical data

	Number of patients	%
Gender		
Female	115	52.8
Male	103	47.2
Age		
Median age (years)	62	
Range (years)	26–87	
Primary site		
NSCLC	110	50.5
Malignant melanoma	19	8.7
Breast cancer	27	12.4
Gastrointestinal cancer	26	11.9
Renal/urogenital cancer	21	9.6
Other	15	6.9
Histology		
Adenocarcinoma	167	76.6
Malignant melanoma	19	8.7
Clear cell carcinoma	18	8.2
Others	14	6.4
PpIX fluorescence		
No	156	71.6
Yes	62	28.4
Degree of surgical resection on MRI		
Complete	123	56.4
Incomplete	43	19.7
Questionable	52	23.8
Adjuvant radiation therapy		
Whole-brain radiation therapy	107	49.1
Stereotactic radiosurgery	34	15.6
Local fractionated radiation	33	15.1
No radiation	44	20.2
Local in-brain progression	51	23.4
Distant in-brain progression	56	25.7

Discussion

This study represents one of the largest analyses of PpIX-fluorescence in brain metastases. The main observations of the present analysis were as follows: (1) PpIX-behaviour of cerebral metastases had no statistically significant influence on the degree of surgical resection, (2) a trend towards a significant higher local recurrence rate in PpIX-non fluorescent metastases, and (3) PpIX-fluorescent metastases had a favorable outcome with a prolonged progression-free interval and overall survival in the present series.

In our present study, PpIX fluorescence behaviour had no influence on the extent of resection or strategy of adjuvant therapy. The dichotomized degree of surgical resection was not significant related to the dichotomized PpIX-fluorescent

Table 2 5-ALA behaviour of cerebral metastases

	Total number of patients	ALA-positive	%	ALA-negative	%
Primary site					
NSCLC	110	36	32.7	74	67.3
Malignant melanoma	19	4	21.1	15	78.9
Breast cancer	27	9	33.3	18	66.7
Gastrointestinal cancer	26	4	15.4	22	84.6
Renal/urogenital cancer	21	8	38.1	13	61.9
Other	15	1	6.7	14	93.3
Histology					
Adenocarcinoma	167	53	31.7	114	68.3
Malignant melanoma	19	4	21.1	15	78.9
Clear cell carcinoma	18	4	22.2	14	77.8
Others	14	1	7.1	13	92.9
Degree of surgical resection on MRI					
Complete	123	32	0.26	91	0.74
Incomplete	43	15	0.35	28	0.65
Questionable	52	13	0.25	39	0.75
Adjuvant radiation therapy					
Whole-brain radiation therapy	107	42	39.3	65	60.7
Stereotactic radiosurgery	34	3	8.8	31	91.2
Local fractionated radiation	33	8	24.2	25	75.8
No radiation	44	9	20.5	35	79.5
Local in-brain progression	51	8	15.7	43	84.3
Distant in-brain progression	56	6	10.7	50	89.3

and non-fluorescent cerebral metastases. Unintended remnants of metastatic tumor tissue are frequently observed after intended complete metastasectomy, and can be verified by an early postoperative MRI [2, 10]. Moreover, residual tumor tissue is believed to be a risk factor for a later local recurrence [8, 10]. In contrast to malignant glioma, 5-ALA fluorescent guidance of cerebral metastases resection might not be optimal to detect residual metastatic tumor tissue after macroscopically complete resection. Several previous studies reported 5-ALA fluorescence behavior of cerebral metastases [1, 4, 9, 19, 23, 28, 33–35]. The occurrence of PpIX-fluorescent cerebral metastases ranged between 0 and 100%. However, most studies included less than 10 patients: Apart from previous studies, three further studies with more than 10 patients with totally 114 patients showed PpIX-fluorescence of cerebral metastases in 52%, 73% and 82%, respectively [4, 19, 33]. PpIX-fluorescence of the tumour bed can frequently be observed after metastases resection, but residual tumor cells can only be histologically verified by a subset of biopsies taken from these areas [9, 28, 33]. Furthermore, a strong PpIX-fluorescence of the adjacent tumour bed occurs even in 5-ALA negative metastases [9, 28]. Therefore, 5-ALA technique does not allow reliable visualization of residual tumor after metastases resection, and a strongly fluorescent resection cavity does not necessarily contain residual tumor. However, current evidence is poor and further studies are required [13].

Nevertheless, PpIX fluorescence of cerebral metastases might be of prognostic value. In the present study we observed a trend towards a significantly higher local recurrence rate in PpIX-non fluorescent metastases and a significantly progression-free and overall survival in PpIX-fluorescent metastases. The trend towards an improved local control and a longer progression-free survival cannot be explained by a better degree of surgical resection in these metastases. This is in line with our previous report [7]. Interestingly and unexpectedly, overall survival was also correlated with the fluorescence behaviour. Overall survival was independent of the treatment modalities in almost all recent phase III studies including patients with single cerebral metastases [3, 15, 18, 24]. This suggests that the overall survival is not related to the occurrence and treatment of single brain metastases but to systemic cancer progression. PpIX-fluorescence of cerebral metastases might be an intrinsic factor related to a more benign character of brain metastases and the primary cancer. Loss of PpIX-fluorescence might reflect a more aggressive behaviour of brain metastases. The more aggressive behaviour was not correlated with a specific histological subtype or primary site in the present and all recent studies. The less aggressive behaviour of strongly fluorescent

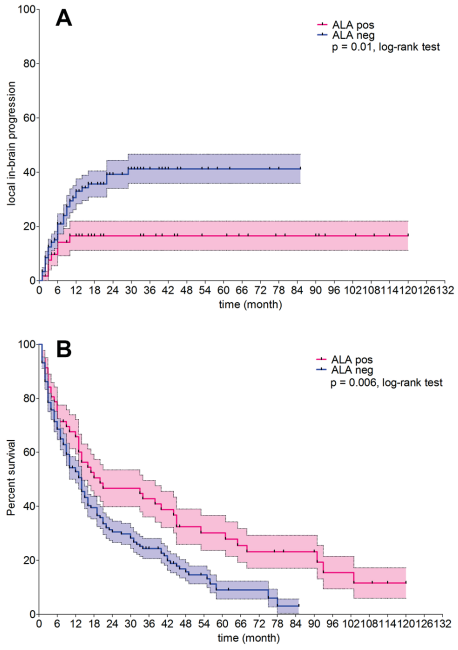

Fig. 1 Local in-brain progression and overall survival. Figure shows significant differences in the local in-brain-progression rate (**a**) and the overall survival (**b**) of 5-ALA positive and 5-ALA negative metastases

metastasesprobably relies on differences in the signaling of PpIX-fluorescent and non-fluorescent metastases: The ferrochelatase activity is related to PpIX accumulation in malignant cells but also to the aggressiveness of some tumours and to the outcome of patients with certain cancer types [7, 13, 14, 26]. However, further translational and clinical studies are required to estimate the diagnostic and prognostic use of 5-ALA in cerebral metastases.

Limitations

We do acknowledge several limitations in our present study: (1) it represents a secondary analysis with an updated follow-up of patients included in two previous studies and 82 additional patients. Prospective and controlled studies provide much more evidence, however, these studies are not yet available and this study is one of the largest analysis of PpIX-fluorescence in brain metastases, (2) As many retrospective metastases studies, this analysis includes a heterogeneous patient population. In particular, state of the adjuvant treatment changed since the first patients were treated. Adjuvant treatment concepts are well-known to influence the local recurrence rate [3, 15, 18, 24]. We do believe that the longer progression-free interval and overall survival time could also be due to a subgroup of patients receiving whole-brain radiation therapy. However, a subgroup analysis was not intended for statistical reasons as multiple testing requires a correction of the significance level. (3) Apart from the 5-ALA fluorescence behaviour, many other factors such as the growth pattern of cerebral metastases or the mode of surgical resection (piecemeal vs. *en bloc* resection) might additionally influence the outcome and may confound our present results [21, 22, 32]. (4) The degree of resection was dichotomized into complete versus incomplete or questionable complete resections. A reliable estimation of the resection degree might not have been possible in all cases [10]. Therefore, questionable tumor tissue was statistically considered like residual tumor tissue and might represent an additional bias in these results. Reducing the uncertainty in diagnosing residual tumor tissue on an early postoperative MRI represents a challenge to neuroradiology. (5) PpIX fluorescence was dichotomized into fluorescent or non-fluorescent (either non- or faintly fluorescent) by the neurosurgeon. However, some cerebral metastases show a patchy pattern of fluorescence and fluorescence intensity might range from a vague intensity to a solid deep red. Possibly, different fluorescence intensities might also be related to different outcomes. Furthermore, PpIX fluorescence intensity was related to the surgeon's impression and might also vary according to the equipment used [25]. A quantitative estimation of 5-ALA fluorescence might give a more objective value and represents a challenge for further studies. (6) The finding that PpIX positive metastases have a better prognosis would have some interest for oncologic biology, but to date does not seem so be significant for clinical purposes. Only half of the cerebral metastases exhibited PpIX-fluoresence. Furthermore, no studies showed a surgical or oncological benefit of 5-ALA fluorescence-guided resections. Furthermore, a strongly fluorescent resection cavity does not necessarily contain residual tumor tissue [9, 13].

Acknowledgements We thank Maria Smuga and Osman Auale for their help.

Funding The present study was not funded.

Compliance with ethical standards

Ethical statement Informed consent was obtained. The present analysis was performed in accordance with the Declaration of Helsinki and with the acceptance of the local Research Ethics Committee and institutional review board (internal study numbers: 3307 and 5269).

Conflict of interest Prof. Sabel and PD Dr. Rapp work as consultants for Johnson & Johnson Company and Integra Company. Dr. Dibué-Adjei is an employee of LivaNova PLC, manufacturer of vagus nerve stimulators. All other authors certify that they have no affiliations with or involvement in any organiation or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

References

1. Belloch JP, Rovira V, Llacer JL, Riesgo PA, Cremades A (2014) Fluorescence-guided surgery in high grade gliomas using an exoscope system. Acta Neurochir (Wien) 156:653–660
2. Benveniste RJ, Ferraro N, Tsimpas A (2014) Yield and utility of routine postoperative imaging after resection of brain metastases. J Neurooncol 118:363–367
3. Brown PD, Ballman KV, Cerhan JH, Anderson SK, Carrero XW, Whitton AC, Greenspoon J, Parney IF, Laack NNI, Ashman JB, Bahary JP, Hadjipanayis CG, Urbanic JJ, Barker FG 2nd, Farace E, Khuntia D, Giannini C, Buckner JC, Galanis E, Roberge D (2017) Postoperative stereotactic radiosurgery compared with whole brain radiotherapy for resected metastatic brain disease (NCCTG N107C/CEC.3): a multicentre, randomised, controlled, phase 3 trial. Lancet Oncol 18:1049–1060
4. Coburger J, Engelke J, Scheuerle A, Thal DR, Hlavac M, Wirtz CR, Konig R (2014) Tumor detection with 5-aminolevulinic acid fluorescence and Gd-DTPA-enhanced intraoperative MRI at the border of contrast-enhancing lesions: a prospective study based on histopathological assessment. Neurosurg Focus 36:E3
5. Kamp MA, Dibue M, Niemann L, Reichelt DC, Felsberg J, Steiger HJ, Szelenyi A, Rapp M, Sabel M (2012) Proof of principle: supramarginal resection of cerebral metastases in eloquent brain areas. Acta Neurochir (Wien) 154:1981–1986
6. Kamp MA, Dibue M, Santacroce A, Zella SM, Niemann L, Steiger HJ, Rapp M, Sabel M (2013) The tumour is not enough or is it? Problems and new concepts in the surgery of cerebral metastases. Ecancermedicalscience 7:306
7. Kamp MA, Fischer I, Buhner J, Turowski B, Cornelius JF, Steiger HJ, Rapp M, Slotty PJ, Sabel M (2016) 5-ALA fluorescence of cerebral metastases and its impact for the local-in-brain progression. Oncotarget 7:66776–66789
8. Kamp MA, Fischer I, Dibue-Adjei M, Munoz-Bendix C, Cornelius JF, Steiger HJ, Slotty PJ, Turowski B, Rapp M, Sabel M (2017) Predictors for a further local in-brain progression after re-craniotomy of locally recurrent cerebral metastases. Neurosurg Rev 41:813–823
9. Kamp MA, Grosser P, Felsberg J, Slotty PJ, Steiger HJ, Reifenberger G, Sabel M (2012) 5-Aminolevulinic acid (5-ALA)-induced fluorescence in intracerebral metastases: a retrospective study. Acta Neurochir (Wien) 154:223–228; discussion 228
10. Kamp MA, Rapp M, Buhner J, Slotty PJ, Reichelt D, Sadat H, Dibue-Adjei M, Steiger HJ, Turowski B, Sabel M (2015) Early postoperative magnet resonance tomography after resection of cerebral metastases. Acta Neurochir (Wien) 157:1573–1580
11. Kamp MA, Rapp M, Slotty PJ, Turowski B, Sadat H, Smuga M, Dibue-Adjei M, Steiger HJ, Szelenyi A, Sabel M (2015) Incidence of local in-brain progression after supramarginal resection of cerebral metastases. Acta Neurochir (Wien) 157:905–910; discussion 910–901
12. Kamp MA, Slotty PJ, Cornelius JF, Steiger HJ, Rapp M, Sabel M (2016) The impact of cerebral metastases growth pattern on neurosurgical treatment. Neurosurg Rev 41:77–86
13. Kamp MA, Cornelius JF, Steiger HJ, Sabel M (2018) 5-Aminolevulinic acid and brain metastases. In: Hadjipanayis CS, W. (ed) Fluorescence-guided neurosurgery: neuro-oncology and cerebrovascular application. Thieme, New York
14. Kemmner W, Wan K, Ruttinger S, Ebert B, Macdonald R, Klamm U, Moesta KT (2008) Silencing of human ferrochelatase causes abundant protoporphyrin-IX accumulation in colon cancer. FASEB J 22:500–509
15. Kocher M, Soffietti R, Abacioglu U, Villa S, Fauchon F, Baumert BG, Fariselli L, Tzuk-Shina T, Kortmann RD, Carrie C, Ben Hassel M, Kouri M, Valeinis E, van den Berge D, Collette S, Collette L, Mueller RP (2011) Adjuvant 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 29:134–141
16. Kong XTA, Bota D, D.A (2014) Epidemiology of central nervous system metastases. In: Hayat MA (ed) Brain metastases from primary tumors. epidemiology, biology, and therapy, vol 1. Academic Press, London, pp 11–23
17. Lin NU, Lee EQ, Aoyama H, Barani IJ, Barboriak DP, Baumert BG, Bendszus M, Brown PD, Camidge DR, Chang SM, Dancey J, de Vries EG, Gaspar LE, Harris GJ, Hodi FS, Kalkanis SN, Linskey ME, Macdonald DR, Margolin K, Mehta MP, Schiff D, Soffietti R, Suh JH, van den Bent MJ, Vogelbaum MA, Wen PY, Response Assessment in Neuro-Oncology Group (2015) Response assessment criteria for brain metastases: proposal from the RANO group. Lancet Oncol 16:e270–e278
18. Mahajan A, Ahmed S, McAleer MF, Weinberg JS, Li J, Brown P, Settle S, Prabhu SS, Lang FF, Levine N, McGovern S, Sulman E, McCutcheon IE, Azeem S, Cahill D, Tatsui C, Heimberger AB, Ferguson S, Ghia A, Demonte F, Raza S, Guha-Thakurta N, Yang J, Sawaya R, Hess KR, Rao G (2017) Post-operative stereotactic radiosurgery versus observation for completely resected brain metastases: a single-centre, randomised, controlled, phase 3 trial. Lancet Oncol 18:1040–1048
19. Marbacher S, Klinger E, Schwyzer L, Fischer I, Nevzati E, Diepers M, Roelcke U, Fathi AR, Coluccia D, Fandino J (2014) Use of fluorescence to guide resection or biopsy of primary brain tumors and brain metastases. Neurosurg Focus 36:E10
20. Patchell RA, Tibbs PA, Regine WF, Dempsey RJ, Mohiuddin M, Kryscio RJ, Markesbery WR, Foon KA, Young B (1998) Postoperative radiotherapy in the treatment of single metastases to the brain: a randomized trial. JAMA 280:1485–1489
21. Patel AJ, Suki D, Hatiboglu MA, Abouassi H, Shi W, Wildrick DM, Lang FF, Sawaya R (2010) Factors influencing the risk of local recurrence after resection of a single brain metastasis. J Neurosurg 113:181–189
22. Patel AJ, Suki D, Hatiboglu MA, Rao VY, Fox BD, Sawaya R (2015) Impact of surgical methodology on the complication rate and functional outcome of patients with a single brain metastasis. J Neurosurg 122:1132–1143
23. Piquer J, Llacer JL, Rovira V, Riesgo P, Rodriguez R, Cremades A (2014) Fluorescence-guided surgery and biopsy in gliomas with an exoscope system. Biomed Res Int. https://doi.org/10.1155/2014/207974
24. Roos DE, Smith JG, Stephens SW (2011) Radiosurgery versus surgery, both with adjuvant whole brain radiotherapy, for solitary brain metastases: a randomised controlled trial. Clin Oncol (R Coll Radiol) 23:646–651
25. Sabel M, Knipps J, Neumann LM, Kieslich M, Steiger HJ, Rapp M, Kamp MA (2018) Quantification of ALA-fluorescence induced by a modified commercially available head lamp and a surgical microscope. Neurosurg Rev 41:1079–1083

26. Salas S, Brulard C, Terrier P, Ranchere-Vince D, Neuville A, Guillou L, Lae M, Leroux A, Verola O, Jean-Emmanuel K, Bonvalot S, Blay JY, Le Cesne A, Aurias A, Coindre JM, Chibon F (2015) Gene expression profiling of desmoid tumors by cDNA microarrays and correlation with progression-free survival. Clin Cancer Res 21:4194–4200
27. Sawaya R (2001) Considerations in the diagnosis and management of brain metastases. Oncology 15:1144–1154, 1157 – 1148; discussion 1158, 1163 – 1145
28. Schucht P, Beck J, Vajtai I, Raabe A (2011) Paradoxical fluorescence after administration of 5-aminolevulinic acid for resection of a cerebral melanoma metastasis. Acta Neurochir 153:1497–1499
29. Stummer W, Kamp MA (2009) The importance of surgical resection in malignant glioma. Curr Opin Neurol 22:645–649
30. Stummer W, Pichlmeier U, Meinel T, Wiestler OD, Zanella F, Reulen HJ, Group AL-GS (2006) Fluorescence-guided surgery with 5-aminolevulinic acid for resection of malignant glioma: a randomised controlled multicentre phase III trial. Lancet Oncol 7:392–401
31. Stummer W, Stocker S, Novotny A, Heimann A, Sauer O, Kempski O, Plesnila N, Wietzorrek J, Reulen HJ (1998) In vitro and in vivo porphyrin accumulation by C6 glioma cells after exposure to 5-aminolevulinic acid. J Photochem Photobiol B 45:160–169
32. Suki D, Abouassi H, Patel AJ, Sawaya R, Weinberg JS, Groves MD (2008) Comparative risk of leptomeningeal disease after resection or stereotactic radiosurgery for solid tumor metastasis to the posterior fossa. J Neurosurg 108:248–257
33. Utsuki S, Miyoshi N, Oka H, Miyajima Y, Shimizu S, Suzuki S, Fujii K (2007) Fluorescence-guided resection of metastatic brain tumors using a 5-aminolevulinic acid-induced protoporphyrin IX: pathological study. Brain Tumor Pathol 24:53–55
34. Valdes PA, Leblond F, Kim A, Harris BT, Wilson BC, Fan X, Tosteson TD, Hartov A, Ji S, Erkmen K, Simmons NE, Paulsen KD, Roberts DW (2011) Quantitative fluorescence in intracranial tumor: implications for ALA-induced PpIX as an intraoperative biomarker. J Neurosurg 115:11–17
35. Widhalm G, Minchev G, Woehrer A, Preusser M, Kiesel B, Furtner J, Mert A, Di Ieva A, Tomanek B, Prayer D, Marosi C, Hainfellner JA, Knosp E, Wolfsberger S (2012) Strong 5-aminolevulinic acid-induced fluorescence is a novel intraoperative marker for representative tissue samples in stereotactic brain tumor biopsies. Neurosurg Rev 35:381–391; discussion 391
36. Yoo H, Kim YZ, Nam BH, Shin SH, Yang HS, Lee JS, Zo JI, Lee SH (2009) Reduced local recurrence of a single brain metastasis through microscopic total resection. J Neurosurg 110:730–736

3.3 Predictors for a further local in-brain progression after re-craniotomy of locally recurrent cerebral metastases

Neurosurgical Review (2018) 41:813–823
https://doi.org/10.1007/s10143-017-0931-z

ORIGINAL ARTICLE

Predictors for a further local in-brain progression after re-craniotomy of locally recurrent cerebral metastases

Marcel A. Kamp[1] · Igor Fischer[2] · Maxine Dibué-Adjei[1] · Christopher Munoz-Bendix[1] · Jan-Frederick Cornelius[1] · Hans-Jakob Steiger[1] · Philipp J. Slotty[1] · Bernd Turowski[3] · Marion Rapp[1] · Michael Sabel[1]

Received: 8 September 2017 / Revised: 1 November 2017 / Accepted: 20 November 2017 / Published online: 20 December 2017

Abstract
Treatment of recurrent cerebral metastases is an emerging challenge due to the high local failure rate after surgery or radiosurgery and the improved prognosis of patients with malignancies. A total of 36 patients with 37 metastases who underwent surgery for a local in-brain progression of a cerebral metastasis after previous metastasectomy were retrospectively analyzed. Degree of surgical resection on an early postoperative MRI within 72 h after surgery was correlated with the local in-brain progression rate and overall survival. Complete surgical resection of locally recurrent cerebral metastases as confirmed by early postoperative MRI could only be achieved in 37.8%. Detection of residual tumor tissue on an early MRI following recurrent metastasis surgery correlated with further local in-brain progression when defining a significance level of $p = 0.05$ but not after Šidák or Bonferroni significance level correction for multiple testing: However, definite local tumor control could finally be achieved in 91.9% after adjuvant therapy. Overall survival after recurrent metastasectomy was significantly higher as predicted by diagnosis-specific graded prognostic assessment (12.9 ± 2.3 vs. 8.4 ± 0.7 months; $p < 0.0001$). However, our series involved a limited number of heterogeneous patients. A larger, prospective, and controlled study is required. Considering the adequate local tumor control achieved in the vast majority of patients, surgery of recurrent metastases may represent one option in a multi-modal treatment approach of patients suffering from locally recurrent cerebral metastases.

Keywords Postoperative MRI · Metastasis · Recurrence · Recurrent metastasis · Surgery · Resection

Introduction

Cerebral metastases are the most common cranial neoplasms [16, 31]. About 20 to 40% of cancer patients develop cerebral metastases [11, 12]. Although modern targeted cancer therapies have led to new therapeutic strategies that may improve prognosis of cancer patients, they also may alter the incidence and behavior of cerebral metastases. For HER2-positive breast cancer patients, HER2-targeted therapies were believed to be associated with a higher incidence of cerebral metastases over historical estimates [27].

Surgical resection of single cerebral metastases is one important approach in a multi-modal treatment, and its benefit is well documented [33, 38]. Subsequently, resection of single metastases is recommended by international guidelines for large tumors with a diameter of more than 2–3 cm, for surgically accessible metastases and patients with severe neurological burden and good general health [38]. However, surgical resection of cerebral metastases is frequently associated with failure of local control. Postresection local tumor progression occurs in up to 60% of patients without any adjuvant therapy and in nearly 30% of patients receiving adjuvant whole-brain radiation therapy (WBRT) [18, 24, 32, 44]. The comparatively high local failure rate after surgery or radiosurgery combined with the increased number and the improved prognosis of patients with malignancies has led to an increasing incidence of recurrent cerebral metastases.

Treatment of recurrent cerebral metastases is an emerging challenge. Stereotactic radiosurgery and fractionated local or

✉ Marcel A. Kamp
MarcelAlexander.Kamp@med.uni-duesseldorf.de

[1] Department of Neurosurgery, Medical Faculty, Heinrich Heine University, Moorenstraße 5, D-40225 Düsseldorf, Germany

[2] Division of Informatics and Statistics, Department of Neurosurgery, Medical Faculty, Heinrich Heine University, Moorenstraße 5, D-40225 Düsseldorf, Germany

[3] Institute for Diagnostic and Interventional Radiology Medical Faculty, Heinrich Heine University, Moorenstraße 5, D-40225 Düsseldorf, Germany

WBRT of locally recurrent metastases are well described and therefore represent valuable radiological treatment options [10, 23, 25]. As prospective and controlled studies are lacking, the oncological impact of (re-)irradiation of locally progressive metastases remains disputable. Re-irradiation harbors a significant risk of local complications such as radionecrosis [38]. An alternative treatment option is the microsurgical resection of recurrent metastases. Surgery for recurrent metastases is recommended by the latest European and American guidelines especially for patients with locally accessible metastases, good neurological condition and stable extracranial disease, and a relatively long latency to recurrence [1, 3, 7, 38]. However, the oncological impact of craniotomy for recurrent cerebral metastases remains disputable, and high-quality analyses have yet to be published. Recent evidence (evidence level IIIB) has been obtained from five retrospective case series [2, 4, 8, 22, 36]. All of these included both patients suffering from local and distant in-brain progression. Risk of perioperative surgical complications, rate of incomplete surgical resections, and incidence of further local in-brain progressions will likely be higher for locally recurrent metastases with extensive previous surgical and radio-oncological treatment as compared to distant metastases without any previous local therapy. While recent studies focused on identification of factors influencing overall survival, predictors of local failure after resection of recurrent metastases have yet to be identified. Therefore, the present study aims to identify risk factors of further local in-brain progression after re-craniotomy for locally progressive brain metastases.

Material and methods

Ethical statement

Scientific use of the clinical data was approved by the local ethics committee of the Medical Faculty of the Heinrich Heine University, Düsseldorf, Germany (study ID 5947R).

Eligibility for retrospective analysis

Using an integrated medical record system, we performed a retrospective analysis of data on patients fulfilling the inclusion criteria. Inclusion criteria were (1) local progression of a previously surgically treated cerebral metastasis, (2) first recurrence, (3) previous craniotomy and surgical re-resection, (4) histopathological confirmation of local progression of a cerebral carcinoma or malignant melanoma metastasis, (5) complete set of preoperative imaging (MRI ± CT) and early postoperative MRI within 72 h after surgery, (6) subsequent clinical and radiological follow-up, and (7) surgical treatment between January 2010 and April 2017. Patients with tumors other than cerebral carcinoma metastasis (e.g., glioma, cerebral lymphoma, or sarcoma), patients with multiple local recurrences, patients with only radiotherapeutically treated metastases, and patients with leptomeningeal metastases were excluded from this study (Fig. 1).

Surgery

Standard white light-assisted, microsurgical circumferential resection of the cerebral metastasis was performed for all metastases. The routine surgical setup included the intraoperative use of neuronavigation and ultrasound. Surgery was performed as awake surgery in an asleep-awake-asleep protocol for all patients with eloquently situated recurrent metastases [17]. An eloquent brain region was defined according to the literature as a cortical or subcortical brain area at which we expect intraoperative stimulation to elicit changes in neurologic conditions (particularly regarding speech, movement, and tactile sensation) or to elicit a response in electrophysiological recordings in corresponding areas [14, 17].

Neuroradiological imaging

Preoperative, postoperative, and follow-up imaging was performed by a 1.5 T MRI including T1, T2, T2*, T2, DWI, ADC, and T1 postgadolinium sequences (Avanto, Siemens, Erlangen, Germany) as described before [13]. All radiological assessments were independently evaluated by one neuroradiologist (B.T.). The extent of surgical resection was evaluated by an early postoperative 1.5 T MRI within 72 h after surgery. Residual contrast-enhancing parts in the T1 sequences as well as T2 and diffusion sequences were examined for residual tumor [13].

Adjuvant standard treatment and follow-up

Adjuvant standard treatment following surgery was stipulated in the interdisciplinary tumor board. In general, adjuvant radiation therapy was recommended unless limited by previous radiation therapies. A fractionated local cavity boost radiation therapy with 10 × 3 Gy on the resection cavity and on 5 mm of the adjacent tissue (clinical target volume) was considered for completely resected metastases, and an integrated stereotactic boost was applied to residual tumor tissue. Patients were clinically followed from the time of surgery until decease or referral to a palliative care ward including a contrast-enhanced MRI every 3 months.

Definition of outcome measures

Local recurrence was defined as appearance of a tumor recurrence within or at the border of the resection cavity according to the RANO criteria for cerebral metastases [26]. For incomplete metastasis resection on the early

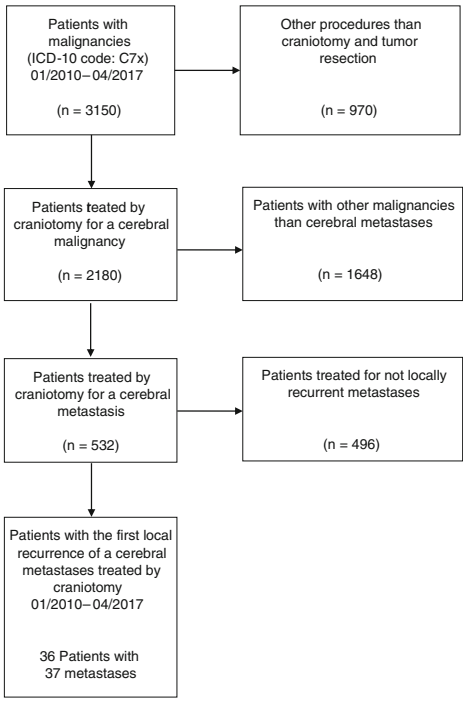

Fig. 1 Flow chart of patient inclusion

postoperative MRI < 72 h after surgery, local progression was considered when residual metastasis volume increased by more than 25% [18]. Local tumor control was assumed if no local recurrence occurred in the observation period (till follow-up or death of the patient). Distant in-brain progression was defined as new contrast-enhancing lesions in the follow-up MRIs at least 2 cm from the site of the resected metastasis. Leptomeningeal carcinomatosis was diagnosed by cranial MRI as diffuse enhancement of meninges and/or by lumbar puncture and confirmation of malignant tumor cells in the cerebrospinal fluid (CSF). For statistical analysis, extent of surgical resection as assessed on the T1, T2, and diffusion sequences in the early postoperative MRI was categorized in (1) residual tumor, (2) no, and (3) questionable residual tumor.

Overall survival (OAS) was defined as the time between surgery of a recurrent metastasis and death; progression-free survival (PFS) was defined as the time span between surgery of a recurrent metastasis and a further (second) local in-brain progression or recurrence or death. Prognosis of patients suffering from cerebral metastases was assessed using the diagnosis-specific graded prognostic assessment (ds-GPA) score [40]. Patients' performance status was evaluated by the Karnofsky performance score and the Eastern Cooperative Oncology Group (ECOG) performance score [21, 30].

Statistical analysis

Epidemiological data, data regarding tumor location and primary tumor, as well as preoperative and postoperative images were collected from charts and an electronic documentation system. Continuous variables are presented as the mean ± standard error of mean (SEM). For nominal-scaled variables, we calculated frequencies and ratios. For categorical data, the Pearson χ^2 test was used to test the independence of variables. Real-valued data were first tested for normality using the Shapiro-Wilk normality test. Its null hypothesis is that the population from which the sample is taken is normally distributed. If the variables were found to have no significant deviation from the normal distribution, either on the linear or on the logarithmic scale, the Welch's *t* test was used to compare the variable distributions. If the variables themselves were normally distributed, the *t* test was applied directly to the data to check whether the distribution means significantly differ. Kaplan-Meier survival curves were compared using the log-rank test, also known as the Mantel-Haenszel or Mantel-Cox test.

A significance level below $p = 0.05$ was considered as significant. As multiple statistical testing was performed, the significance level according to Šidák's and Bonferroni's correction: Šidák's and Bonferroni correction revealed an adjusted *p* value of 0.0051 or 0.005, respectively. The R statistical computing package R version 3.3.2 as released on October 31 2016 (https://r-project.org/) was used to perform all statistical analyses.

Results

Patient cohort

Between January 2010 and April 2017, a total of 3150 patients were surgically treated for a malignancy (according to the ICD-10 code C7x) in our department. Craniotomy and tumor resection were performed in 2180 patients, and 532 of these patients suffered from cerebral metastases. Only 36 patients suffered from local in-brain progression after previous initial surgical resection of a cerebral metastasis. One patient was treated for two different locally recurrent metastases.

Therefore, 36 patients with a total of 37 recurrent metastases matched the inclusion criteria and were included in the further analysis. Patient characteristics are summarized in

Table 1 Patient characteristics

		Total number	Percentage
Total number of patients		36	
Number of metastases		37	
Age	Mean ± standard error of mean (SEM)	58.6 ± 1.8 years	
	Range	34–74 years	
Gender	Female	18	50.0%
	Male	18	50.0%
Histology	Adeno-CA	27/36	75.0%
	Small cell CA	2/36	5.6%
	Clear cell CA	2/36	5.6%
	Squamous cell CA	3/36	8.3%
	Malignant melanoma	2/36	5.6%
Primary cancer	NSCLC	21/36	58.3%
	SCLC	2/36	5.6%
	Malignant melanoma	3/36	8.3%
	Breast cancer	2/36	5.6%
	Gastrointenstinal cancer	5/36	13.9%
	Kidney cancer	1/36	2.8%
	Urogenital cancer	1/36	2.8%
	Carcinom of unknown primary	1/36	2.8%
Systemic disease at the time of recurrent metastasis surgery	Yes	27/37	73.0%
	Range	10/37	27.0%
Preoperative Karnofsky Performance Scale	Mean ± standard error of mean (SEM)	81.2 ± 2.1	
	Median	90	
	Range	50–100	
Eastern Cooperative Oncology Group (ECOG) quality of life index	Mean ± standard error of mean (SEM)	0.5 ± 0.1	
	Median	0	
	Range	0–2	
Prognosis of life expectancy as assessed by ds-GPA	Mean predicted survival ± SEM	8.4 ± 0.7 m	
	Range	3–25.3 m	
Bindal score	Mean ± standard error of mean (SEM)	1.5 ± 1.3	
	Median	2	
	Range	0–3	
Time between first and re-surgery	Mean time ± SEM	9.3 ± 1.6 m	
	Range	1–43 m	
Eloquent location of metastases ($n = 37$)	Eloquent	17/37	45.9%
	Local	20/37	54.1%
Location of metastases ($n = 37$)	Supratentorial location	34/37	91.9%
	Infratentorial location	3/37	8.1%
Previous adjuvant radiation therapy following first surgery	Whole-brain radiation therapy	21/37	56.8%
	Whole-brain and local radiation	1/37	2.7%
	Only fractionated local radiation therapy	7/37	18.9%
	Only single fraction radiosurgery	1/37	2.7%
	None	7/37	18.9%

Table 1 (continued)

		Total number	Percentage
Adjuvant radiation therapy following re-surgery	Whole-brain radiation therapy	6/37	16.2%
	Whole-brain and local radiation	1/37	2.7%
	Only fractionated local radiation therapy	7/37	18.9%
	Only single fraction radiosurgery	5/37	13.5%
	None	18/37	48.6%
Residual tumor on MRI after first surgery	Yes	9/37	24.3%
	No	17/37	45.9%
	Questionable	11/37	29.7%
Residual tumor on MRI after surgery of a recurrent metastasis	Yes	15/37	40.5%
	No	14/37	37.8%
	Questionable	8/37	21.6%
Local in-brain progression	Yes	14/37	37.8%
	No	23/37	62.2%
Distant in-brain progression	Yes	10/37	27.0%
	No	27/37	73.0%
Leptomeningeal carcinomatosis	Yes	13/37	35.1%
	No	24/37	64.9%
Progression-free survival	Mean time to any in-brain progression ± SEM	6.9 ± 1.5 m	
	Range time to any in-brain progression	1–35 m	
	Mean time to local in-brain progression ± SEM	7.3 ± 1.5 m	
	Range time to local in-brain progression	1–35 m	
Overall survival	Mean overall survival ± SEM	12.9 ± 2.3 m	
	Range overall survival	1–48 m	

Table 1. Mean age at surgery of the recurrent metastasis was 58.6 years (range 34–79 years); male to female ratio was 1:1. Over 75% of cerebral metastases were adenocarcinoma metastases and in over 50% of patients originated from a non-small cell lung cancer (NSCLC).

Tumor resection of the first operation was considered to be complete on an early postoperative MRI within 72 h after surgery in 45.9% of patients. After the first surgery, the vast majority of patients were treated by adjuvant irradiation (WBRT in 56.8%, local irradiation in 21.6%, and a combination of both in 2.8%).

Surgery of locally recurrent cerebral metastases

Mean time between initial metastasectomy and resection of the locally recurrent cerebral metastasis was 9.3 ± 1.6 months. Nearly 75% of patients suffered from an uncontrolled systemic disease status and had a life expectancy prognosis of 8.6 ± 0.7 months calculated by ds-GPA, when the surgery for recurrent cerebral metastasis was performed. Twenty four of 36 patients died during follow-up. Mean overall survival was 12.9 ± 2.3 months. Median preoperative Karnofsky performance score was 90 (range 50–100), and median preoperative ECOG performance score was 0 (range 0–2) before resection of the locally recurrent metastasis. No complications or neurological deterioration were observed within the first 30 days after surgery. Two patients showed systemic tumor progression and died within the first 60 days following surgery.

Extent of recurrent metastasectomy was evaluated by early postoperative MRI resection within 72 h after surgery and could not reliably be evaluated in 21.6% of patients. In these cases, potential residual tumors could not reliably be differentiated from dilated vessels in the wall of the resection cavity, pre-existing scar tissue, blood in the resection cavity, or poor image quality (e.g., due to patient agitation). Extent of resection on early postoperative MRI was considered complete in 14/37 metastases (37.8%) and incomplete in 15/37 metastases (40.5%). Due to tumor infiltration of cerebral vessels and/or involvement of cerebral vessels in extensive scar formation after previous therapy ($n = 4$) or infiltration of eloquent brain areas ($n = 3$), surgeon intended intraoperatively a subtotal in 7/15 patients.

In-brain progression rate

Further in-brain progression after recurrent metastasectomy was observed in 24/36 patients (66.7%). In-brain progression at distant sites was seen in 10 patients (27.7%). Leptomeningeal carcinomatosis was observed in 13 patients (36.1%). Mean time to any in-brain progression was 6.9 ± 1.5 months.

Fourteen of 37 metastases (37.8%) showed further in-brain progression. Mean time to local recurrence was 7.3 ± 1.5 months. Neither tumor histology (Pearson χ^2 4.4, p = 0.49) nor the tumors' primary site (Pearson χ^2 4.3, p = 0.74), eloquent metastasis location (Pearson χ^2 2.3×10^{-31}, p = 1), residual tumor detection on an early MRI following the first metastasis surgery (Pearson χ^2 0.17, p = 0.92), irradiation before or following recurrent metastasis resection (Pearson χ^2 1.7, p = 0.77 and Pearson χ^2 2.4, p = 0.66), preoperative KPS (Pearson χ^2 1.8, p = 0.77), and preoperative ECOG score (Pearson χ^2 1.5, p = 0.5) significantly correlated with later in-brain progression. Detection of residual tumor tissue on an early MRI following recurrent metastasis surgery was the only predictor for further local in-brain progression when defining a significance level of p = 0.05 (Pearson χ^2 8, p = 0.018).

If defining a Šidák-adjusted (p = 0.0051) or Bonferroni-adjusted (p = 0.005) significance level, this correlation was not significant anymore. However, log-rank (χ^2 = 2; p = 0.36) analysis and Cox proportional hazard regression (likelihood ratio test: p = 0.34) of the progression-free survival (PFS) showed no correlation between degree of surgical resection and the PFS (Fig. 2).

Of the 14 patients with in-brain progression after resection of a recurrent metastasis, 10 patients were considered for further resection of locally recurrent metastases (totally 15 additional craniotomies and tumor resections). Five patients required one and five patients two additional craniotomy for their locally recurrent metastasis. In addition, 19 patients were [again] received adjuvant irradiation (see Table 1). Local tumor control could finally be achieved in 34/37 metastases (91.9%) assessed by the follow-up MRIs resulting in a failure rate of 8.1% after multiple surgical resections and irradiations.

Overall survival

Mean life expectancy as predicted the ds-GPA Score was 8.4 ± 0.7 months. Mean overall survival after locally recurrent cerebral metastasis resection was 12.9 ± 2.3 months (ds-GPA score vs. OAS: $p < 0.0001$). Although local tumor control could not finally be achieved in all patients, no patient deceased due to an isolated local in-brain progression. However, 2 patients died from an isolated in-brain progression with local, distal in-brain progression and leptomenigeal carcinosis (5.5%) and 12 patients from systemic and cerebral tumor progression (33.3%). Overall survival exceeded 24 months in eight patients (22.2%). The degree of surgical resection had no influence on the overall survival ($p > 0.05$ in the log-rank analysis and Cox proportional hazard regression, Fig. 3).

Discussion

There are three key findings in this study: (1) Complete surgical resection of locally recurrent cerebral metastases as confirmed by early postoperative MRI could only be achieved 37.8%, (2) detection of residual tumor tissue on early postoperative MRI following recurrent metastasis surgery correlated with further local in-brain progression when defining a significance level of p = 0.05 but not after Šidák or Bonferroni significance level correction for multiple testing, and (3) definite local tumor control could finally be achieved in 91.9% despite further local in-brain progression in 37.8%. Overall survival after recurrent metastasectomy was significantly longer than predicted by ds-GPA.

As prospective and controlled studies are lacking deciding upon the best treatment for recurrent cerebral metastases remains a challenge. To our best knowledge, to date, only five retrospective case series have analyzed the impact of surgical resection of locally progressive brain metastases [2, 4, 8, 22, 36]. The oncological impact of a re-craniotomy of locally progressive cerebral metastases after previous surgery with and without previous irradiation remains unclear. Furthermore, local in-brain progression rates are well documented for the first recurrence but not for further recurrences.

In the present study, MRI-verified complete surgical resection of recurrent metastases was achieved in nearly 40% of patients. Rate of incomplete surgical resections was 40.5%. Therefore, proportion of subtotal resections of recurrent metastases is twice the incidence of incomplete resections known from craniotomies for firstly diagnosed cerebral metastases [18]. Several reasons may explain the unsatisfyingly high rate of incomplete resections: (1) Surgery of recurrent cerebral metastases may be more challenging than first craniotomies due to, e.g., scar formation, pseudoprogression, infiltration of cerebral vessels, or eloquent brain areas. Infiltration of cerebral vessels and eloquent brain areas together with extensive scar formation could impede complete surgical resection. In fact, in more than half of incompletely resected metastases in the present study, the surgeons did not intend a complete surgical resection because cerebral vessels were either infiltrated by the metastasis or were involved in extensive scar formation (n = 4) or due to infiltration of eloquent brain areas (n = 3). In comparison, resection had been classified as complete by the surgeon in 92.3% in the previous study analyzing the degree of the first craniotomy for a cranial metastasis [18]. (2) Reliable intraoperative differentiation between scar formation

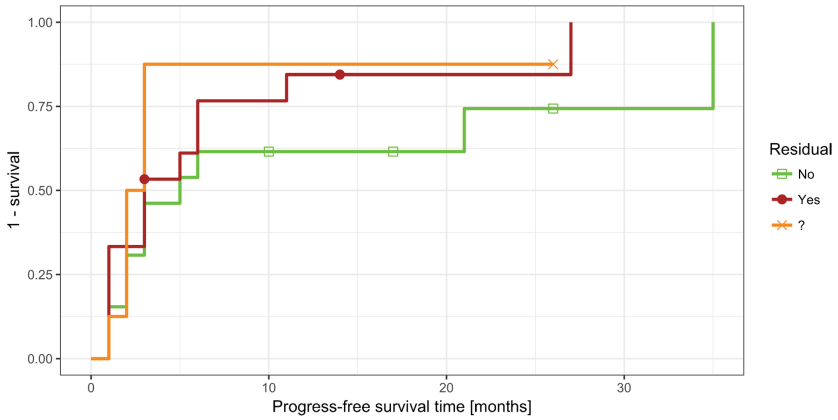

Fig. 2 Time to local in-brain progression rate. Figure 2 summarizes time to local in-brain progression for the subgroups of completely, incompletely, and questionable completely resected locally recurrent metastases. Time to local in-brain progression was defined as time span between surgery of a recurrent metastasis and a further (second) local in-brain progression or recurrence or death

and tumor infiltration by the surgeon may be more difficult after extensive previous treatments leading to higher rate of unintended incomplete surgical resections. (3) Reliable discrimination between posttherapeutic tissue changes on MRI (e.g., scar formation) and residual tumor parts may also be challenging. As we did not gather histopathological samples from the resection cavity, we cannot completely exclude that isolated residual contrast-enhancing parts on the postoperative MRI may not be residual tumor tissue but scar formation. However, residual contrast-enhancing parts on MRI might unlikely be scar if removed contrast-enhancing parts were verified as tumor by histopathological analysis.

The unsatisfying high rate of incomplete resections is in line with some previous reports: The previous study by Schackert and coworkers reported a similarly high rate of subtotal surgical resection of local and distant recurrences (41.8%) [36]. In contrast, others observed no subtotal resections [2]. The local in-brain progression rate was 37.8% and therefore slightly higher than our previously reported local in-brain progression rate after first craniotomy (30.8%) [18]. The higher local in-brain progression rate in the case of recurrence might well be explained by the higher rate of subtotal resections. Possibly, those metastases showing multiple recurrences exhibit more aggressive biological behavior (e.g., as may be

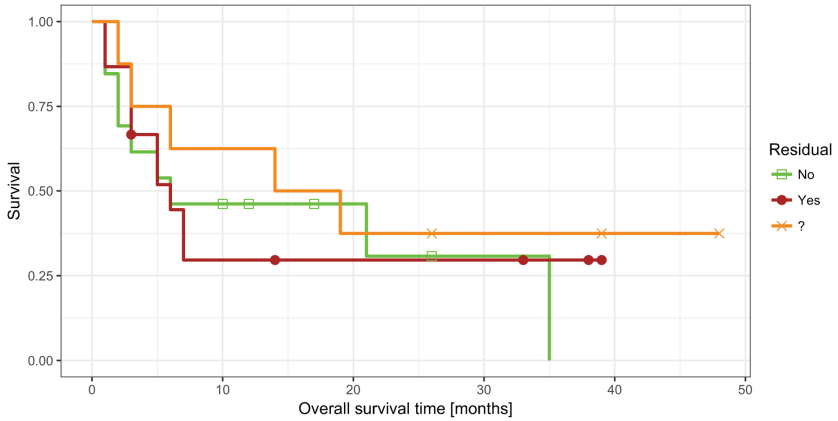

Fig. 3 Overall survival after surgery of a locally recurrent cerebral metastasis

more brain-invasive) than metastases in which local control could be achieved [20].

Extent of surgical resection as assessed by an early postoperative MRI was the only predictor for local in-brain progression. However, this correlation was only significant when defining a significance level of $p = 0.05$ but not after significance level correction for multiple testing. This observation is likely related to the small number of patients included in this study and may be confirmed in a greater patient collective. Extent of surgical resections was recently shown to be crucial for the local in-brain progression rate of cerebral metastases and other (malignant) brain tumors. Residual tumor tissue was verified by early postoperative MRI in up to 20% after first craniotomy of cerebral metastases. Complete surgical resection and residual tumor verification significantly correlate with the rate of local in-brain progression [18]. For malignant glioma, the degree of surgical resection is well known to correlate with the progression-free survival in prospective, randomized, and controlled studies [37, 41–43]. Furthermore, recent retrospective analyses revealed a significant influence of the extent of re-resections of recurrent glioblastoma and the progression-free survival [34, 35]. Our present study suggests that resection degree of recurrent cerebral metastases similarly determines local in-brain progression rate. Beyond complete tumor removal, a "supramarginal" resection with extension of the resection beyond the contrast-enhancing borders of the tumor (or the flair lesion for low-grade glioma) was considered to additionally improve local control in cerebral metastases [17, 19, 34, 44] and low-grade glioma [13] and also results in an improved overall survival of glioblastoma patients [15]. However, the impact of supramarginal resection has yet to be analyzed for recurrent metastases.

The degree of surgical resection of cerebral metastases and all other assessed parameters had no influence on overall survival in the present analysis. Previous studies have revealed different factors influencing overall survival including systemic disease status [4, 8], gender [8], primary tumor [8], preoperative performance as assessed by the Karnofsky performance scale [4, 8, 22], latency to recurrence [8, 36], and again degree of surgical resection [36]. However, the results of all these studies remain contradictory, and predictors identified in one study could not be verified in another. Possible explanations for contradictory results are the long periods in which patients were studied (from 1976 to 2013), the retrospective, uncontrolled study design, heterogeneity of patients included, and the limited number of patients per study. Therefore, prospective and controlled studies are required.

Overall survival was significantly longer as compared to the survival prediction by ds-GPA. Of note, ds-GPA was designed for patients with newly diagnosed cerebral metastases and not for patients with recurrent metastases. One explanation for the better overall survival is likely the high rate in which local control was finally achieved (91.9%). Despite the high rate of local control, leptomeningeal carcinomatosis was observed in 36% of patients.

Limitations

We acknowledge several limitations of our present study: (1) The results of our analysis are limited by the retrospective single-center study design. Other surgical techniques in other neurooncological centers could result in a higher rate of complete surgical resections. Metastases were resected by circumferential stripping of the cerebral metastasis from the surrounding brain tissue. Craniotomies involved use of ultrasound and a navigation system and were performed in a microsurgical approach. For eloquently situated metastases, surgery was performed with intraoperative neurophysiological monitoring and if necessary as awake craniotomy. The technique is state of art, and we are not aware of any significant difference in our technique and that employed by others; (2) the present patient population was heterogeneous regarding the different primary tumors and different tumor stages. Moreover, distribution of histology and primary cancer in the present study does not represent the distribution known from the primary situation [12]: Patients with malignant melanoma (8.3%) or breast cancer (5.6%) metastases were underrepresented in the cohort. Investigating a more homogeneous population with clearly defined adjuvant therapy concepts may allow for a more distinct overview on the oncological impact of employed treatment and techniques. (3) The present patient population was also heterogeneous regarding different adjuvant and systemic therapy concepts before craniotomy of their recurrent metastases: (a) Adjuvant therapy concepts after first and re-craniotomy are still matter of debate and must be evaluated in further studies. WBRT was the gold standard and recommended by the guidelines for a long time. Its oncological impact was questioned after the EORTC 22952-26001 study: WBRT leads to significantly lower local recurrence rate and has no influence on overall survival but significantly impacts patients' neurocognitive function and quality of life [9, 24, 39]. As other neurooncological departments, we do not routinely recommend WBRT after complete surgical resection of a single cerebral metastasis. This is one explanation for the heterogeneity in our patient cohort. Standards for the best adjuvant treatment after metastasectomy are not established and are analyzed in a number of recently published and initiated studies (e.g., NOA-14/HIPPORAD-study, C-O-Met study) [9, 29]. Evidence for the best adjuvant therapy is even scarcer for the recurrence situation. (b) Due to their different primary tumors and tumor stages, the present patient population was more heterogeneous regarding their previous systemic therapy. Next to different biological behavior of various carcinomas [20], the heterogeneity of treatment and treatment response of different cancers may be crucial in understanding their behavior inside and outside of the brain. In particular,

brain metastases of different primary tumors differ in their response rates to chemotherapy. Metastases from breast cancer show an intermediate response, whereas metastases form malignant melanoma and NSCLC show low rates [38]. Furthermore, conventional chemotherapy and target therapies (e.g., in the treatment of malignant melanoma) may beneficially influence cerebral metastatic spread [5, 6]. Therefore, the comparatively low incidence of patients with locally recurrent brain metastasis from malignant melanoma and breast cancer in the present series may reflect the effectiveness of a previous systemic therapy. (4) The number of patients included in the present study is very limited. A larger population is required to achieve more meaningful results. Surprisingly, recraniotomy for cerebral metastases seems to be a comparatively rare indication (e.g., about 1.2% of all surgery for malignancy in our department and 2.2% of all craniotomies in the recent study of Kennion and Holliman) [22], and all recent studies included a limited number of patients (27–69 patients). Well-conducted studies with a larger patient number are needed and may require multi-center pooling of data when possible. (5) Detection of residual tumor tissue on an early MRI following recurrent metastasis surgery was the only predictor for further local in-brain progression when defining a significance level of $p = 0.05$ but not if defining a Šidák-adjusted ($p = 0.0051$) or Bonferroni-adjusted ($p = 0.005$) significance level. Furthermore, no correlation between the PFS and the resection status was observed. A higher number of patients may have led to a stronger correlation. (6) Extent of surgical resection on early postoperative MRI could not be reliably evaluated in 21.6% of patients. This rate is comparable to the previous rate of 18.5% in which a final decision on degree of resection could be made after first craniotomy for cerebral metastases. Reducing this uncertainty represents a challenge to neuroradiology. (7) To date, an early postoperative MRI is probably the gold standard in evaluating the degree of the first surgical resection of cerebral metastases and was recommended by the most recent European guideline for diagnosis and treatment of brain metastases from solid tumors [38]. Despite not being standard in all neurooncological departments, an early postoperative MRI was used to estimate the degree of metastasectomy in several prospective and retrospective studies [e.g., 17–19, 24, 34]. Residual tumor tissue was frequently observed after first metastasectomy and was considered to represent a factor responsible for high recurrence rates seen in these patients [18]. However, the oncological impact of an early postoperative MRI after resection of recurrent brain metastases has yet to be systematically analyzed. As described before, for malignant and firstly diagnosed metastases, postoperative MRI was performed within 72 h after resection [18, 42]. The period of 72 h following surgery allowing valid discrimination between residual tumor and postoperative reactions has been evaluated for malignant glioma but never for cerebral metastases. Furthermore, it remains unclear whether higher field intensities of MRI (e.g., 1.5 vs. 3 T) would enable a more reliable detection of residual tumor tissue. As a differentiation between scar/pseudoprogression and residual and recurrent metastatic tissue remains challenging, metabolic imaging (e.g., by an FET-PET) may be an additional option [28]. (8) The ds-GPA was performed on data of 4259 patients with newly diagnosed cerebral metastasis [40]. As a result, prognostic factors for patients with cerebral metastases were related to the primary site. We used the ds-GPA for an estimation of the prognosis of patients with recurrent metastases. (9) A comparably high percentage (75%) of patients suffered from an uncontrolled systemic disease status. In addition to insufficiency of previous treatment, local in-brain progression as inclusion criteria in the present population may also be a reflection of this uncontrolled systemic disease status. Further studies should analyze potential influence of the systemic disease status on the local recurrence rate.

Conclusions

Systematic analysis of resection of locally progressive cerebral metastasis results in a high percentage of incomplete resections on early postoperative MR and in a comparatively high local in-brain progression rate. The degree of surgical recurrent metastasis resection was the only predictor of local recurrence but had no influence on overall survival. Despite the high rate of incomplete resections and of local in-brain progression, local control could finally be achieved in 91.9% after further surgeries or adjuvant radiation. However, 5.5% of patients died from isolated in-brain progression and 33% patients from systemic and cerebral tumor progression. Mean overall survival was 12.9% months, and 22.2% of patients experienced overall survival exceeding 24 months. However, this study involves a limited number of heterogeneous patients, and larger, prospective controlled studies are therefore required. Considering the adequate local tumor control achieved in the vast majority of patients, surgery of recurrent metastases may represent one option in a multi-modal treatment approach of patients suffering from locally recurrent cerebral metastases.

Compliance with ethical standards

Conflict of interest Prof. Sabel is a consultant for Johnson & Johnson Company and Integra Company. Dr. Dibué-Adjei is an employee of LivaNova PLC, manufacturer of vagus nerve stimulators. All other authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements) or non-financial interest (such as personal or professional relationships, affiliations, knowledge, or beliefs) in the subject matter or materials discussed in this manuscript.

Ethical approval Scientific use of the clinical data was approved by the local ethics committee of the Medical Faculty of the Heinrich Heine University, Düsseldorf, Germany (study ID 5947R).

Informed consent Informed consent for scientific use was routinely obtained for all malignant tumor patients.

References

1. Al-Shamy G, Sawaya R (2009) Management of brain metastases: the indispensable role of surgery. J Neuro-Oncol 92(3):275–282. https://doi.org/10.1007/s11060-009-9839-y
2. Al-Zabin M, Ullrich WO, Brawanski A, Proescholdt MA (2010) Recurrent brain metastases from lung cancer: the impact of reoperation. Acta Neurochir 152(11):1887–1892. https://doi.org/10.1007/s00701-010-0721-7
3. Ammirati M, Cobbs CS, Linskey ME, Paleologos NA, Ryken TC, Burri SH, Asher AL, Loeffler JS, Robinson PD, Andrews DW, Gaspar LE, Kondziolka D, McDermott M, Mehta MP, Mikkelsen T, Olson JJ, Patchell RA, Kalkanis SN (2010) The role of retreatment in the management of recurrent/progressive brain metastases: a systematic review and evidence-based clinical practice guideline. J Neuro-Oncol 96(1):85–96. https://doi.org/10.1007/s11060-009-0055-6
4. Arbit E, Wronski M, Burt M, Galicich JH (1995) The treatment of patients with recurrent brain metastases. A retrospective analysis of 109 patients with nonsmall cell lung cancer. Cancer 76(5):765–773. https://doi.org/10.1002/1097-0142(19950901)76:5<765::AID-CNCR2820760509>3.0.CO;2-E
5. Berghoff AS, Preusser M (2015) The future of targeted therapies for brain metastases. Future Oncol 11(16):2315–2327. https://doi.org/10.2217/fon.15.127
6. Berghoff AS, Preusser M (2017) Targeted therapies for melanoma brain metastases. Curr Treat Options Neurol 19(4):13. https://doi.org/10.1007/s11940-017-0449-2
7. Bhangoo SS, Linskey ME, Kalkanis SN, American Association of Neurologic S, Congress of Neurologic S (2011) Evidence-based guidelines for the management of brain metastases. Neurosurg Clin N Am 22(1):97–104, viii. https://doi.org/10.1016/j.nec.2010.09.001
8. Bindal RK, Sawaya R, Leavens ME, Hess KR, Taylor SH (1995) Reoperation for recurrent metastatic brain tumors. J Neurosurg 83(4):600–604. https://doi.org/10.3171/jns.1995.83.4.0600
9. Brown PD, Ballman KV, Cerhan JH, Anderson SK, Carrero XW, Whitton AC, Greenspoon J, Parney IF, Laack NNI, Ashman JB, Bahary JP, Hadjipanayis CG, Urbanic JJ, Barker FG, 2nd, Farace E, Khuntia D, Giannini C, Buckner JC, Galanis E, Roberge D (2017) Postoperative stereotactic radiosurgery compared with whole brain radiotherapy for resected metastatic brain disease (NCCTG N107C/CEC.3): a multicentre, randomised, controlled, phase 3 trial. Lancet Oncol 18:1049–1060, 8, DOI: https://doi.org/10.1016/S1470-2045(17)30441-2
10. Caballero JA, Sneed PK, Lamborn KR, Ma L, Denduluri S, Nakamura JL, Barani IJ, McDermott MW (2012) Prognostic factors for survival in patients treated with stereotactic radiosurgery for recurrent brain metastases after prior whole brain radiotherapy. Int J Radiat Oncol Biol Phys 83(1):303–309. https://doi.org/10.1016/j.ijrobp.2011.06.1987
11. Chang EL, Wefel JS, Hess KR, Allen PK, Lang FF, Kornguth DG, Arbuckle RB, Swint JM, Shiu AS, Maor MH, Meyers CA (2009) Neurocognition in patients with brain metastases treated with radiosurgery or radiosurgery plus whole-brain irradiation: a randomised controlled trial. Lancet Oncol 10(11):1037–1044. https://doi.org/10.1016/S1470-2045(09)70263-3
12. DeAngelis LM (2001) Brain tumors. N Engl J Med 344(2):114–123. https://doi.org/10.1056/NEJM200101113440207
13. Duffau H (2015) Resecting diffuse low-grade gliomas to the boundaries of brain functions: a new concept in surgical neuro-oncology. J Neurosurg Sci 59(4):361–371
14. Duffau H, Capelle L, Denvil D, Sichez N, Gatignol P, Taillandier L, Lopes M, Mitchell MC, Roche S, Muller JC, Bitar A, Sichez JP, van Effenterre R (2003) Usefulness of intraoperative electrical subcortical mapping during surgery for low-grade gliomas located within eloquent brain regions: functional results in a consecutive series of 103 patients. J Neurosurg 98(4):764–778. https://doi.org/10.3171/jns.2003.98.4.0764
15. Eyupoglu IY, Hore N, Fan Z, Buslei R, Merkel A, Buchfelder M, Savaskan NE (2015) Intraoperative vascular DIVA surgery reveals angiogenic hotspots in tumor zones of malignant gliomas. Sci Rep 5(1):7958. https://doi.org/10.1038/srep07958
16. Gavrilovic IT, Posner JB (2005) Brain metastases: epidemiology and pathophysiology. J Neuro-Oncol 75(1):5–14. https://doi.org/10.1007/s11060-004-8093-6
17. Kamp MA, Dibue M, Niemann L, Reichelt DC, Felsberg J, Steiger HJ, Szelenyi A, Rapp M, Sabel M (2012) Proof of principle: supramarginal resection of cerebral metastases in eloquent brain areas. Acta Neurochir 154(11):1981–1986. https://doi.org/10.1007/s00701-012-1463-5
18. Kamp MA, Rapp M, Buhner J, Slotty PJ, Reichelt D, Sadat H, Dibue-Adjei M, Steiger HJ, Turowski B, Sabel M (2015) Early postoperative magnet resonance tomography after resection of cerebral metastases. Acta Neurochir 157(9):1573–1580. https://doi.org/10.1007/s00701-015-2479-4
19. Kamp MA, Rapp M, Slotty PJ, Turowski B, Sadat H, Smuga M, Dibue-Adjei M, Steiger HJ, Szelenyi A, Sabel M (2015) Incidence of local in-brain progression after supramarginal resection of cerebral metastases. Acta Neurochir 157(6):905–910; discussion 910-901. https://doi.org/10.1007/s00701-015-2405-9
20. Kamp MA, Slotty PJ, Cornelius JF, Steiger HJ, Rapp M, Sabel M (2016) The impact of cerebral metastases growth pattern on neurosurgical treatment. **Neurosurg Rev**
21. Karnofsky DA, WH, Craver LF, Burchenal JH (1948) The use of the nitrogen mustards in the palliative treatment of carcinoma. With particular reference to bronchogenic carcinoma. Cancer 1:634–656
22. Kennion O, Holliman D (2017) Outcome after craniotomy for recurrent cranial metastases. Br J Neurosurg:1–5
23. Kim DH, Schultheiss TE, Radany EH, Badie B, Pezner RD (2013) Clinical outcomes of patients treated with a second course of stereotactic radiosurgery for locally or regionally recurrent brain metastases after prior stereotactic radiosurgery. J Neuro-Oncol 115(1):37–43. https://doi.org/10.1007/s11060-013-1191-6
24. Kocher M, Soffietti R, Abacioglu U, Villa S, Fauchon F, Baumert BG, Fariselli L, Tzuk-Shina T, Kortmann RD, Carrie C, Ben Hassel M, Kouri M, Valeinis E, van den Berge D, Collette S, Collette L, Mueller RP (2011) Adjuvant 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 29(2):134–141. https://doi.org/10.1200/JCO.2010.30.1655
25. Kondziolka D, Kano H, Harrison GL, Yang HC, Liew DN, Niranjan A, Brufsky AM, Flickinger JC, Lunsford LD (2011) Stereotactic radiosurgery as primary and salvage treatment for brain metastases from breast cancer. Clinical article. J Neurosurg 114(3):792–800. https://doi.org/10.3171/2010.8.JNS10461
26. Lin NU, Lee EQ, Aoyama H, Barani IJ, Barboriak DP, Baumert BG, Bendszus M, Brown PD, Camidge DR, Chang SM, Dancey J, de Vries EG, Gaspar LE, Harris GJ, Hodi FS, Kalkanis SN, Linskey ME, Macdonald DR, Margolin K, Mehta MP, Schiff D, Soffietti R,

Suh JH, van den Bent MJ, Vogelbaum MA, Wen PY, Response Assessment in Neuro-Oncology g (2015) Response assessment criteria for brain metastases: proposal from the RANO group. Lancet Oncol 16:e270–e278

27. Lin NU, Winer EP (2007) Brain metastases: the HER2 paradigm. Clin Cancer Res 13(6):1648–1655. https://doi.org/10.1158/1078-0432.CCR-06-2478
28. Lohmann P, Stoffels G, Ceccon G, Rapp M, Sabel M, Filss CP, Kamp MA, Stegmayr C, Neumaier B, Shah NJ, Langen KJ, Galldiks N (2017) Radiation injury vs. recurrent brain metastasis: combining textural feature radiomics analysis and standard parameters may increase 18F-FET PET accuracy without dynamic scans. Eur Radiol 27(7):2916–2927. https://doi.org/10.1007/s00330-016-4638-2
29. Mahajan A, Ahmed S, McAleer MF, Weinberg JS, Li J, Brown P, Settle S, Prabhu SS, Lang FF, Levine N, McGovern S, Sulman E, McCutcheon IE, Azeem S, Cahill D, Tatsui C, Heimberger AB, Ferguson S, Ghia A, Demonte F, Raza S, Guha-Thakurta N, Yang J, Sawaya R, Hess KR, Rao G (2017) Post-operative stereotactic radiosurgery versus observation for completely resected brain metastases: a single-centre, randomised, controlled, phase 3 trial. Lancet Oncol 18(8):1040–1048. https://doi.org/10.1016/S1470-2045(17)30414-X
30. Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, Carbone PP (1982) Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 5(6):649–655. https://doi.org/10.1097/00000421-198212000-00014
31. Patchell RA (2003) The management of brain metastases. Cancer Treat Rev 29(6):533–540. https://doi.org/10.1016/S0305-7372(03)00105-1
32. Patchell RA, Tibbs PA, Regine WF, Dempsey RJ, Mohiuddin M, Kryscio RJ, Markesbery WR, Foon KA, Young B (1998) Postoperative radiotherapy in the treatment of single metastases to the brain: a randomized trial. JAMA 280(17):1485–1489
33. Patchell RA, Tibbs PA, Walsh JW, Dempsey RJ, Maruyama Y, Kryscio RJ, Markesbery WR, Macdonald JS, Young B (1990) A randomized trial of surgery in the treatment of single metastases to the brain. The. N Engl J Med 322(8):494–500. https://doi.org/10.1056/NEJM199002223220802
34. Pessina F, Navarria P, Cozzi L, Ascolese AM, Maggi G, Rossi M, Riva M, Scorsetti M, Bello L (2016) Role of surgical resection in patients with single large brain metastases: feasibility, morbidity, and local control evaluation. World Neurosurg 94:6–12. https://doi.org/10.1016/j.wneu.2016.06.098
35. Ringel F, Pape H, Sabel M, Krex D, Bock HC, Misch M, Weyerbrock A, Westermaier T, Senft C, Schucht P, Meyer B, Simon M, group SNs (2016) Clinical benefit from resection of recurrent glioblastomas: results of a multicenter study including 503 patients with recurrent glioblastomas undergoing surgical resection. Neuro-Oncology 18:96–104, 1, DOI: https://doi.org/10.1093/neuonc/nov145
36. Schackert G, Schmiedel K, Lindner C, Leimert M, Kirsch M (2013) Surgery of recurrent brain metastases: retrospective analysis of 67 patients. Acta Neurochir 155(10):1823–1832. https://doi.org/10.1007/s00701-013-1821-y
37. Senft C, Bink A, Franz K, Vatter H, Gasser T, Seifert V (2011) Intraoperative MRI guidance and extent of resection in glioma surgery: a randomised, controlled trial. Lancet Oncol 12(11):997–1003. https://doi.org/10.1016/S1470-2045(11)70196-6
38. Soffietti R, Abacioglu U, Baumert B, Combs SE, Kinhult S, Kros JM, Marosi C, Metellus P, Radbruch A, Villa Freixa SS, Brada M, Carapella CM, Preusser M, Le Rhun E, Ruda R, Tonn JC, Weber DC, Weller M (2017) Diagnosis and treatment of brain metastases from solid tumors: guidelines from the European Association of Neuro-Oncology (EANO). Neuro-Oncology 19(2):162–174. https://doi.org/10.1093/neuonc/now241
39. Soffietti R, Kocher M, Abacioglu UM, Villa S, Fauchon F, Baumert BG, Fariselli L, Tzuk-Shina T, Kortmann RD, Carrie C, Ben Hassel M, Kouri M, Valeinis E, van den Berge D, Mueller RP, Tridello G, Collette L, Bottomley A (2013) A European Organisation for Research and Treatment of Cancer phase III trial of adjuvant whole-brain radiotherapy versus observation in patients with one to three brain metastases from solid tumors after surgical resection or radiosurgery: quality-of-life results. J Clin Oncol 31(1):65–72. https://doi.org/10.1200/JCO.2011.41.0639
40. Sperduto PW, Chao ST, Sneed PK, Luo X, Suh J, Roberge D, Bhatt A, Jensen AW, Brown PD, Shih H, Kirkpatrick J, Schwer A, Gaspar LE, Fiveash JB, Chiang V, Knisely J, Sperduto CM, Mehta M (2010) 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 77(3):655–661. https://doi.org/10.1016/j.ijrobp.2009.08.025
41. Stummer W, Kamp MA (2009) The importance of surgical resection in malignant glioma. Curr Opin Neurol 22(6):645–649. https://doi.org/10.1097/WCO.0b013e3283320165
42. Stummer W, Pichlmeier U, Meinel T, Wiestler OD, Zanella F, Reulen HJ, Group AL-GS (2006) Fluorescence-guided surgery with 5-aminolevulinic acid for resection of malignant glioma: a randomised controlled multicentre phase III trial. Lancet Oncol 7:392–401
43. Stummer W, Reulen HJ, Meinel T, Pichlmeier U, Schumacher W, Tonn JC, Rohde V, Oppel F, Turowski B, Woiciechowsky C, Franz K, Pietsch T, Group AL-GS (2008) Extent of resection and survival in glioblastoma multiforme: identification of and adjustment for bias. Neurosurgery 62:564–576 discussion 564-576
44. Yoo H, Kim YZ, Nam BH, Shin SH, Yang HS, Lee JS, Zo JI, Lee SH (2009) Reduced local recurrence of a single brain metastasis through microscopic total resection. J Neurosurg 110(4):730–736. https://doi.org/10.3171/2008.8.JNS08448

4. Discussion

4.1 Risk factors for in-brain local progression in elderly patients after resection of cerebral metastases

With permission from Scientific Reports, May 2019; Volume 9 (1): Page 7431

Although the exact incidence of cerebral metastases from solid cancers is unknown, intracerebral metastases are the most frequent brain tumors with a 3-5 times higher incidence than newly diagnosed primary malignant brain tumors each year [282,283]. Incidence of cerebral metastases was considered to increase from 2.8–11.1 per 100,000 population in the years before 1990 to an incidence of 7–14.3 per 100,000 population in more recent studies [283]. Cumulative incidence of cerebral metastases may be age-related as the highest cumulative incidence is observed in patients with primary breast cancer at the age between 20 and 39 years, in lung cancer patients at the fifth decade and in malignant melanoma patients at the sixth decade of life [28]. Cumulative incidence is considered to be lowest for all primary cancers in the age group above 70 years, with exception of melanoma [28]. Despite the presumably lower incidence of cerebral metastases in elderly patients, incidence in this subgroup increases due to the high number of elderly patients, general increase of occurrence of cerebral metastases, improved diagnosis of brain metastases and better treatment of the primary cancer. Moreover, age above 60 years was one major risk factor for impaired overall survival (OS) in an early prospective randomized study comparing combined treatment of surgery and adjuvant whole-brain radiation therapy (WBRT) with an exclusive WBRT [284]. A recent individual patient data meta-analysis of 3 randomized trials of stereotactic radiosurgery (SRS) with or without WBRT for 1 to 4 cerebral metastases suggested that age might be a factor influencing the efficiency of an adjuvant WBRT following SRS. For patients < 50 years of age, SRS alone favoured survival and an additional WBRT did not impact the distant in-brain progression rate. Adjuvant WBRT significantly decreased the risk of new cerebral metastases without affecting the OS in patients aged > 50 years [285]. Some recent retrospective studies reported age as a risk factor for a reduced survival [286]. The Dutch prospective and randomized study (surgery and WBRT vs. WBRT alone) identified age as a major determinant for OS [284,223]. Age is therefore still considered to be a determinant of treatment and prognosis in this pathology in recent guidelines [162]. Recent studies analyzing the impact of metastasectomy in elderly patients focused on reporting perioperative mortality and morbidity rates but not on evaluation of oncological outcome parameters.

The main results of our analysis are as follows: (1) the local in-brain recurrence after surgical resection of a brain metastases in patients above 65 years of age is 25.6 % with a median time to occurrence of three months; (2) in patients above 65 years of age tumor-remnant in an early postoperative MRI was the only risk factor for local in-brain recurrence and (3) the median overall survival was 13 months in the present series.

Most studies analyzing the impact of cerebral metastasis resection focus on reporting perioperative morbidity and mortality rates but omit oncological outcome parameters such as (local) in-brain progression and survival. Median overall survival was 13 months after metastasectomy in the present retrospective series of elderly patients aged 65 years and over. It ranged between 2.8 and 18 months in recent prospective randomized and controlled phase III trials including surgery as treatment of cerebral metastases (e.g. 11.6 and 12.2 months in the NCCTG N107C/CEC·3 trial by Brown et al. [287]; 17 and 18 months in the study by Mahajan et al. [288]; 2.8 months in the trial by Roos et al. [289], 10.7 and 10.9 months in the EORTC 22952-26001 study by Kocher et al. [11], respectively). Although results from retrospective studies have limited comparability to those derived from prospective randomized and controlled phase III trials, median survival in the present analysis seems to be comparable to those in recent phase III studies. However, overall survival was related to the treatment of cerebral metastases only in early phase III trials from the 1990s (Patchell et al. [222]; Vecht et al. [223]) but not in more recent phase III trials (e.g. Kocher et al. [11]; Brown et al. [287]; Mahajan et al. [288]). Occurrence of single cerebral metastasis and the choice of their treatment modalities may therefore be insufficient to predict survival of patients – even in elderly patients. In contrast, treatment of cerebral metastases is well known to influence the local and distant in-brain progression as well as patients' quality of life. In the present study, local recurrence rate was 25.6%, the distant development rate was 26.9 %. These rates are congruent with our previous results and the recurrence rates reported in prospective randomized and controlled phase III trials. Therefore, elderly patients have comparable in-brain progression and overall survival as reported from previous oncologic patient cohorts.

After thorough analysis, tumor-remnant in the early postoperative MRI as described in [159] was the only statistically significant risk factor for local recurrence. Relevance of early postoperative MRI in oncological patients has already been defined [159,290]. Although many factors (e.g. surgical technique, number of metastases, local control) have been proposed as the cause of local

recurrence and distant development or carcinomatous meningitis [252,251,290,40,96,246], we could not establish another association or correlation in patients above 65 years of age.

In the present population, we observed no severe complication and no case fatalities within the first 30 days after surgery. The pre- and postoperative NIHSS, as well as KPS and follow-up visits showed no immediate or mediate deteriorations or complications. The median pre- and postoperative NIHSS was 1 without significant differences suggesting no new neurological deficits due to metastasectomy and a favorable overall surgical outcome. Perioperative morbidity and mortality were considered to be elevated in elderly patients in some neurosurgical but non-oncological series [291]. However, this may only partially be true for geriatric patients with cerebral metastases. Within a retrospective analysis of a United States inpatient sample, 4.907 patients aged 64 years and above were identified who underwent brain metastases resection. This study concluded that surgical resection of brain metastases among the elderly up to the ninth decade of life is feasible but that age above 80 years and comorbidities were important prognostic factors for inpatient outcome [292].

Our study presents some limitations: (1) 78 geriatric patients suffering from cerebral metastases within a period of 7 years were included. This is based on a very dense net of exclusion criteria. Therefore, this cohort might not be representative for all geriatric patients. However, the present cohort is heterogeneous in terms of different primary sites and adjuvant therapies. Furthermore, a subgroup analysis for patients with urgent or acute surgery for brain metastasis was not performed. Due to the acute setting, proper planning and supplementary accessories might have been impossible to accomplish and thus have resulted in a higher probability of tumor-remnant or an increased risk of complications. (2) Extent of surgical resection was analysed by an early postoperative-MRI. In the current literature, only few retrospective studies analysed the impact of this method in diagnosing residual tumor tissue [163,159]. A definite conclusion regarding the resection degree was not possible in 28.2% for several reasons, e.g. residual tumor tissue could not reliably be differentiated from dilated vessels in the wall of the resection cavity, poor image quality (e.g. due to patient motion), blood in the resection. The early postoperative MRI revealed an incomplete surgical resection in 19.2%. The comparatively high rate of incompletely and questionably completely resected metastases is in line with previous non-geriatric series [159]. (3) A median time-to-local recurrence of 3 ± 2.9 months (0 - 10 months) is fairly low. Time-to-local in brain-progression was therefore lower as in the recent phase III trials (e.g. 7.6 months and not reached in the recent phase III trial by Mahajan et.al. [288]). The reason for the comparatively low

time-to-local in-brain progression remains unclear. One explanation might be the high rate of incomplete surgical resection or patients without any adjuvant radiation therapy (19.2% each) and the significant correlation between verification of tumor remnants on an early MRI and a later local in-brain progression. We are not aware of any studies directly analyzing a potential correlation between local recurrence and death. Several recent phase III studies addressed the local control and / or the overall survival after treatment of 1 – 4 cerebral metastases. Except the study by El Gantery et al. [293], none of the studies observed an effect of the therapy modality on the overall survival but nearly all studies showed a significant effect on the local control. [5, 6, 10, 11, 13] (4) Current prognostic indicators were not performed or analyzed in our population. A comparative analysis between our data and known literature cannot be performed. (5) Moreover, preoperative evaluation of the geriatric population should be required in order to increase quality of care, identify unknown entities, reduce complications and improve outcome [294]. There are many tools to preoperatively assess geriatric patients. Although there are still some discrepancies [295] and new innovative tools are being studied [296], the most common and thorough tool utilized to identify those patients with higher risk for worse outcome or a greater benefit from surgical treatment is the comprehensive geriatric assessment [297]. Interestingly, most of the tools (if not all) use the KPS described in 1948 as a base [298]. Still, a unified guideline for this subgroup of patients has yet to be established. In our study, we did not perform any geriatric assessment. Nonetheless, the pre- and postoperative NIHSS, as well as KPS and follow-up visits showed no immediate or mediate deteriorations or complications, and more importantly, they represent an adequate parameter. However designed for other reasons and purposes [299-301], the NIHSS seems a feasible tool. (6) The influence of comorbidities, multi-organ metastatic disease, current medication and other elective or palliative surgeries was not taken into account. (7) Controlled or absent systemic neoplastic disease was assumed according to the clinical status and routine blood work. No evidence was established to prove that fact. (8) Another subgroup analysis of patients, in whom a palliative intervention therapy was performed, was also not analyzed separately. How this affects the course of disease, the type of therapy received additionally or the influence on overall survival remains unknown. (9) Patients' adherence, compliance, complications or changes altogether regarding adjuvant therapy were not analyzed. (10) Preoperative elaborate analysis of geriatric patients was not performed.

Local in-brain recurrence after surgical resection of a brain metastasis in patients above 65 years of age was 25.6%. Tumor-remnant in early postoperative MRI is the only risk factor for local in-brain recurrence. Mean overall survival was 13 months. Oncological parameters in the present cohort seem not to differ from recent phase III studies with non-geriatric patients.

4.2 Implication of 5-ALA fluorescence of cerebral metastases on local recurrence and overall survival

With permission from Journal of Neuro-Oncology, February 2019; Volume 141 (3): Pages 547-553

Treatment of cerebral metastases remains challenging, as treatment should ensure a long-lasting local control without affecting the quality of life. In particular, local control of cerebral metastases might be a problem as local in-brain progression rates were up to 50% in recent studies [11,10,12]. Incomplete and piecemeal-resections of cerebral metastases were considered as risk factors for local in-brain progression [40,251,252,302,303,159,304-306]. 5-aminolevulinic acid (5-ALA) fluorescence-guided resection technique was first introduced for malignant glioma. This technique is related to a more exhaustive surgical resection and subsequently an improved progression-free survival [307,160,308]. Recently, PpIX-fluorescence in cerebral metastases was considered a favorable parameter for a long-lasting local tumor control after metastasectomy – independent of the degree of surgical resection [309]. Although no correlation was found in the later study between the PpIX-fluorescence in cerebral metastases and the overall survival, the relatively small study group might have skewed the results.

This study represents one of the largest analyses of PpIX-fluorescence in brain metastases. The main observations of the present analysis were as follows: (1) PpIX-behavior of cerebral metastases had no statistically significant influence on the degree of surgical resection, (2) a trend towards a significant higher local recurrence rate in PpIX-non-fluorescent metastases, and (3) PpIX-fluorescent metastases had a favorable outcome with a prolonged progression-free interval and overall survival in the present series.

In our present study, PpIX fluorescence behavior had no influence on the extent of resection or strategy of adjuvant therapy. The dichotomized degree of surgical resection was not significant related to the dichotomized PpIX-fluorescent and non-fluorescent cerebral metastases. Unintended remnants of metastatic tumor tissue are frequently observed after intended complete metastasectomy, and can be verified by an early postoperative MRI [163,159]. Moreover, residual tumor tissue is believed to be a risk factor for a later local recurrence [159,304]. In contrast to malignant glioma, 5-ALA fluorescent guidance of cerebral metastases resection might not be optimal to detect residual metastatic tumor tissue after macroscopically complete resection. Several previous studies reported 5-ALA fluorescence behavior of cerebral metastases [310-318]. Most

studies included less than 10 patients. Apart from previous studies, three further studies with more than 10 patients with totally 114 patients showed PpIX-fluorescence of cerebral metastases in 52%, 73% and 82%, respectively [316,313,311]. PpIX-fluorescence of the tumor bed can frequently be observed after metastases resection, but residual tumor cells can only be histologically verified by a subset of biopsies taken from these areas [312,315,316]. Furthermore, a strong PpIX-fluorescence of the adjacent tumor bed occurs even in 5-ALA negative metastases [315,312]. Therefore, 5-ALA technique does not allow reliable visualization of residual tumor after metastases resection, and a strongly fluorescent resection cavity does not necessarily contain residual tumor. However, current evidence is poor and further studies are required [319]. Nevertheless, PpIX fluorescence of cerebral metastases might be of prognostic value. In the present study we observed a trend towards a significantly higher local recurrence rate in PpIX-non-fluorescent metastases and a significantly progression-free and overall survival in PpIX-fluorescent metastases. The trend towards an improved local control and a longer progression-free survival cannot be explained by a better degree of surgical resection in these metastases. This is in line with our previous report [320]. Interestingly and unexpectedly, overall survival was also correlated with the fluorescence behavior. Overall survival was independent of the treatment modalities in almost all recent phase III studies including patients with single cerebral metastases [287,11,288,289]. This suggests that the overall survival is not related to the occurrence and treatment of single brain metastases but to systemic cancer progression. PpIX-fluorescence of cerebral metastases might be an intrinsic factor related to a more benign character of brain metastases and the primary cancer. Loss of PpIX-fluorescence might reflect a more aggressive behavior of brain metastases. The more aggressive behavior was not correlated with a specific histological subtype or primary site in the present and all recent studies. The less aggressive behavior of strongly fluorescent metastases probably relies on differences in the signaling of PpIX-fluorescent and non-fluorescent metastases: the ferrochelatase activity is related to PpIX accumulation in malignant cells but also to the aggressiveness of some tumors and to the outcome of patients with certain cancer types [321,309,319,322]. However, further translational and clinical studies are required to estimate the diagnostic and prognostic use of 5-ALA in cerebral metastases.

We do acknowledge several limitations in our present study: (1) it represents a secondary analysis with an updated follow-up of patients included in two previous studies and 82 additional patients, resulting in one of the largest analysis of PpIX-fluorescence in brain metastases, (2) As many retrospective metastases studies, this analysis includes a heterogeneous patient population. In particular, state of the adjuvant treatment changed since the first patients were treated. Adjuvant

treatment concepts are well-known to influence the local recurrence rate [287,11,288,289]. We do believe that the longer progression-free interval and overall survival time could also be due to a subgroup of patients receiving whole-brain radiation therapy. However, a subgroup analysis was not intended for statistical reasons as multiple testing requires a correction of the significance level. (3) Apart from the 5-ALA fluorescence behavior, many other factors such as the growth pattern of cerebral metastases or the mode of surgical resection (piecemeal vs. *en bloc* resection) might additionally influence the outcome and may confound our present results [40,252,251]. (4) The degree of resection was dichotomized into complete vs. incomplete or questionable complete resections. A reliable estimation of the resection degree might not have been possible in all cases [159]. Therefore, questionable tumor tissue was statistically considered like residual tumor tissue and might represent an additional bias in these results. Reducing the uncertainty in diagnosing residual tumor tissue on an early postoperative MRI represents a challenge to neuroradiology. (5) PpIX fluorescence was dichotomized into fluorescent or non-fluorescent (either non- or faintly fluorescent) by the neurosurgeon. However, some cerebral metastases show a patchy pattern of fluorescence and fluorescence intensity might range from a vague intensity to a solid deep red. Possibly, different fluorescence intensities might also be related to different outcomes. Furthermore, PpIX fluorescence intensity was related to the surgeon´s impression and might also vary according to the equipment used [323]. A quantitative estimation of 5-ALA fluorescence might give a more objective value and represents a challenge for further studies. (6) The finding that PpIX positive metastases have a better prognosis would have some interest for oncologic biology, but to date does not seem so be significant for clinical purposes. Only half of the cerebral metastases exhibited PpIX-fluorescence. Furthermore, no studies showed a surgical or oncological benefit of 5-ALA fluorescence-guided resections. Moreover, a strongly fluorescent resection cavity does not necessarily contain residual tumor tissue [312,319].

4.3 Predictors for a further local in-brain progression after re-craniotomy of locally recurrent cerebral metastases

With permission from Neurosurgical Review, July 2018; Volume 41 (3): Pages 813-823

About 20 to 40% of cancer patients develop cerebral metastases [240,324]. Surgical resection of single cerebral metastases is one important approach in a multimodal treatment and its benefit is well documented [222,290]. Subsequently, resection of single metastases is recommended by international guidelines for large tumors with a diameter of more than 2 - 3 cm, for surgically accessible metastases and patients with severe neurological burden and good general health [290]. However, surgical resection of cerebral metastases is frequently associated with failure of local control. Post-resection local tumor progression occurs in up to 60% of patients without any adjuvant therapy and in nearly 30% of patients receiving adjuvant whole-brain radiation therapy (WBRT) [12,10,11,159]. The comparatively high local failure rate after surgery or radiosurgery combined with the increased number and the improved prognosis of patients with malignancies has led to an increasing incidence of recurrent cerebral metastases. Treatment of recurrent cerebral metastases is an emerging challenge. Stereotactic radiosurgery, fractionated local or WBRT of locally recurrent metastases are well described and therefore represent valuable radiological treatment options [325-327]. As prospective and controlled studies are lacking, the oncological impact of (re-) irradiation of locally progressive metastases remains disputable. Re-irradiation harbors a significant risk of local complications such as radionecrosis [290]. An alternative treatment option is the microsurgical resection of recurrent metastases. Surgery for recurrent metastases is recommended by the latest European and American guidelines especially for patients with locally accessible metastases, good neurological condition and stable extracranial disease, and a relatively long latency to recurrence [290,328-330]. However, the oncological impact of craniotomy for recurrent cerebral metastases remains disputable and high-quality analyses have yet to be published. Recent evidence (evidence level IIIB) has been obtained from five retrospective case series [264,262,249,331,332]. All of these included both patients suffering from local and distant in-brain progression. Risk of peri-operative surgical complications, rate of incomplete surgical resections and incidence of further local in-brain progressions will likely be higher for locally recurrent metastases with extensive previous surgical and radio-oncological treatment as compared to distant metastases without any previous local therapy. While recent studies focused on identification of factors influencing overall survival, predictors of local failure after resection of recurrent metastases have yet to be identified.

There are three key findings in this study: 1) complete surgical resection of locally recurrent cerebral metastases as confirmed by early postoperative MRI could only be achieved 37.8%; 2) detection of residual tumor tissue on early postoperative MRI following recurrent metastases surgery correlated with further local in-brain progression when defining a significance level of $p = 0.05$ but not after Šidák- or Bonferroni significance level correction for multiple testing and; 3) definite local tumor control could finally be achieved in 91.9% despite further local in-brain progression in 37.8%. Overall survival after recurrent metastasectomy was significantly longer than predicted by ds-GPA.

As prospective and controlled studies are lacking deciding upon the best treatment for recurrent cerebral metastases remains a challenge. To our best knowledge, to date only 5 retrospective case series have analyzed the impact of surgical resection of locally progressive brain metastases [332,331,264,262,249]. The oncological impact of a re-craniotomy of locally progressive cerebral metastases after previous surgery with and without previous irradiation remains unclear. Furthermore, local in-brain progression rates are well documented for the first recurrence but not for further recurrences. In the present study MRI-verified complete surgical resection of recurrent metastases was achieved in nearly 40% of patients. Rate of incomplete surgical resections was 40.5%. Therefore, proportion of subtotal resections of recurrent metastases is twice the incidence of incomplete resections known from craniotomies for firstly diagnosed cerebral metastases [159].

Several reasons may explain the unsatisfyingly high rate of incomplete resections: (1) Surgery of recurrent cerebral metastases may be more challenging than first craniotomies due to e.g. scar formation, pseudo progression, infiltration of cerebral vessels or eloquent brain areas. Infiltration of cerebral vessels and eloquent brain areas together with extensive scar formation could impede complete surgical resection. In fact, in more than half of incompletely resected metastases in the present study, the surgeons did not intend a complete surgical resection because cerebral vessels were either infiltrated by the metastasis or were involved in extensive scar formation ($n = 4$) or due to infiltration of eloquent brain areas ($n = 3$). In comparison, resection had been classified as complete by the surgeon in 92.3% in the previous study analysing the degree of the first craniotomy for a cranial metastasis [159]. (2) Reliable intraoperative differentiation between scar formation and tumor infiltration by the surgeon may be more difficult after extensive previous treatments leading to higher rate of unintended incomplete surgical resections. (3) Reliable discrimination between post-therapeutic tissue changes on MRI (e.g. scar formation) and residual tumor parts may also be challenging. As we did not gather histo-pathological samples from the resection cavity, we

cannot completely exclude that isolated residual contrast-enhancing parts on the postoperative MRI may not be residual tumor tissue but scar formation. However, residual contrast-enhancing parts on MRI might unlikely be scar if removed contrast-enhancing parts were verified as tumor by histopathological analysis. The unsatisfying high rate of incomplete resections is in line with some previous reports: The previous study by Schackert and coworkers [332] reported a similarly high rate of subtotal surgical resection of local and distant recurrences (41.8%). In contrast, others observed no subtotal resections [264]. The local in-brain progression rate was 37.8% and therefore slightly higher than our previously reported local in-brain progression rate after first craniotomy (30.8%) [159]. The higher local in-brain progression rate in the case of recurrence might well be explained by the higher rate of subtotal resections. Possibly, those metastases showing multiple recurrences exhibit more aggressive biological behavior (e.g. as may be more brain-invasive) than metastases in which local control could be achieved [302]. Extent of surgical resection as assessed by an early postoperative MRI was the only predictor for local in-brain progression. Extent of surgical resections was recently shown to be crucial for the local in-brain progression rate of cerebral metastases and other (malignant) brain tumors. Residual tumor tissue was verified by early postoperative MRI in up to 20% after first craniotomy of cerebral metastases. Complete surgical resection and residual tumor verification significantly correlates with the rate of local in-brain progression [159]. For malignant glioma, the degree of surgical resection is well known to correlate with the progression-free survival in prospective, randomized and controlled studies [161,307,333,334]. Furthermore, recent retrospective analyses revealed a significant influence of the extent of re-resections of recurrent glioblastoma and the progression-free survival [335,336]. Our present study suggests that resection degree of recurrent cerebral metastases similarly determines local in-brain progression rate. Beyond complete tumor removal, a “supramarginal” resection with extension of the resection beyond the contrast-enhancing borders of the tumor (or the flair lesion for low-grade glioma) was considered to additionally improve local control in cerebral metastases [12,335,306,303] and low-grade glioma [337] and also results in an improved overall survival of glioblastoma patients [338]. However, the impact of supramarginal resection has yet to be analyzed for recurrent metastases. The degree of surgical resection of cerebral metastases and all other assessed parameters had no influence on overall survival in the present analysis. Previous studies have revealed different factors influencing overall survival including systemic disease status [262,249], gender [249], primary tumor [249], pre-operative performance as assessed by the Karnofsky Performance Scale [249,262,331], latency to recurrence [249,332], and again degree of surgical resection [332]. Overall survival was significantly longer as compared to the survival prediction by ds-GPA. Of note, ds-GPA was designed for patients with newly

diagnosed cerebral metastases and not for patients with recurrent metastases. One explanation for the better overall survival is likely the high rate in which local control was finally achieved (91.9%). Despite the high rate of local control, leptomeningeal carcinomatosis was observed in 36% of patients.

We acknowledge several limitations of our present study: (1) the results of our analysis are limited by the retrospective single-center study design. Other surgical techniques in other neuro-oncological centers could result in a higher rate of complete surgical resections. Metastases were resected by circumferential stripping of the cerebral metastasis from the surrounding brain tissue. Craniotomies involved use of ultrasound, a navigation system and were performed in a microsurgical approach. For eloquently situated metastases, surgery was performed with intraoperative neurophysiological monitoring and if necessary as awake craniotomy. The technique is state-of-art and we are not aware of any significant difference in our technique and that employed by others; (2) the present patient population was heterogeneous regarding the different primary tumors and different tumor stages. Moreover, distribution of histology and primary cancer in the present study does not represent the distribution known from the primary situation [324]: Patients with malignant melanoma (8,3%) or breast cancer (5,6%) metastases were underrepresented in the cohort. (3) The present patient population was also heterogeneous regarding different adjuvant and systemic therapy concepts before craniotomy of their recurrent metastases: (a) Adjuvant therapy concepts after first and re-craniotomy are still matter of debate and must be evaluated in further studies. WBRT was the gold standard and recommended by the guidelines for a long time. It´s oncological impact was questioned after the EORTC 22952-26001 study: WBRT leads to significantly lower local recurrence rate, has no influence on overall survival but significantly impacts patients' neurocognitive function and quality of life [287,11,236]. As other neurooncological departments, we do not routinely recommend WBRT after complete surgical resection of a single cerebral metastasis. This is one explanation for the heterogeneity in our patient cohort. Standards for the best adjuvant treatment after metastasectomy are not established and are analyzed in a number of recently published and initiated studies (e.g. NOA-14 / HIPPORAD-study, C-O-Met study) [288,287]. Evidence for the best adjuvant therapy is even scarcer for the recurrence situation. (b) Due to their different primary tumors and tumor stages, the present patient population was more heterogeneous regarding their previous systemic therapy. Next to different biological behavior of various carcinomas [302] the heterogeneity of treatment and treatment response of different cancers may be crucial in understanding their behavior in and outside of the brain. In particular, brain metastases of different primary tumors differ in their response rates to

chemotherapy. Metastases from breast cancer show an intermediate response whereas metastases form malignant melanoma and NSCLC show low rates [290]. Furthermore, conventional chemotherapy and target therapies, (e.g. in the treatment of malignant melanoma), may beneficially influence cerebral metastatic spread [339,340]. Therefore, the comparatively low incidence of patients with locally recurrent brain metastasis from malignant melanoma and breast cancer in the present series may reflect the effectiveness of a previous systemic therapy. (4) the number of patients included in the present study is very limited. Surprisingly, re-craniotomy for cerebral metastases seems to be a comparatively rare indication (e.g. about 1.2% of all surgery for malignancy in our department and 2.2% of all craniotomies in the recent study of Kennion *et* Holliman) [331] and all recent studies included a limited number of patients (27 – 69 patients). Well-conducted studies with a larger patient number are needed and may require multi-center pooling of data when possible; (5) Detection of residual tumor tissue on an early MRI following recurrent metastases surgery was the only predictor for further local in-brain progression when defining a significance level of $p = 0.05$ but not if defining a Šidák- ($p = 0.0051$) or Bonferroni-adjusted ($p = 0.005$) significance level. Furthermore, no correlation between the PFS and the resection status was observed. A higher number of patients may have led to a stronger correlation; (6) extent of surgical resection on early postoperative MRI could not be reliably evaluated in 21.6% of patients. This rate is comparable to the previous rate of 18.5% in which a final decision on degree of resection could be made after first craniotomy for cerebral metastases. Reducing this uncertainty represents a challenge to neuroradiology; (7) to date, an early postoperative MRI is probably the gold standard in evaluating the degree of the first surgical resection of cerebral metastases and was recommended by the most recent European guideline for diagnosis and treatment of brain metastases from solid tumors [290]. Despite not being standard in all neurooncological department, an early postoperative MRI was used to estimate the degree of metastasectomy in several prospective and retrospective studies use [335,11,341,306,159,303]. Residual tumor tissue was frequently observed after first metastasectomy and was considered to represent a factor responsible for high recurrence rates seen in these patients [159]. However, the oncological impact of an early postoperative MRI after resection of recurrent brain metastases has yet to be systematically analysed. As described before, for malignant and firstly diagnosed metastases, postoperative MRI was performed within 72 hours after resection [159,160]. The period of 72 hours following surgery allowing valid discrimination between residual tumor and postoperative reactions has been evaluated for malignant glioma but never for cerebral metastases. Furthermore, it remains unclear whether higher field intensities of MRI (e.g. 1.5 vs. 3 T) would enable a more reliable detection of residual tumor tissue. As a differentiation between scar / pseudo

progression and residual and recurrent metastatic tissue remains challenging, metabolic imaging (e.g. by an FET-PET) may be an additional option [342]; (8) the diagnosis-specific Graded Prognostic Assessment (ds-GPA) was performed on data of 4,259 patients with newly diagnosed cerebral metastasis [343]. As a result, prognostic factors for patients with cerebral metastases were related to the primary site. We used the ds-GPA for an estimation of the prognosis of patients with recurrent metastases. (9) A comparably high percentage (75%) of patients suffered from an uncontrolled systemic diseases status. In addition to insufficiency of previous treatment, local in-brain-progression as inclusion criteria in the present population may also be a reflection of this uncontrolled systemic disease status. Further studies should analyze potential influence of the systemic disease status on the local recurrence rate. Systematic analysis of resection of locally progressive cerebral metastasis results in a high percentage of incomplete resections on early post-operative MR and in a comparatively high local in-brain progression rate. The degree of surgical recurrent metastases resection was the only predictor of local recurrence but had no influence on overall survival. Despite the high rate of incomplete resections and of local in-brain progression, local control could finally be achieved in 91.9% after further surgeries or adjuvant radiation. However, 5.5% of patients died from isolated in-brain-progression and 33% patients from systemic and cerebral tumor progression. Mean overall survival was 12.9 months and 22.2% of patients experienced overall survival exceeding 24 months. Considering the adequate local tumor control achieved in the vast majority of patients, surgery of recurrent metastases may represent one option in a multi-modal treatment approach of patients suffering from locally recurrent cerebral metastases.

5. References

1. Stewart BW WC (2014) *World Cancer Report 2014*. Internation Agency for Research on Cancer/World Health Organization, Lyon, France
2. Malvezzi M, Bertuccio P, Levi F, La Vecchia C, Negri E (2014) *European cancer mortality predictions for the year 2014*. Ann Oncol 25:1650-1656. doi:10.1093/annonc/mdu138
3. Kumar V AA, Aster JC (2015) *Robbins and Cotran Pathologic Basis of Disease*. Ninth Edition edn. Saunders, Philadelphia, USA
4. Jackel MC, Rausch H (1999) *[Distant metastasis of squamous epithelial carcinomas of the upper aerodigestive tract. The effect of clinical tumor parameters and course of illness]*. HNO 47:38-44
5. de Bree R, Deurloo EE, Snow GB, Leemans CR (2000) *Screening for distant metastases in patients with head and neck cancer*. Laryngoscope 110:397-401. doi:10.1097/00005537-200003000-00012
6. Hay ID (1987) *Brain metastases from papillary thyroid carcinoma*. Arch Intern Med 147:607, 611
7. Posner JB (1992) *Management of brain metastases*. Rev Neurol (Paris) 148:477-487
8. Johnson JD, Young B (1996) *Demographics of brain metastasis*. Neurosurgery clinics of North America 7:337-344
9. Wen PY, Loeffler JS (1999) *Management of brain metastases*. Oncology (Williston Park) 13:941-954, 957-961; discussion 961-942, 949
10. Patchell RA, Tibbs PA, Regine WF, Dempsey RJ, Mohiuddin M, Kryscio RJ, Markesbery WR, Foon KA, Young B (1998) *Postoperative radiotherapy in the treatment of single metastases to the brain: a randomized trial*. JAMA : the journal of the American Medical Association 280:1485-1489
11. Kocher M, Soffietti R, Abacioglu U, Villa S, Fauchon F, Baumert BG, Fariselli L, Tzuk-Shina T, Kortmann RD, Carrie C, Ben Hassel M, Kouri M, Valeinis E, van den Berge D, Collette S, Collette L, Mueller RP (2011) *Adjuvant whole-brain radiotherapy versus observation after radiosurgery or surgical resection of one to three cerebral metastases: results of the EORTC 22952-26001 study*. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 29:134-141. doi:10.1200/JCO.2010.30.1655
12. Miekisiak G, Yoo K, Sandler AL, Kulik TB, Chen JF, Winn HR (2009) *The role of adenosine in hypercarbic hyperemia: in vivo and in vitro studies in adenosine 2(A) receptor knockout and wild-type mice*. Journal of neurosurgery 110:981-988. doi:10.3171/2008.8.JNS08460
13. Weller M (2015) *Hirnmetastasen und Meningeosis Neoplastica (S2k)*. Leitlinien fur Diagnostik und Therapie in der Neurologie. AWMF-Registernummer 030/060, Germany
14. Cavaliere R SD, Wen P, Huntoon K (2016) *Bradley's Neurology in Clinical Practice*. Nervous System Metastases. Elsevier USA
15. Sneed PK KN, Rubenstein JL (2014) *Abeloff's Clinical Oncology*. Brain Metastases and Neoplastic Meningitis, Fifth edn. Livingstone, Philadelphia, USA
16. Wasserstrom WR, Glass JP, Posner JB (1982) *Diagnosis and treatment of leptomeningeal metastases from solid tumors: experience with 90 patients*. Cancer 49:759-772
17. Yap HY, Yap BS, Tashima CK, DiStefano A, Blumenschein GR (1978) *Meningeal carcinomatosis in breast cancer*. Cancer 42:283-286
18. Chamberlain MC, Kormanik PA (1997) *Prognostic significance of coexistent bulky metastatic central nervous system disease in patients with leptomeningeal metastases*. Arch Neurol 54:1364-1368
19. Jayson GC, Howell A (1996) *Carcinomatous meningitis in solid tumours*. Ann Oncol 7:773-786

20. Balm M, Hammack J (1996) *Leptomeningeal carcinomatosis. Presenting features and prognostic factors*. Arch Neurol 53:626-632
21. Grossman SA, Krabak MJ (1999) *Leptomeningeal carcinomatosis*. Cancer Treat Rev 25:103-119. doi:10.1053/ctrv.1999.0119
22. DeAngelis LM (1998) *Current diagnosis and treatment of leptomeningeal metastasis*. J Neurooncol 38:245-252
23. Kesari S, Batchelor TT (2003) *Leptomeningeal metastases*. Neurol Clin 21:25-66
24. Kaplan JG, DeSouza TG, Farkash A, Shafran B, Pack D, Rehman F, Fuks J, Portenoy R (1990) *Leptomeningeal metastases: comparison of clinical features and laboratory data of solid tumors, lymphomas and leukemias*. J Neurooncol 9:225-229
25. Jaeckle KA (2006) *Neoplastic meningitis from systemic malignancies: diagnosis, prognosis and treatment*. Semin Oncol 33:312-323. doi:10.1053/j.seminoncol.2006.04.016
26. Society AC (2015) *Cancer Facts & Figures 2015*. American Cancer Society, Atlanta, USA
27. Schouten LJ, Rutten J, Huveneers HA, Twijnstra A (2002) *Incidence of brain metastases in a cohort of patients with carcinoma of the breast, colon, kidney, and lung and melanoma*. Cancer 94:2698-2705
28. Barnholtz-Sloan JS, Sloan AE, Davis FG, Vigneau FD, Lai P, Sawaya RE (2004) *Incidence proportions of brain metastases in patients diagnosed (1973 to 2001) in the Metropolitan Detroit Cancer Surveillance System*. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 22:2865-2872. doi:10.1200/JCO.2004.12.149
29. de Bree R, Mehta DM, Snow GB, Quak JJ (2001) *Intracranial metastases in patients with squamous cell carcinoma of the head and neck*. Otolaryngol Head Neck Surg 124:217-221. doi:10.1067/mhn.2001.112478
30. Takes RP, Rinaldo A, Silver CE, Haigentz M, Jr., Woolgar JA, Triantafyllou A, Mondin V, Paccagnella D, de Bree R, Shaha AR, Hartl DM, Ferlito A (2012) *Distant metastases from head and neck squamous cell carcinoma. Part I. Basic aspects*. Oral Oncol 48:775-779. doi:10.1016/j.oraloncology.2012.03.013
31. Choi HJ, Cho BC, Sohn JH, Shin SJ, Kim SH, Kim JH, Yoo NC (2009) *Brain metastases from hepatocellular carcinoma: prognostic factors and outcome: brain metastasis from HCC*. J Neurooncol 91:307-313. doi:10.1007/s11060-008-9713-3
32. Mahmoud-Ahmed AS, Suh JH, Kupelian PA, Klein EA, Peereboom DM, Dreicer R, Barnett GH (2002) *Brain metastases from bladder carcinoma: presentation, treatment and survival*. J Urol 167:2419-2422
33. Tremont-Lukats IW, Bobustuc G, Lagos GK, Lolas K, Kyritsis AP, Puduvalli VK (2003) *Brain metastasis from prostate carcinoma: The M. D. Anderson Cancer Center experience*. Cancer 98:363-368. doi:10.1002/cncr.11522
34. Sutton MA, Watkins HL, Green LK, Kadmon D (1996) *Intracranial metastases as the first manifestation of prostate cancer*. Urology 48:789-793. doi:10.1016/S0090-4295(96)00238-5
35. Posner J (1995) *Neurologic Complications of Cancer*. Oxford University Press, Philadelphia, USA
36. Ogawa K, Yoshii Y, Aoki Y, Nagai Y, Tsuchida Y, Toita T, Kakinohana Y, Tamaki W, Iraha S, Adachi G, Hirakawa M, Kamiyama K, Inamine M, Hyodo A, Murayama S (2008) *Treatment and prognosis of brain metastases from gynecological cancers*. Neurologia medico-chirurgica 48:57-62; discussion 62-53
37. McWilliams RR, Giannini C, Hay ID, Atkinson JL, Stafford SL, Buckner JC (2003) *Management of brain metastases from thyroid carcinoma: a study of 16 pathologically confirmed cases over 25 years*. Cancer 98:356-362. doi:10.1002/cncr.11488
38. Lemke J, Scheele J, Kapapa T, Wirtz CR, Henne-Bruns D, Kornmann M (2013) *Brain metastasis in pancreatic cancer*. Int J Mol Sci 14:4163-4173. doi:10.3390/ijms14024163
39. Posner JB (1996) *Brain metastases: 1995. A brief review*. J Neurooncol 27:287-293

40. Suki D, Abouassi H, Patel AJ, Sawaya R, Weinberg JS, Groves MD (2008) *Comparative risk of leptomeningeal disease after resection or stereotactic radiosurgery for solid tumor metastasis to the posterior fossa*. Journal of neurosurgery 108:248-257. doi:10.3171/JNS/2008/108/2/0248
41. Nelson WG, De Marzo AM, Isaacs WB (2003) *Prostate cancer*. The New England journal of medicine 349:366-381. doi:10.1056/NEJMra021562
42. Jemal A, Siegel R, Ward E, Murray T, Xu J, Smigal C, Thun MJ (2006) *Cancer statistics, 2006*. CA: a cancer journal for clinicians 56:106-130
43. Winn HR (2011) *Youmans Neurological Surgery*, vol 2. Sixth edn. Elsevier Saunders, Philadelphia, PA, USA
44. Guomundsson KR (1970) *A survey of tumors of the central nervous system in Iceland during the 10-year period 1954-1963*. Acta Neurol Scand 46:538-552
45. Percy AK, Elveback LR, Okazaki H, Kurland LT (1972) *Neoplasms of the central nervous system. Epidemiologic considerations*. Neurology 22:40-48
46. Fogelholm R, Uutela T, Murros K (1984) *Epidemiology of central nervous system neoplasms. A regional survey in Central Finland*. Acta Neurol Scand 69:129-136
47. Walker AE, Robins M, Weinfeld FD (1985) *Epidemiology of brain tumors: the national survey of intracranial neoplasms*. Neurology 35:219-226
48. Counsell CE, Collie DA, Grant R (1996) *Incidence of intracranial tumours in the Lothian region of Scotland, 1989-90*. J Neurol Neurosurg Psychiatry 61:143-150
49. Materljan E, Materljan B, Sepcic J, Tuskan-Mohar L, Zamolo G, Erman-Baldini I (2004) *Epidemiology of central nervous system tumors in Labin area, Croatia, 1974-2001*. Croat Med J 45:206-212
50. Smedby KE, Brandt L, Backlund ML, Blomqvist P (2009) *Brain metastases admissions in Sweden between 1987 and 2006*. Br J Cancer 101:1919-1924. doi:10.1038/sj.bjc.6605373
51. Takakura KS, K; Hojo, S; Hirano, A (1982) *Metastatic Tumors of the Central Nervous System*. Igaku Shoin, New York
52. Posner JB (1980) *Brain Metastases: a clinician's view*, vol 2. Brain metastasis. GK Hall, Boston, USA
53. Baker GS, Kernohan JW, Kiefer EJ (1951) *Metastatic tumors of the brain*. Surg Clin North Am 31:1143-1145
54. Chang DB, Yang PC, Luh KT, Kuo SH, Hong RL, Lee LN (1992) *Late survival of non-small cell lung cancer patients with brain metastases. Influence of treatment*. Chest 101:1293-1297
55. Lang EF, Slater J (1964) *Metastatic Brain Tumors. Results of Surgical and Nonsurgical Treatment*. Surg Clin North Am 44:865-872
56. Le Chevalier T, Smith FP, Caille P, Constans JP, Rouesse JG (1985) *Sites of primary malignancies in patients presenting with cerebral metastases. A review of 120 cases*. Cancer 56:880-882
57. MacGee EE (1971) *Surgical treatment of cerebral metastases from lung cancer. The effect on quality and duration of survival*. Journal of neurosurgery 35:416-420. doi:10.3171/jns.1971.35.4.0416
58. Markesbery WR, Brooks WH, Gupta GD, Young AB (1978) *Treatment for patients with cerebral metastases*. Arch Neurol 35:754-756
59. Sundaresan N, Galicich JH (1985) *Surgical treatment of brain metastases. Clinical and computerized tomography evaluation of the results of treatment*. Cancer 55:1382-1388
60. Zimm S, Wampler GL, Stablein D, Hazra T, Young HF (1981) *Intracerebral metastases in solid-tumor patients: natural history and results of treatment*. Cancer 48:384-394
61. Tsukada Y, Fouad A, Pickren JW, Lane WW (1983) *Central nervous system metastasis from breast carcinoma. Autopsy study*. Cancer 52:2349-2354

62. Vieth RG, Odom GL (1965) *Intracranial metastases and their neurosurgical treatment*. Journal of neurosurgery 23:375-383. doi:10.3171/jns.1965.23.4.0375
63. Chason JL, Walker FB, Landers JW (1963) *Metastatic carcinoma in the central nervous system and dorsal root ganglia. A prospective autopsy study*. Cancer 16:781-787
64. Castaldo JE, Bernat JL, Meier FA, Schned AR (1983) *Intracranial metastases due to prostatic carcinoma*. Cancer 52:1739-1747
65. Taylor HG, Lefkowitz M, Skoog SJ, Miles BJ, McLeod DG, Coggin JT (1984) *Intracranial metastases in prostate cancer*. Cancer 53:2728-2730
66. Stein M, Steiner M, Klein B, Beck D, Atad J, Kuten A, Robinson E, Goldsher D (1986) *Involvement of the central nervous system by ovarian carcinoma*. Cancer 58:2066-2069
67. Bloch JL, Nieh PT, Walzak MP (1987) *Brain metastases from transitional cell carcinoma*. J Urol 137:97-99
68. Dauplat J, Nieberg RK, Hacker NF (1987) *Central nervous system metastases in epithelial ovarian carcinoma*. Cancer 60:2559-2562
69. Steinfeld AD, Zelefsky M (1987) *Brain metastases from carcinoma of bladder*. Urology 29:375-376
70. Lewis AJ (1988) *Sarcoma metastatic to the brain*. Cancer 61:593-601
71. Anderson RS, el-Mahdi AM, Kuban DA, Higgins EM (1992) *Brain metastases from transitional cell carcinoma of urinary bladder*. Urology 39:17-20
72. Martinez-Manas RM, Brell M, Rumia J, Ferrer E (1998) *Brain metastases in endometrial carcinoma*. Gynecol Oncol 70:282-284. doi:10.1006/gyno.1998.5021
73. Posner JB (1995) *Neurologic complications of cancer*. Contemporary neurology series, vol 45. F.A. Davis, Philadelphia
74. Posner JB, Chernik NL (1978) *Intracranial metastases from systemic cancer*. Adv Neurol 19:579-592
75. Aronson SM, Garcia JH, Aronson BE (1964) *Metastatic Neoplasms of the Brain: Their Frequency in Relation to Age*. Cancer 17:558-563
76. de la Monte SM, Hutchins GM, Moore GW (1988) *Influence of age on the metastatic behavior of breast carcinoma*. Hum Pathol 19:529-534
77. Sorensen JB, Hansen HH, Hansen M, Dombernowsky P (1988) *Brain metastases in adenocarcinoma of the lung: frequency, risk groups, and prognosis*. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 6:1474-1480. doi:10.1200/jco.1988.6.9.1474
78. Graus F, Walker RW, Allen JC (1983) *Brain metastases in children*. J Pediatr 103:558-561
79. Vannucci RC, Baten M (1974) *Cerebral metastatic disease in childhood*. Neurology 24:981-985
80. Tasdemiroglu E, Patchell RA (1997) *Cerebral metastases in childhood malignancies*. Acta neurochirurgica 139:182-187
81. Fell DA, Leavens ME, McBride CM (1980) *Surgical versus nonsurgical management of metastatic melanoma of the brain*. Neurosurgery 7:238-242
82. Sampson JH, Carter JH, Jr., Friedman AH, Seigler HF (1998) *Demographics, prognosis, and therapy in 702 patients with brain metastases from malignant melanoma*. Journal of neurosurgery 88:11-20. doi:10.3171/jns.1998.88.1.0011
83. Amer MH, Al-Sarraf M, Baker LH, Vaitkevicius VK (1978) *Malignant melanoma and central nervous system metastases: incidence, diagnosis, treatment and survival*. Cancer 42:660-668
84. Pickren JL, G; Tsukada, Y; Lane, WW; (1983) *Brain metastases: an autopsy study*. Cancer Tret Symp 52:2349-2354
85. Yaar M, Park HY (2012) *Melanocytes: a window into the nervous system*. J Invest Dermatol 132:835-845. doi:10.1038/jid.2011.386

86. Clarke JL, Perez HR, Jacks LM, Panageas KS, Deangelis LM (2010) *Leptomeningeal metastases in the MRI era*. Neurology 74:1449-1454. doi:10.1212/WNL.0b013e3181dc1a69
87. Lara-Medina F, Crismatt A, Villarreal-Garza C, Alvarado-Miranda A, Flores-Hernandez L, Gonzalez-Pinedo M, Gamboa-Vignolle C, Ruiz-Gonzalez JD, Arrieta O (2012) *Clinical features and prognostic factors in patients with carcinomatous meningitis secondary to breast cancer*. Breast J 18:233-241. doi:10.1111/j.1524-4741.2012.01228.x
88. Umemura S, Tsubouchi K, Yoshioka H, Hotta K, Takigawa N, Fujiwara K, Horita N, Segawa Y, Hamada N, Takata I, Yamane H, Kamei H, Kiura K, Tanimoto M (2012) *Clinical outcome in patients with leptomeningeal metastasis from non-small cell lung cancer: Okayama Lung Cancer Study Group*. Lung Cancer 77:134-139. doi:10.1016/j.lungcan.2012.03.002
89. Morris PG, Reiner AS, Szenberg OR, Clarke JL, Panageas KS, Perez HR, Kris MG, Chan TA, DeAngelis LM, Omuro AM (2012) *Leptomeningeal metastasis from non-small cell lung cancer: survival and the impact of whole brain radiotherapy*. J Thorac Oncol 7:382-385. doi:10.1097/JTO.0b013e3182398e4f
90. Raizer JJ, Hwu WJ, Panageas KS, Wilton A, Baldwin DE, Bailey E, von Althann C, Lamb LA, Alvarado G, Bilsky MH, Gutin PH (2008) *Brain and leptomeningeal metastases from cutaneous melanoma: survival outcomes based on clinical features*. Neuro Oncol 10:199-207. doi:10.1215/15228517-2007-058
91. Taillibert S, Laigle-Donadey F, Chodkiewicz C, Sanson M, Hoang-Xuan K, Delattre JY (2005) *Leptomeningeal metastases from solid malignancy: a review*. J Neurooncol 75:85-99. doi:10.1007/s11060-004-8101-x
92. Norris LK, Grossman SA, Olivi A (1997) *Neoplastic meningitis following surgical resection of isolated cerebellar metastasis: a potentially preventable complication*. J Neurooncol 32:215-223
93. DeAngelis LM, Mandell LR, Thaler HT, Kimmel DW, Galicich JH, Fuks Z, Posner JB (1989) *The role of postoperative radiotherapy after resection of single brain metastases*. Neurosurgery 24:798-805
94. Johnson MD, Avkshtol V, Baschnagel AM, Meyer K, Ye H, Grills IS, Chen PY, Maitz A, Olson RE, Pieper DR, Krauss DJ (2016) *Surgical Resection of Brain Metastases and the Risk of Leptomeningeal Recurrence in Patients Treated With Stereotactic Radiosurgery*. Int J Radiat Oncol Biol Phys 94:537-543. doi:10.1016/j.ijrobp.2015.11.022
95. Ahn JH, Lee SH, Kim S, Joo J, Yoo H, Lee SH, Shin SH, Gwak HS (2012) *Risk for leptomeningeal seeding after resection for brain metastases: implication of tumor location with mode of resection*. Journal of neurosurgery 116:984-993. doi:10.3171/2012.1.JNS111560
96. Suki D, Hatiboglu MA, Patel AJ, Weinberg JS, Groves MD, Mahajan A, Sawaya R (2009) *Comparative risk of leptomeningeal dissemination of cancer after surgery or stereotactic radiosurgery for a single supratentorial solid tumor metastasis*. Neurosurgery 64:664-674; discussion 674-666. doi:10.1227/01.NEU.0000341535.53720.3E
97. Horne SD, Pollick SA, Heng HH (2015) *Evolutionary mechanism unifies the hallmarks of cancer*. Int J Cancer 136:2012-2021. doi:10.1002/ijc.29031
98. Pietras K, Ostman A (2010) *Hallmarks of cancer: interactions with the tumor stroma*. Exp Cell Res 316:1324-1331. doi:10.1016/j.yexcr.2010.02.045
99. Hanahan D, Weinberg RA (2011) *Hallmarks of cancer: the next generation*. Cell 144:646-674. doi:10.1016/j.cell.2011.02.013
100. Popper HH (2016) *Progression and metastasis of lung cancer*. Cancer Metastasis Rev 35:75-91. doi:10.1007/s10555-016-9618-0

101. Catalano V, Turdo A, Di Franco S, Dieli F, Todaro M, Stassi G (2013) *Tumor and its microenvironment: a synergistic interplay*. Semin Cancer Biol 23:522-532. doi:10.1016/j.semcancer.2013.08.007
102. Jeevan DS, Cooper JB, Braun A, Murali R, Jhanwar-Uniyal M (2016) *Molecular Pathways Mediating Metastases to the Brain via Epithelial-to-Mesenchymal Transition: Genes, Proteins, and Functional Analysis*. Anticancer Res 36:523-532
103. Menyhart O, Harami-Papp H, Sukumar S, Schafer R, Magnani L, de Barrios O, Gyorffy B (2016) *Guidelines for the selection of functional assays to evaluate the hallmarks of cancer*. Biochim Biophys Acta 1866:300-319. doi:10.1016/j.bbcan.2016.10.002
104. Sancho P, Barneda D, Heeschen C (2016) *Hallmarks of cancer stem cell metabolism*. Br J Cancer 114:1305-1312. doi:10.1038/bjc.2016.152
105. Pavlova NN, Thompson CB (2016) *The Emerging Hallmarks of Cancer Metabolism*. Cell Metab 23:27-47. doi:10.1016/j.cmet.2015.12.006
106. Dalmay T, Edwards DR (2006) *MicroRNAs and the hallmarks of cancer*. Oncogene 25:6170-6175. doi:10.1038/sj.onc.1209911
107. Gavrilovic IT, Posner JB (2005) *Brain metastases: epidemiology and pathophysiology*. J Neurooncol 75:5-14. doi:10.1007/s11060-004-8093-6
108. Perry AB, AJ. (2010) *Practical Surgical Neuropathology: A Diagnostic Approach*. Saunders Elsevier, USA
109. Delattre JY, Krol G, Thaler HT, Posner JB (1988) *Distribution of brain metastases*. Arch Neurol 45:741-744
110. Chamberlain MC (2010) *Brain metastases: a medical neuro-oncology perspective*. Expert Rev Neurother 10:563-573. doi:10.1586/ern.10.30
111. Paget S (1989) *The distribution of secondary growths in cancer of the breast. 1889*. Cancer Metastasis Rev 8:98-101
112. Zhang C, Yu D (2011) *Microenvironment determinants of brain metastasis*. Cell Biosci 1:8. doi:10.1186/2045-3701-1-8
113. Fidler IJ (2011) *The role of the organ microenvironment in brain metastasis*. Semin Cancer Biol 21:107-112. doi:10.1016/j.semcancer.2010.12.009
114. Carbonell WS, Ansorge O, Sibson N, Muschel R (2009) *The vascular basement membrane as "soil" in brain metastasis*. PloS one 4:e5857. doi:10.1371/journal.pone.0005857
115. Khuntia D, Brown P, Li J, Mehta MP (2006) *Whole-brain radiotherapy in the management of brain metastasis*. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 24:1295-1304. doi:10.1200/JCO.2005.04.6185
116. Langer CJ, Mehta MP (2005) *Current management of brain metastases, with a focus on systemic options*. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 23:6207-6219. doi:10.1200/JCO.2005.03.145
117. Norden AD, Wen PY, Kesari S (2005) *Brain metastases*. Curr Opin Neurol 18:654-661
118. Chang JE, Robins HI, Mehta MP (2007) *Therapeutic advances in the treatment of brain metastases*. Clin Adv Hematol Oncol 5:54-64
119. Suh JH, Chao ST, Vogelbaum MA (2009) *Management of brain metastases*. Curr Neurol Neurosci Rep 9:223-230
120. Iguchi Y, Mano K, Goto Y, Nakano T, Nomura F, Shimokata T, Iwamizu-Watanabe S, Hashizume Y (2007) *Miliary brain metastases from adenocarcinoma of the lung: MR imaging findings with clinical and post-mortem histopathologic correlation*. Neuroradiology 49:35-39. doi:10.1007/s00234-006-0152-6
121. Schiff D, O'neill, B.P. (2005) *Principles of Neurooncology*. The management of brain metastases. McGraw-Hill, USA
122. Burger PCS, B. (2007) *Tumors of the central nervous system*. Metastatic and secondary neoplasms. American Registry of Pathology Press, USA

123. Quattrocchi CC, Errante Y, Gaudino C, Mallio CA, Giona A, Santini D, Tonini G, Zobel BB (2012) *Spatial brain distribution of intra-axial metastatic lesions in breast and lung cancer patients*. J Neurooncol 110:79-87. doi:10.1007/s11060-012-0937-x
124. Abbott NJ, Ronnback L, Hansson E (2006) *Astrocyte-endothelial interactions at the blood-brain barrier*. Nat Rev Neurosci 7:41-53. doi:10.1038/nrn1824
125. Abbott NJ (2004) *Evidence for bulk flow of brain interstitial fluid: significance for physiology and pathology*. Neurochem Int 45:545-552. doi:10.1016/j.neuint.2003.11.006
126. Ge S, Song L, Pachter JS (2005) *Where is the blood-brain barrier ... really?* J Neurosci Res 79:421-427. doi:10.1002/jnr.20313
127. Gartner LP (2017) *Textbook of Histology*. 4th Edition edn. Elsevier, USA
128. Constanzo LS (2014) *Physiology*. 5th edn. Saunder-Elsevier, USA
129. Begley DJ, Brightman MW (2003) *Structural and functional aspects of the blood-brain barrier*. Prog Drug Res 61:39-78
130. Pardridge WM (2003) *Blood-brain barrier drug targeting: the future of brain drug development*. Mol Interv 3:90-105, 151. doi:10.1124/mi.3.2.90
131. el-Bacha RS, Minn A (1999) *Drug metabolizing enzymes in cerebrovascular endothelial cells afford a metabolic protection to the brain*. Cell Mol Biol (Noisy-le-grand) 45:15-23
132. Hawkins BT, Davis TP (2005) *The blood-brain barrier/neurovascular unit in health and disease*. Pharmacol Rev 57:173-185. doi:10.1124/pr.57.2.4
133. Wolburg H, Lippoldt A (2002) *Tight junctions of the blood-brain barrier: development, composition and regulation*. Vascul Pharmacol 38:323-337
134. Abbott NJ (2000) *Inflammatory mediators and modulation of blood-brain barrier permeability*. Cell Mol Neurobiol 20:131-147
135. Kis B, Deli MA, Kobayashi H, Abraham CS, Yanagita T, Kaiya H, Isse T, Nishi R, Gotoh S, Kangawa K, Wada A, Greenwood J, Niwa M, Yamashita H, Ueta Y (2001) *Adrenomedullin regulates blood-brain barrier functions in vitro*. Neuroreport 12:4139-4142
136. Papadopoulos MC, Saadoun S, Davies DC, Bell BA (2001) *Emerging molecular mechanisms of brain tumour oedema*. Br J Neurosurg 15:101-108
137. Davies DC (2002) *Blood-brain barrier breakdown in septic encephalopathy and brain tumours*. J Anat 200:639-646
138. Gilhus NEB, M.P.; Brainin, M. (2011) *European Handbook of Neurological Management*. Brain Metastases, 2nd Edition edn. Blackwell-Wiley, England
139. Chamberlain MC (2000) *Neoplastic meningitis: a guide to diagnosis and treatment*. Curr Opin Neurol 13:641-648
140. Nussbaum ES, Djalilian HR, Cho KH, Hall WA (1996) *Brain metastases. Histology, multiplicity, surgery, and survival*. Cancer 78:1781-1788
141. Posner JB (1977) *Management of central nervous system metastases*. Semin Oncol 4:81-91
142. Da Silva AN, Schiff D (2007) *Dural and skull base metastases*. Cancer Treat Res 136:117-141
143. Laigle-Donadey F, Taillibert S, Martin-Duverneuil N, Hildebrand J, Delattre JY (2005) *Skull-base metastases*. J Neurooncol 75:63-69. doi:10.1007/s11060-004-8099-0
144. Chamoun RB, DeMonte F (2011) *Management of skull base metastases*. Neurosurgery clinics of North America 22:61-66, vi-ii. doi:10.1016/j.nec.2010.08.005
145. Laigle-Donadey F, Taillibert S, Mokhtari K, Hildebrand J, Delattre JY (2005) *Dural metastases*. J Neurooncol 75:57-61. doi:10.1007/s11060-004-8098-1
146. Nayak L, Abrey LE, Iwamoto FM (2009) *Intracranial dural metastases*. Cancer 115:1947-1953. doi:10.1002/cncr.24203
147. Kalita O (2011) *Current insights into surgery for intramedullary spinal cord metastases: a literature review*. Int J Surg Oncol 2011:989506. doi:10.1155/2011/989506

148. Schiff D, O'Neill BP (1996) *Intramedullary spinal cord metastases: clinical features and treatment outcome*. Neurology 47:906-912
149. Groves MD (2011) *Leptomeningeal disease*. Neurosurgery clinics of North America 22:67-78, vii. doi:10.1016/j.nec.2010.08.006
150. Clarke JL (2012) *Leptomeningeal metastasis from systemic cancer*. Continuum (Minneap Minn) 18:328-342. doi:10.1212/01.CON.0000413661.58045.e7
151. Tonn JCW, M.; Jutka, J.T. (2010) *Oncology of CNS Tumors Part 1*. Brain Metastases. Springer, Germany
152. Schaefer PW, Budzik RF, Jr., Gonzalez RG (1996) *Imaging of cerebral metastases*. Neurosurgery clinics of North America 7:393-423
153. Sze G, Milano E, Johnson C, Heier L (1990) *Detection of brain metastases: comparison of contrast-enhanced MR with unenhanced MR and enhanced CT*. AJNR Am J Neuroradiol 11:785-791
154. Davis PC, Hudgins PA, Peterman SB, Hoffman JC, Jr. (1991) *Diagnosis of cerebral metastases: double-dose delayed CT vs contrast-enhanced MR imaging*. AJNR Am J Neuroradiol 12:293-300
155. Muroff LR, Runge VM (1995) *The use of MR contrast in neoplastic disease of the brain*. Top Magn Reson Imaging 7:137-157
156. Cha S (2009) *Neuroimaging in neuro-oncology*. Neurotherapeutics 6:465-477. doi:10.1016/j.nurt.2009.05.002
157. Barajas RF, Jr., Cha S (2016) *Metastasis in Adult Brain Tumors*. Neuroimaging Clin N Am 26:601-620. doi:10.1016/j.nic.2016.06.008
158. Walker MT, Kapoor V (2007) *Neuroimaging of parenchymal brain metastases*. Cancer Treat Res 136:31-51
159. Kamp MA, Rapp M, Buhner J, Slotty PJ, Reichelt D, Sadat H, Dibue-Adjei M, Steiger HJ, Turowski B, Sabel M (2015) *Early postoperative magnet resonance tomography after resection of cerebral metastases*. Acta neurochirurgica 157:1573-1580. doi:10.1007/s00701-015-2479-4
160. Stummer W, Pichlmeier U, Meinel T, Wiestler OD, Zanella F, Reulen HJ, Group AL-GS (2006) *Fluorescence-guided surgery with 5-aminolevulinic acid for resection of malignant glioma: a randomised controlled multicentre phase III trial*. The lancet oncology 7:392-401. doi:10.1016/S1470-2045(06)70665-9
161. Senft C, Bink A, Franz K, Vatter H, Gasser T, Seifert V (2011) *Intraoperative MRI guidance and extent of resection in glioma surgery: a randomised, controlled trial*. The lancet oncology 12:997-1003. doi:10.1016/S1470-2045(11)70196-6
162. Soffietti R, Abacioglu U, Baumert B, Combs SE, Kinhult S, Kros JM, Marosi C, Metellus P, Radbruch A, Villa Freixa SS, Brada M, Carapella CM, Preusser M, Le Rhun E, Rudà R, Tonn JC, Weber DC, Weller M (2017) *Diagnosis and treatment of brain metastases from solid tumors: guidelines from the European Association of Neuro-Oncology (EANO)*. Neuro-Oncology 19:162-174. doi:10.1093/neuonc/now241
163. Benveniste RJ, Ferraro N, Tsimpas A (2014) *Yield and utility of routine postoperative imaging after resection of brain metastases*. J Neurooncol 118:363-367. doi:10.1007/s11060-014-1440-3
164. Jung TY, Chung WK, Oh IJ (2014) *The prognostic significance of surgically treated hydrocephalus in leptomeningeal metastases*. Clin Neurol Neurosurg 119:80-83. doi:10.1016/j.clineuro.2014.01.023
165. Gleissner B, Chamberlain MC (2006) *Neoplastic meningitis*. Lancet neurology 5:443-452. doi:10.1016/S1474-4422(06)70443-4
166. Lucignani G, Bombardieri E (2004) *Molecular imaging: seeing the invisible beyond the "hot spot"*. Q J Nucl Med Mol Imaging 48:1-3

167. Galldiks N, Stoffels G, Ruge MI, Rapp M, Sabel M, Reifenberger G, Erdem Z, Shah NJ, Fink GR, Coenen HH, Langen KJ (2013) *Role of O-(2-18F-fluoroethyl)-L-tyrosine PET as a diagnostic tool for detection of malignant progression in patients with low-grade glioma*. J Nucl Med 54:2046-2054. doi:10.2967/jnumed.113.123836
168. Kickingereder P, Dorn F, Blau T, Schmidt M, Kocher M, Galldiks N, Ruge MI (2013) *Differentiation of local tumor recurrence from radiation-induced changes after stereotactic radiosurgery for treatment of brain metastasis: case report and review of the literature*. Radiat Oncol 8:52. doi:10.1186/1748-717X-8-52
169. Palumbo B (2008) *Brain tumour recurrence: brain single-photon emission computerized tomography, PET and proton magnetic resonance spectroscopy*. Nucl Med Commun 29:730-735. doi:10.1097/MNM.0b013e3283000049
170. Stippich C (2010) *[Presurgical functional magnetic resonance imaging]*. Radiologe 50:110-122. doi:10.1007/s00117-009-1893-0
171. Duffau H (2006) *New concepts in surgery of WHO grade II gliomas: functional brain mapping, connectionism and plasticity--a review*. J Neurooncol 79:77-115. doi:10.1007/s11060-005-9109-6
172. Schonberg T, Pianka P, Hendler T, Pasternak O, Assaf Y (2006) *Characterization of displaced white matter by brain tumors using combined DTI and fMRI*. Neuroimage 30:1100-1111. doi:10.1016/j.neuroimage.2005.11.015
173. Stippich C, Heiland S, Tronnier V, Mohr A, Sartor K (2002) *[Functional magnetic resonance imaging: Physiological background, technical aspects and prerequisites for clinical use]*. Rofo 174:43-49. doi:10.1055/s-2002-19542
174. Hajnal JV, Myers R, Oatridge A, Schwieso JE, Young IR, Bydder GM (1994) *Artifacts due to stimulus correlated motion in functional imaging of the brain*. Magn Reson Med 31:283-291
175. Hoeller M, Krings T, Reinges MH, Hans FJ, Gilsbach JM, Thron A (2002) *Movement artefacts and MR BOLD signal increase during different paradigms for mapping the sensorimotor cortex*. Acta neurochirurgica 144:279-284; discussion 284. doi:10.1007/s007010200036
176. Seto E, Sela G, McIlroy WE, Black SE, Staines WR, Bronskill MJ, McIntosh AR, Graham SJ (2001) *Quantifying head motion associated with motor tasks used in fMRI*. Neuroimage 14:284-297. doi:10.1006/nimg.2001.0829
177. Boxerman JL, Bandettini PA, Kwong KK, Baker JR, Davis TL, Rosen BR, Weisskoff RM (1995) *The intravascular contribution to fMRI signal change: Monte Carlo modeling and diffusion-weighted studies in vivo*. Magn Reson Med 34:4-10
178. Hlustik P, Noll DC, Small SL (1998) *Suppression of vascular artifacts in functional magnetic resonance images using MR angiograms*. Neuroimage 7:224-231
179. Krings T, Erberich SG, Roessler F, Reul J, Thron A (1999) *MR blood oxygenation level-dependent signal differences in parenchymal and large draining vessels: implications for functional MR imaging*. AJNR Am J Neuroradiol 20:1907-1914
180. Holodny AI, Schulder M, Liu WC, Maldjian JA, Kalnin AJ (1999) *Decreased BOLD functional MR activation of the motor and sensory cortices adjacent to a glioblastoma multiforme: implications for image-guided neurosurgery*. AJNR Am J Neuroradiol 20:609-612
181. Holodny AI, Schulder M, Liu WC, Wolko J, Maldjian JA, Kalnin AJ (2000) *The effect of brain tumors on BOLD functional MR imaging activation in the adjacent motor cortex: implications for image-guided neurosurgery*. AJNR Am J Neuroradiol 21:1415-1422
182. Schreiber A, Hubbe U, Ziyeh S, Hennig J (2000) *The influence of gliomas and nonglial space-occupying lesions on blood-oxygen-level-dependent contrast enhancement*. AJNR Am J Neuroradiol 21:1055-1063

183. Stippich C, Kress B, Ochmann H, Tronnier V, Sartor K (2003) *[Preoperative functional magnetic resonance tomography (FMRI) in patients with rolandic brain tumors: indication, investigation strategy, possibilities and limitations of clinical application]*. Rofo 175:1042-1050. doi:10.1055/s-2003-40920
184. Reinges MH, Nguyen HH, Krings T, Hutter BO, Rohde V, Gilsbach JM (2004) *Course of brain shift during microsurgical resection of supratentorial cerebral lesions: limits of conventional neuronavigation*. Acta neurochirurgica 146:369-377; discussion 377. doi:10.1007/s00701-003-0204-1
185. Roberts DW, Hartov A, Kennedy FE, Miga MI, Paulsen KD (1998) *Intraoperative brain shift and deformation: a quantitative analysis of cortical displacement in 28 cases*. Neurosurgery 43:749-758; discussion 758-760
186. Rades D, Kuhnel G, Wildfang I, Borner AR, Schmoll HJ, Knapp W (2001) *Localised disease in cancer of unknown primary (CUP): the value of positron emission tomography (PET) for individual therapeutic management*. Ann Oncol 12:1605-1609
187. Rusthoven KE, Koshy M, Paulino AC (2004) *The role of fluorodeoxyglucose positron emission tomography in cervical lymph node metastases from an unknown primary tumor*. Cancer 101:2641-2649. doi:10.1002/cncr.20687
188. Moller AK, Loft A, Berthelsen AK, Pedersen KD, Graff J, Christensen CB, Costa JC, Skovgaard LT, Perell K, Petersen BL, Daugaard G (2012) *A prospective comparison of 18F-FDG PET/CT and CT as diagnostic tools to identify the primary tumor site in patients with extracervical carcinoma of unknown primary site*. Oncologist 17:1146-1154. doi:10.1634/theoncologist.2011-0449
189. Varadhachary GR, Raber MN (2014) *Cancer of unknown primary site*. The New England journal of medicine 371:757-765. doi:10.1056/NEJMra1303917
190. Al-Brahim N, Ross C, Carter B, Chorneyko K (2005) *The value of postmortem examination in cases of metastasis of unknown origin-20-year retrospective data from a tertiary care center*. Ann Diagn Pathol 9:77-80
191. Fletcher C (2013) *Introduction*. In: Diagnostic Histopathology of Tumors. Saunders Elsevier, USA, p 1
192. Kleinberg L (2008) *Brain Metastasis: A Multidisciplinary Approach*. 1st edn. Demos, USA
193. Lee SH (2012) *Role of chemotherapy on brain metastasis*. Prog Neurol Surg 25:110-114. doi:10.1159/000331183
194. Mut M (2012) *Surgical treatment of brain metastasis: a review*. Clin Neurol Neurosurg 114:1-8. doi:10.1016/j.clineuro.2011.10.013
195. Galicich JH, French LA, Melby JC (1961) *Use of dexamethasone in treatment of cerebral edema associated with brain tumors*. J Lancet 81:46-53
196. McClelland S, 3rd, Long DM (2008) *Genesis of the use of corticosteroids in the treatment and prevention of brain edema*. Neurosurgery 62:965-967; discussion 967-968. doi:10.1227/01.neu.0000318183.25783.77
197. Vecht CJ, Hovestadt A, Verbiest HB, van Vliet JJ, van Putten WL (1994) *Dose-effect relationship of dexamethasone on Karnofsky performance in metastatic brain tumors: a randomized study of doses of 4, 8, and 16 mg per day*. Neurology 44:675-680
198. Glantz MJ, Cole BF, Forsyth PA, Recht LD, Wen PY, Chamberlain MC, Grossman SA, Cairncross JG (2000) *Practice parameter: anticonvulsant prophylaxis in patients with newly diagnosed brain tumors. Report of the Quality Standards Subcommittee of the American Academy of Neurology*. Neurology 54:1886-1893
199. Ryken TC, McDermott M, Robinson PD, Ammirati M, Andrews DW, Asher AL, Burri SH, Cobbs CS, Gaspar LE, Kondziolka D, Linskey ME, Loeffler JS, Mehta MP, Mikkelsen T, Olson JJ, Paleologos NA, Patchell RA, Kalkanis SN (2010) *The role of steroids in the management of brain metastases: a systematic review and evidence-based clinical practice guideline*. J Neurooncol 96:103-114. doi:10.1007/s11060-009-0057-4

200. Fetell MR, Grossman SA, Fisher JD, Erlanger B, Rowinsky E, Stockel J, Piantadosi S (1997) *Preirradiation paclitaxel in glioblastoma multiforme: efficacy, pharmacology, and drug interactions. New Approaches to Brain Tumor Therapy Central Nervous System Consortium*. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 15:3121-3128. doi:10.1200/JCO.1997.15.9.3121
201. Trevor A (2013) *Katzung & Trevor's Pharmacology Examination and Board Review*. 10th Edition edn. McGraw Hill- Lange, USA
202. Chiu CH, Tsai CM, Chen YM, Chiang SC, Liou JL, Perng RP (2005) *Gefitinib is active in patients with brain metastases from non-small cell lung cancer and response is related to skin toxicity*. Lung Cancer 47:129-138. doi:10.1016/j.lungcan.2004.05.014
203. Ceresoli GL, Cappuzzo F, Gregorc V, Bartolini S, Crino L, Villa E (2004) *Gefitinib in patients with brain metastases from non-small-cell lung cancer: a prospective trial*. Ann Oncol 15:1042-1047. doi:10.1093/annonc/mdh276
204. Wu C, Li YL, Wang ZM, Li Z, Zhang TX, Wei Z (2007) *Gefitinib as palliative therapy for lung adenocarcinoma metastatic to the brain*. Lung Cancer 57:359-364. doi:10.1016/j.lungcan.2007.03.011
205. Wu YL, Zhou C, Cheng Y, Lu S, Chen GY, Huang C, Huang YS, Yan HH, Ren S, Liu Y, Yang JJ (2013) *Erlotinib as second-line treatment in patients with advanced non-small-cell lung cancer and asymptomatic brain metastases: a phase II study (CTONG-0803)*. Ann Oncol 24:993-999. doi:10.1093/annonc/mds529
206. Kim JE, Lee DH, Choi Y, Yoon DH, Kim SW, Suh C, Lee JS (2009) *Epidermal growth factor receptor tyrosine kinase inhibitors as a first-line therapy for never-smokers with adenocarcinoma of the lung having asymptomatic synchronous brain metastasis*. Lung Cancer 65:351-354. doi:10.1016/j.lungcan.2008.12.011
207. Zee YK, Chin TM, Wong AS (2009) *Fatal cystic change of brain metastasis after response to gefitinib in non-small-cell lung cancer*. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 27:e145-146. doi:10.1200/JCO.2009.22.4501
208. Porta R, Sanchez-Torres JM, Paz-Ares L, Massuti B, Reguart N, Mayo C, Lianes P, Queralt C, Guillem V, Salinas P, Catot S, Isla D, Pradas A, Gurpide A, de Castro J, Polo E, Puig T, Taron M, Colomer R, Rosell R (2011) *Brain metastases from lung cancer responding to erlotinib: the importance of EGFR mutation*. The European respiratory journal 37:624-631. doi:10.1183/09031936.00195609
209. Jamal-Hanjani M, Spicer J (2012) *Epidermal growth factor receptor tyrosine kinase inhibitors in the treatment of epidermal growth factor receptor-mutant non-small cell lung cancer metastatic to the brain*. Clin Cancer Res 18:938-944. doi:10.1158/1078-0432.CCR-11-2529
210. Costa DB, Shaw AT, Ou SH, Solomon BJ, Riely GJ, Ahn MJ, Zhou C, Shreeve SM, Selaru P, Polli A, Schnell P, Wilner KD, Wiltshire R, Camidge DR, Crino L (2015) *Clinical Experience With Crizotinib in Patients With Advanced ALK-Rearranged Non-Small-Cell Lung Cancer and Brain Metastases*. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 33:1881-1888. doi:10.1200/JCO.2014.59.0539
211. Solomon BJ, Cappuzzo F, Felip E, Blackhall FH, Costa DB, Kim DW, Nakagawa K, Wu YL, Mekhail T, Paolini J, Tursi J, Usari T, Wilner KD, Selaru P, Mok TS (2016) *Intracranial Efficacy of Crizotinib Versus Chemotherapy in Patients With Advanced ALK-Positive Non-Small-Cell Lung Cancer: Results From PROFILE 1014*. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 34:2858-2865. doi:10.1200/JCO.2015.63.5888
212. Gadgeel SM, Shaw AT, Govindan R, Gandhi L, Socinski MA, Camidge DR, De Petris L, Kim DW, Chiappori A, Moro-Sibilot DL, Duruisseaux M, Crino L, De Pas T, Dansin E, Tessmer A, Yang JC, Han JY, Bordogna W, Golding S, Zeaiter A, Ou SI (2016) *Pooled Analysis of CNS Response to Alectinib in Two Studies of Pretreated Patients With ALK-*

Positive Non-Small-Cell Lung Cancer. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 34:4079-4085. doi:10.1200/JCO.2016.68.4639

213. Sperduto PW, Wang M, Robins HI, Schell MC, Werner-Wasik M, Komaki R, Souhami L, Buyyounouski MK, Khuntia D, Demas W, Shah SA, Nedzi LA, Perry G, Suh JH, Mehta MP (2013) *A phase 3 trial of whole brain radiation therapy and stereotactic radiosurgery alone versus WBRT and SRS with temozolomide or erlotinib for non-small cell lung cancer and 1 to 3 brain metastases: Radiation Therapy Oncology Group 0320*. Int J Radiat Oncol Biol Phys 85:1312-1318. doi:10.1016/j.ijrobp.2012.11.042
214. De Braganca KC, Janjigian YY, Azzoli CG, Kris MG, Pietanza MC, Nolan CP, Omuro AM, Holodny AI, Lassman AB (2010) *Efficacy and safety of bevacizumab in active brain metastases from non-small cell lung cancer*. J Neurooncol 100:443-447. doi:10.1007/s11060-010-0200-2
215. Ewend MG, Brem S, Gilbert M, Goodkin R, Penar PL, Varia M, Cush S, Carey LA (2007) *Treatment of single brain metastasis with resection, intracavity carmustine polymer wafers, and radiation therapy is safe and provides excellent local control*. Clin Cancer Res 13:3637-3641. doi:10.1158/1078-0432.CCR-06-2095
216. Chu FC, Hilaris BB (1961) *Value of radiation theray in the management of intracranial metastases*. Cancer 14:577-581
217. Chao JH, Phillips R, Nickson JJ (1954) *Roentgen-ray therapy of cerebral metastases*. Cancer 7:682-689
218. Order SE, Hellman S, Von Essen CF, Kligerman MM (1968) *Improvement in quality of survival following whole-brain irradiation for brain metastasis*. Radiology 91:149-153. doi:10.1148/91.1.149
219. Cairncross JG, Kim JH, Posner JB (1980) *Radiation therapy for brain metastases*. Ann Neurol 7:529-541. doi:10.1002/ana.410070606
220. Nieder C, Berberich W, Schnabel K (1997) *Tumor-related prognostic factors for remission of brain metastases after radiotherapy*. Int J Radiat Oncol Biol Phys 39:25-30
221. Dyke CG (1935) *The roentgen ray treatment of tumors of the brain and skull*. Bulletin of the New York Academy of Medicine 11:392-402
222. Patchell RA, Tibbs PA, Walsh JW, Dempsey RJ, Maruyama Y, Kryscio RJ, Markesbery WR, Macdonald JS, Young B (1990) *A randomized trial of surgery in the treatment of single metastases to the brain*. The New England journal of medicine 322:494-500. doi:10.1056/NEJM199002223220802
223. Vecht CJ, Haaxma-Reiche H, Noordijk EM, Padberg GW, Voormolen JH, Hoekstra FH, Tans JT, Lambooij N, Metsaars JA, Wattendorff AR, et al. (1993) *Treatment of single brain metastasis: radiotherapy alone or combined with neurosurgery?* Ann Neurol 33:583-590. doi:10.1002/ana.410330605
224. Towne E (1925) *Roentgen-Ray Treatment of Tumors of the Brain*. JAMA : the journal of the American Medical Association 84:1813
225. Regine WF, Huhn JL, Patchell RA, St Clair WH, Strottmann J, Meigooni A, Sanders M, Young AB (2002) *Risk of symptomatic brain tumor recurrence and neurologic deficit after radiosurgery alone in patients with newly diagnosed brain metastases: results and implications*. Int J Radiat Oncol Biol Phys 52:333-338
226. Patchell RA, Regine WF, Loeffler JS, Sawaya R, Andrews DW, Chin LS (2006) *Radiosurgery plus whole-brain radiation therapy for brain metastases*. JAMA : the journal of the American Medical Association 296:2089-2090; author reply 2090-2081. doi:10.1001/jama.296.17.2089
227. Andrews DW, Scott CB, Sperduto PW, Flanders AE, Gaspar LE, Schell MC, Werner-Wasik M, Demas W, Ryu J, Bahary JP, Souhami L, Rotman M, Mehta MP, Curran WJ, Jr. (2004) *Whole brain radiation therapy with or without stereotactic radiosurgery boost for*

patients with one to three brain metastases: phase III results of the RTOG 9508 randomised trial. Lancet 363:1665-1672. doi:10.1016/S0140-6736(04)16250-8

228. Lo SS, Chang EL, Suh JH (2005) *Stereotactic radiosurgery with and without whole-brain radiotherapy for newly diagnosed brain metastases*. Expert Rev Neurother 5:487-495. doi:10.1586/14737175.5.4.487
229. Sneed PK, Lamborn KR, Forstner JM, McDermott MW, Chang S, Park E, Gutin PH, Phillips TL, Wara WM, Larson DA (1999) *Radiosurgery for brain metastases: is whole brain radiotherapy necessary?* Int J Radiat Oncol Biol Phys 43:549-558
230. Sneed PK, Suh JH, Goetsch SJ, Sanghavi SN, Chappell R, Buatti JM, Regine WF, Weltman E, King VJ, Breneman JC, Sperduto PW, Mehta MP (2002) *A multi-institutional review of radiosurgery alone vs. radiosurgery with whole brain radiotherapy as the initial management of brain metastases*. Int J Radiat Oncol Biol Phys 53:519-526
231. Aoyama H, Shirato H, Tago M, Nakagawa K, Toyoda T, Hatano K, Kenjyo M, Oya N, Hirota S, Shioura H, Kunieda E, Inomata T, Hayakawa K, Katoh N, Kobashi G (2006) *Stereotactic radiosurgery plus whole-brain radiation therapy vs stereotactic radiosurgery alone for treatment of brain metastases: a randomized controlled trial*. JAMA : the journal of the American Medical Association 295:2483-2491. doi:10.1001/jama.295.21.2483
232. Samlowski WE, Watson GA, Wang M, Rao G, Klimo P, Jr., Boucher K, Shrieve DC, Jensen RL (2007) *Multimodality treatment of melanoma brain metastases incorporating stereotactic radiosurgery (SRS)*. Cancer 109:1855-1862. doi:10.1002/cncr.22605
233. Hara W, Tran P, Li G, Su Z, Puataweepong P, Adler JR, Soltys SG, Chang SD, Gibbs IC (2009) *Cyberknife for Brain Metastases of Malignant Melanoma and Renal Cell Carcinoma*. Neurosurgery 64:A26-A32. doi:10.1227/01.NEU.0000339118.55334.EA
234. Manon R, O'Neill A, Knisely J, Werner-Wasik M, Lazarus HM, Wagner H, Gilbert M, Mehta M, Eastern Cooperative Oncology G (2005) *Phase II trial of radiosurgery for one to three newly diagnosed brain metastases from renal cell carcinoma, melanoma, and sarcoma: an Eastern Cooperative Oncology Group study (E 6397)*. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 23:8870-8876. doi:10.1200/JCO.2005.01.8747
235. Kondziolka D, Patel A, Lunsford LD, Kassam A, Flickinger JC (1999) *Stereotactic radiosurgery plus whole brain radiotherapy versus radiotherapy alone for patients with multiple brain metastases*. Int J Radiat Oncol Biol Phys 45:427-434
236. Soffietti R, Kocher M, Abacioglu UM, Villa S, Fauchon F, Baumert BG, Fariselli L, Tzuk-Shina T, Kortmann RD, Carrie C, Ben Hassel M, Kouri M, Valeinis E, van den Berge D, Mueller RP, Tridello G, Collette L, Bottomley A (2013) *A European Organisation for Research and Treatment of Cancer phase III trial of adjuvant whole-brain radiotherapy versus observation in patients with one to three brain metastases from solid tumors after surgical resection or radiosurgery: quality-of-life results*. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 31:65-72. doi:10.1200/JCO.2011.41.0639
237. Coia LR (1992) *The role of radiation therapy in the treatment of brain metastases*. Int J Radiat Oncol Biol Phys 23:229-238
238. Borgelt B, Gelber R, Kramer S, Brady LW, Chang CH, Davis LW, Perez CA, Hendrickson FR (1980) *The palliation of brain metastases: final results of the first two studies by the Radiation Therapy Oncology Group*. Int J Radiat Oncol Biol Phys 6:1-9
239. Soon YY, Tham IW, Lim KH, Koh WY, Lu JJ (2014) *Surgery or radiosurgery plus whole brain radiotherapy versus surgery or radiosurgery alone for brain metastases*. The Cochrane database of systematic reviews:CD009454. doi:10.1002/14651858.CD009454.pub2
240. Chang EL, Wefel JS, Hess KR, Allen PK, Lang FF, Kornguth DG, Arbuckle RB, Swint JM, Shiu AS, Maor MH, Meyers CA (2009) *Neurocognition in patients with brain*

metastases treated with radiosurgery or radiosurgery plus whole-brain irradiation: a randomised controlled trial. The lancet oncology 10:1037-1044. doi:10.1016/S1470-2045(09)70263-3

241. Brown PD, Jaeckle K, Ballman KV, Farace E, Cerhan JH, Anderson SK, Carrero XW, Barker FG, 2nd, Deming R, Burri SH, Menard C, Chung C, Stieber VW, Pollock BE, Galanis E, Buckner JC, Asher AL (2016) *Effect of Radiosurgery Alone vs Radiosurgery With Whole Brain Radiation Therapy on Cognitive Function in Patients With 1 to 3 Brain Metastases: A Randomized Clinical Trial*. JAMA : the journal of the American Medical Association 316:401-409. doi:10.1001/jama.2016.9839
242. Fuentes R, Bonfill X, Exposito J (2006) *Surgery versus radiosurgery for patients with a solitary brain metastasis from non-small cell lung cancer*. The Cochrane database of systematic reviews:CD004840. doi:10.1002/14651858.CD004840.pub2
243. Telera S, Fabi A, Pace A, Vidiri A, Anelli V, Carapella CM, Marucci L, Crispo F, Sperduti I, Pompili A (2013) *Radionecrosis induced by stereotactic radiosurgery of brain metastases: results of surgery and outcome of disease*. J Neurooncol 113:313-325. doi:10.1007/s11060-013-1120-8
244. Muacevic A, Wowra B, Siefert A, Tonn JC, Steiger HJ, Kreth FW (2008) *Microsurgery plus whole brain irradiation versus Gamma Knife surgery alone for treatment of single metastases to the brain: a randomized controlled multicentre phase III trial*. J Neurooncol 87:299-307. doi:10.1007/s11060-007-9510-4
245. Weinberg JS, Lang FF, Sawaya R (2001) *Surgical management of brain metastases*. Curr Oncol Rep 3:476-483
246. Vogelbaum MA, Suh JH (2006) *Resectable brain metastases*. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 24:1289-1294. doi:10.1200/JCO.2005.04.6235
247. Mintz AH, Kestle J, Rathbone MP, Gaspar L, Hugenholtz H, Fisher B, Duncan G, Skingley P, Foster G, Levine M (1996) *A randomized trial to assess the efficacy of surgery in addition to radiotherapy in patients with a single cerebral metastasis*. Cancer 78:1470-1476
248. Rades D, Kieckebusch S, Haatanen T, Lohynska R, Dunst J, Schild SE (2008) *Surgical resection followed by whole brain radiotherapy versus whole brain radiotherapy alone for single brain metastasis*. Int J Radiat Oncol Biol Phys 70:1319-1324. doi:10.1016/j.ijrobp.2007.08.009
249. Bindal RK, Sawaya R, Leavens ME, Hess KR, Taylor SH (1995) *Reoperation for recurrent metastatic brain tumors*. Journal of neurosurgery 83:600-604. doi:10.3171/jns.1995.83.4.0600
250. Bindal RK, Sawaya R, Leavens ME, Lee JJ (1993) *Surgical treatment of multiple brain metastases*. Journal of neurosurgery 79:210-216. doi:10.3171/jns.1993.79.2.0210
251. Patel AJ, Suki D, Hatiboglu MA, Rao VY, Fox BD, Sawaya R (2015) *Impact of surgical methodology on the complication rate and functional outcome of patients with a single brain metastasis*. Journal of neurosurgery 122:1132-1143. doi:10.3171/2014.9.JNS13939
252. Patel AJ, Suki D, Hatiboglu MA, Abouassi H, Shi W, Wildrick DM, Lang FF, Sawaya R (2010) *Factors influencing the risk of local recurrence after resection of a single brain metastasis*. Journal of neurosurgery 113:181-189. doi:10.3171/2009.11.JNS09659
253. Neves S, Mazal PR, Wanschitz J, Rudnay AC, Drlicek M, Czech T, Wustinger C, Budka H (2001) *Pseudogliomatous growth pattern of anaplastic small cell carcinomas metastatic to the brain*. Clin Neuropathol 20:38-42
254. Baumert BG, Rutten I, Dehing-Oberije C, Twijnstra A, Dirx MJ, Debougnoux-Huppertz RM, Lambin P, Kubat B (2006) *A pathology-based substrate for target definition in radiosurgery of brain metastases*. Int J Radiat Oncol Biol Phys 66:187-194. doi:10.1016/j.ijrobp.2006.03.050

255. Berghoff AS, Rajky O, Winkler F, Bartsch R, Furtner J, Hainfellner JA, Goodman SL, Weller M, Schittenhelm J, Preusser M (2013) *Invasion patterns in brain metastases of solid cancers*. Neuro Oncol 15:1664-1672. doi:10.1093/neuonc/not112
256. Jallo GI (2001) *CUSA EXcel ultrasonic aspiration system*. Neurosurgery 48:695-697
257. Schackert G, Lindner C, Petschke S, Leimert M, Kirsch M (2013) *Retrospective study of 127 surgically treated patients with multiple brain metastases: indication, prognostic factors, and outcome*. Acta neurochirurgica 155:379-387. doi:10.1007/s00701-012-1606-8
258. Stark AM, Tscheslog H, Buhl R, Held-Feindt J, Mehdorn HM (2005) *Surgical treatment for brain metastases: prognostic factors and survival in 177 patients*. Neurosurgical review 28:115-119. doi:10.1007/s10143-004-0364-3
259. Yamamoto M, Serizawa T, Shuto T, Akabane A, Higuchi Y, Kawagishi J, Yamanaka K, Sato Y, Jokura H, Yomo S, Nagano O, Kenai H, Moriki A, Suzuki S, Kida Y, Iwai Y, Hayashi M, Onishi H, Gondo M, Sato M, Akimitsu T, Kubo K, Kikuchi Y, Shibasaki T, Goto T, Takanashi M, Mori Y, Takakura K, Saeki N, Kunieda E, Aoyama H, Momoshima S, Tsuchiya K (2014) *Stereotactic radiosurgery for patients with multiple brain metastases (JLGK0901): a multi-institutional prospective observational study*. The lancet oncology 15:387-395. doi:10.1016/S1470-2045(14)70061-0
260. Gaspar L, Scott C, Rotman M, Asbell S, Phillips T, Wasserman T, McKenna WG, Byhardt R (1997) *Recursive partitioning analysis (RPA) of prognostic factors in three Radiation Therapy Oncology Group (RTOG) brain metastases trials*. Int J Radiat Oncol Biol Phys 37:745-751
261. Mintz BJ, Tuhrim S, Alexander S, Yang WC, Shanzer S (1984) *Intracranial metastases in the initial staging of bronchogenic carcinoma*. Chest 86:850-853
262. Arbit E, Wronski M, Burt M, Galicich JH (1995) *The treatment of patients with recurrent brain metastases. A retrospective analysis of 109 patients with nonsmall cell lung cancer*. Cancer 76:765-773
263. Truong MT, St Clair EG, Donahue BR, Rush SC, Miller DC, Formenti SC, Knopp EA, Han K, Golfinos JG (2006) *Results of surgical resection for progression of brain metastases previously treated by gamma knife radiosurgery*. Neurosurgery 59:86-97; discussion 86-97. doi:10.1227/01.NEU.0000219858.80351.38
264. Al-Zabin M, Ullrich WO, Brawanski A, Proescholdt MA (2010) *Recurrent brain metastases from lung cancer: the impact of reoperation*. Acta neurochirurgica 152:1887-1892. doi:10.1007/s00701-010-0721-7
265. Vecil GG, Suki D, Maldaun MV, Lang FF, Sawaya R (2005) *Resection of brain metastases previously treated with stereotactic radiosurgery*. Journal of neurosurgery 102:209-215. doi:10.3171/jns.2005.102.2.0209
266. Kalkanis SN, Kondziolka D, Gaspar LE, Burri SH, Asher AL, Cobbs CS, Ammirati M, Robinson PD, Andrews DW, Loeffler JS, McDermott M, Mehta MP, Mikkelsen T, Olson JJ, Paleologos NA, Patchell RA, Ryken TC, Linskey ME (2010) *The role of surgical resection in the management of newly diagnosed brain metastases: a systematic review and evidence-based clinical practice guideline*. J Neurooncol 96:33-43. doi:10.1007/s11060-009-0061-8
267. Sperduto PW, Berkey B, Gaspar LE, Mehta M, Curran W (2008) *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 70:510-514. doi:10.1016/j.ijrobp.2007.06.074
268. Sperduto PW, Kased N, Roberge D, Xu Z, Shanley R, Luo X, Sneed PK, Chao ST, Weil RJ, Suh J, Bhatt A, Jensen AW, Brown PD, Shih HA, Kirkpatrick J, Gaspar LE, Fiveash JB, Chiang V, Knisely JP, Sperduto CM, Lin N, Mehta M (2012) *Summary report on the graded prognostic assessment: an accurate and facile diagnosis-specific tool to estimate*

survival for patients with brain metastases. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 30:419-425. doi:10.1200/JCO.2011.38.0527
269. Karnofsky DAA, W.H.; Craver, L.F.; Burchenal, J.H. (1948) *The use of the nitrogen mustards in the palliative treatment of carcinoma*. Cancer 1:634-656
270. Soffietti RC, P.; Delattre, J.Y.; et.al. (2011) *European Handbook of Neurological Management*, vol 1. Brain Metastases Chapter 30. Blackwell Publishing, UK
271. Paek SH, Audu PB, Sperling MR, Cho J, Andrews DW (2005) *Reevaluation of surgery for the treatment of brain metastases: review of 208 patients with single or multiple brain metastases treated at one institution with modern neurosurgical techniques*. Neurosurgery 56:1021-1034; discussion 1021-1034
272. Lang FF, Sawaya R (1996) *Surgical management of cerebral metastases*. Neurosurgery clinics of North America 7:459-484
273. Munoz-Bendix C, Steiger HJ, Kamp MA (2017) *Outcome following surgical treatment of chronic subdural hematoma in the oldest-old population*. Neurosurgical review. doi:10.1007/s10143-017-0853-9
274. Ortman JM VV, Hogan H (2014) *An Aging Nation: The Older Population in the United States, Current Population Reports*. Washington, DC, USA
275. Naeim AR, DB; Ganz, PA (2012) *Management of Cancer in the Older Patient*. Saunders-Elsevier, USA
276. Chen CC, Kenefick AL, Tang ST, McCorkle R (2004) *Utilization of comprehensive geriatric assessment in cancer patients*. Crit Rev Oncol Hematol 49:53-67
277. Reuben DB, Seeman TE, Keeler E, Hayes RP, Bowman L, Sewall A, Hirsch SH, Wallace RB, Guralnik JM (2004) *Refining the categorization of physical functional status: the added value of combining self-reported and performance-based measures*. The journals of gerontology Series A, Biological sciences and medical sciences 59:1056-1061
278. Terret C (2008) *How and why to perform a geriatric assessment in clinical practice*. Ann Oncol 19 Suppl 7:vii300-303. doi:10.1093/annonc/mdn478
279. Pal SK, Katheria V, Hurria A (2010) *Evaluating the older patient with cancer: understanding frailty and the geriatric assessment*. CA: a cancer journal for clinicians 60:120-132. doi:10.3322/caac.20059
280. Stuck AE, Siu AL, Wieland GD, Adams J, Rubenstein LZ (1993) *Comprehensive geriatric assessment: a meta-analysis of controlled trials*. Lancet 342:1032-1036
281. Rothenbacher D, Lutz MP, Porzsolt F (1997) *Treatment decisions in palliative cancer care: patients' preferences for involvement and doctors' knowledge about it*. Eur J Cancer 33:1184-1189
282. Sawaya R (2001) *Considerations in the diagnosis and management of brain metastases*. Oncology (Williston Park) 15:1144-1154, 1157-1148; discussion 1158, 1163-1145
283. Kong XTA, D; Bota, D.A. (2014) *Epidemiology of Central Nervous System Metastases*. In: Hayat MA (ed) Brain Metastases from Primary Tumors. Epidemiology, Biology, and Therapy, vol 1. Academic Press, pp 11 - 23
284. Noordijk EM, Vecht CJ, Haaxma-Reiche H, Padberg GW, Voormolen JH, Hoekstra FH, Tans JT, Lambooij N, Metsaars JA, Wattendorff AR, et al. (1994) *The choice of treatment of single brain metastasis should be based on extracranial tumor activity and age*. Int J Radiat Oncol Biol Phys 29:711-717
285. Sahgal A, Aoyama H, Kocher M, Neupane B, Collette S, Tago M, Shaw P, Beyene J, Chang EL (2015) *Phase 3 trials of stereotactic radiosurgery with or without whole-brain radiation therapy for 1 to 4 brain metastases: individual patient data meta-analysis*. Int J Radiat Oncol Biol Phys 91:710-717. doi:10.1016/j.ijrobp.2014.10.024
286. Stark AM, Stohring C, Hedderich J, Held-Feindt J, Mehdorn HM (2011) *Surgical treatment for brain metastases: Prognostic factors and survival in 309 patients with regard*

to patient age. Journal of clinical neuroscience : official journal of the Neurosurgical Society of Australasia 18:34-38. doi:10.1016/j.jocn.2010.03.046

287. Brown PD, Ballman KV, Cerhan JH, Anderson SK, Carrero XW, Whitton AC, Greenspoon J, Parney IF, Laack NNI, Ashman JB, Bahary JP, Hadjipanayis CG, Urbanic JJ, Barker FG, 2nd, Farace E, Khuntia D, Giannini C, Buckner JC, Galanis E, Roberge D (2017) *Postoperative stereotactic radiosurgery compared with whole brain radiotherapy for resected metastatic brain disease (NCCTG N107C/CEC.3): a multicentre, randomised, controlled, phase 3 trial*. The lancet oncology 18:1049-1060. doi:10.1016/S1470-2045(17)30441-2
288. Mahajan A, Ahmed S, McAleer MF, Weinberg JS, Li J, Brown P, Settle S, Prabhu SS, Lang FF, Levine N, McGovern S, Sulman E, McCutcheon IE, Azeem S, Cahill D, Tatsui C, Heimberger AB, Ferguson S, Ghia A, Demonte F, Raza S, Guha-Thakurta N, Yang J, Sawaya R, Hess KR, Rao G (2017) *Post-operative stereotactic radiosurgery versus observation for completely resected brain metastases: a single-centre, randomised, controlled, phase 3 trial*. The lancet oncology 18:1040-1048. doi:10.1016/S1470-2045(17)30414-X
289. Roos DE, Smith JG, Stephens SW (2011) *Radiosurgery versus surgery, both with adjuvant whole brain radiotherapy, for solitary brain metastases: a randomised controlled trial*. Clinical oncology 23:646-651. doi:10.1016/j.clon.2011.04.009
290. Soffietti R, Abacioglu U, Baumert B, Combs SE, Kinhult S, Kros JM, Marosi C, Metellus P, Radbruch A, Villa Freixa SS, Brada M, Carapella CM, Preusser M, Le Rhun E, Ruda R, Tonn JC, Weber DC, Weller M (2017) *Diagnosis and treatment of brain metastases from solid tumors: guidelines from the European Association of Neuro-Oncology (EANO)*. Neuro Oncol 19:162-174. doi:10.1093/neuonc/now241
291. Munoz-Bendix C, Pannewitz R, Remmel D, Steiger HJ, Turowski B, Slotty PJ, Kamp MA (2017) *Outcome following surgical treatment of chronic subdural hematoma in the oldest-old population*. Neurosurgical review 40:461-468. doi:10.1007/s10143-016-0803-y
292. Grossman R, Mukherjee D, Chang DC, Purtell M, Lim M, Brem H, Quinones-Hinojosa A (2011) *Predictors of inpatient death and complications among postoperative elderly patients with metastatic brain tumors*. Ann Surg Oncol 18:521-528. doi:10.1245/s10434-010-1299-2
293. El Gantery MM, Abd El Baky HM, El Hossieny HA, Mahmoud M, Youssef O (2014) *Management of brain metastases with stereotactic radiosurgery alone versus whole brain irradiation alone versus both*. Radiat Oncol 9:116. doi:10.1186/1748-717X-9-116
294. Tan HJ, Saliba D, Kwan L, Moore AA, Litwin MS (2016) *Burden of Geriatric Events Among Older Adults Undergoing Major Cancer Surgery*. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 34:1231-1238. doi:10.1200/JCO.2015.63.4592
295. Extermann M, Aapro M, Bernabei R, Cohen HJ, Droz JP, Lichtman S, Mor V, Monfardini S, Repetto L, Sorbye L, Topinkova E, Task Force on CGAotISoGO (2005) *Use of comprehensive geriatric assessment in older cancer patients: recommendations from the task force on CGA of the International Society of Geriatric Oncology (SIOG)*. Crit Rev Oncol Hematol 55:241-252. doi:10.1016/j.critrevonc.2005.06.003
296. Min L, Hall K, Finlayson E, Englesbe M, Palazzolo W, Chan CL, Hou H, Miller A, Diehl KM (2017) *Estimating Risk of Postsurgical General and Geriatric Complications Using the VESPA Preoperative Tool*. JAMA Surg. doi:10.1001/jamasurg.2017.2635
297. *National Institutes of Health Consensus Development Conference Statement: geriatric assessment methods for clinical decision-making* (1988). Journal of the American Geriatrics Society 36:342-347
298. Karnofsky DA (1948) *Chemotherapy of neoplastic disease; agents of clinical value*. The New England journal of medicine 239:299-305. doi:10.1056/NEJM194808192390805

299. Kasner SE (2006) *Clinical interpretation and use of stroke scales*. Lancet neurology 5:603-612. doi:10.1016/S1474-4422(06)70495-1
300. Appelros P, Terent A (2004) *Characteristics of the National Institute of Health Stroke Scale: results from a population-based stroke cohort at baseline and after one year*. Cerebrovasc Dis 17:21-27. doi:10.1159/000073894
301. Brott T, Adams HP, Jr., Olinger CP, Marler JR, Barsan WG, Biller J, Spilker J, Holleran R, Eberle R, Hertzberg V, et al. (1989) *Measurements of acute cerebral infarction: a clinical examination scale*. Stroke; a journal of cerebral circulation 20:864-870
302. Kamp MA, Slotty PJ, Cornelius JF, Steiger HJ, Rapp M, Sabel M (2016) *The impact of cerebral metastases growth pattern on neurosurgical treatment*. Neurosurgical review. doi:10.1007/s10143-016-0760-5
303. Kamp MA, Rapp M, Slotty PJ, Turowski B, Sadat H, Smuga M, Dibue-Adjei M, Steiger HJ, Szelenyi A, Sabel M (2015) *Incidence of local in-brain progression after supramarginal resection of cerebral metastases*. Acta neurochirurgica 157:905-910; discussion 910-901. doi:10.1007/s00701-015-2405-9
304. Kamp MA, Fischer I, Dibue-Adjei M, Munoz-Bendix C, Cornelius JF, Steiger HJ, Slotty PJ, Turowski B, Rapp M, Sabel M (2017) *Predictors for a further local in-brain progression after re-craniotomy of locally recurrent cerebral metastases*. Neurosurgical review. doi:10.1007/s10143-017-0931-z
305. Kamp MA, Dibue M, Santacroce A, Zella SM, Niemann L, Steiger HJ, Rapp M, Sabel M (2013) *The tumour is not enough or is it? Problems and new concepts in the surgery of cerebral metastases*. Ecancermedicalscience 7:306. doi:10.3332/ecancer.2013.306
306. Kamp MA, Dibue M, Niemann L, Reichelt DC, Felsberg J, Steiger HJ, Szelenyi A, Rapp M, Sabel M (2012) *Proof of principle: supramarginal resection of cerebral metastases in eloquent brain areas*. Acta neurochirurgica 154:1981-1986. doi:10.1007/s00701-012-1463-5
307. Stummer W, Kamp MA (2009) *The importance of surgical resection in malignant glioma*. Curr Opin Neurol 22:645-649. doi:10.1097/WCO.0b013e3283320165
308. Stummer W, Stocker S, Novotny A, Heimann A, Sauer O, Kempski O, Plesnila N, Wietzorrek J, Reulen HJ (1998) *In vitro and in vivo porphyrin accumulation by C6 glioma cells after exposure to 5-aminolevulinic acid*. J Photochem Photobiol B 45:160-169
309. Kamp MA, Fischer I, Buhner J, Turowski B, Cornelius JF, Steiger HJ, Rapp M, Slotty PJ, Sabel M (2016) *5-ALA fluorescence of cerebral metastases and its impact for the local-in-brain progression*. Oncotarget. doi:10.18632/oncotarget.11488
310. Belloch JP, Rovira V, Llacer JL, Riesgo PA, Cremades A (2014) *Fluorescence-guided surgery in high grade gliomas using an exoscope system*. Acta neurochirurgica 156:653-660. doi:10.1007/s00701-013-1976-6
311. Coburger J, Engelke J, Scheuerle A, Thal DR, Hlavac M, Wirtz CR, Konig R (2014) *Tumor detection with 5-aminolevulinic acid fluorescence and Gd-DTPA-enhanced intraoperative MRI at the border of contrast-enhancing lesions: a prospective study based on histopathological assessment*. Neurosurgical focus 36:E3. doi:10.3171/2013.11.FOCUS13463
312. Kamp MA, Grosser P, Felsberg J, Slotty PJ, Steiger HJ, Reifenberger G, Sabel M (2012) *5-aminolevulinic acid (5-ALA)-induced fluorescence in intracerebral metastases: a retrospective study*. Acta neurochirurgica 154:223-228; discussion 228. doi:10.1007/s00701-011-1200-5
313. Marbacher S, Klinger E, Schwyzer L, Fischer I, Nevzati E, Diepers M, Roelcke U, Fathi AR, Coluccia D, Fandino J (2014) *Use of fluorescence to guide resection or biopsy of primary brain tumors and brain metastases*. Neurosurgical focus 36:E10. doi:10.3171/2013.12.FOCUS13464

314. Piquer J, Llacer JL, Rovira V, Riesgo P, Rodriguez R, Cremades A (2014) *Fluorescence-guided surgery and biopsy in gliomas with an exoscope system*. Biomed Res Int 2014:207974. doi:10.1155/2014/207974
315. Schucht P, Beck J, Vajtai I, Raabe A (2011) *Paradoxical fluorescence after administration of 5-aminolevulinic acid for resection of a cerebral melanoma metastasis*. Acta neurochirurgica 153:1497-1499. doi:10.1007/s00701-011-0991-8
316. Utsuki S, Miyoshi N, Oka H, Miyajima Y, Shimizu S, Suzuki S, Fujii K (2007) *Fluorescence-guided resection of metastatic brain tumors using a 5-aminolevulinic acid-induced protoporphyrin IX: pathological study*. Brain Tumor Pathol 24:53-55. doi:10.1007/s10014-007-0223-3
317. Valdes PA, Leblond F, Kim A, Harris BT, Wilson BC, Fan X, Tosteson TD, Hartov A, Ji S, Erkmen K, Simmons NE, Paulsen KD, Roberts DW (2011) *Quantitative fluorescence in intracranial tumor: implications for ALA-induced PpIX as an intraoperative biomarker*. Journal of neurosurgery 115:11-17. doi:10.3171/2011.2.JNS101451
318. Widhalm G, Minchev G, Woehrer A, Preusser M, Kiesel B, Furtner J, Mert A, Di Ieva A, Tomanek B, Prayer D, Marosi C, Hainfellner JA, Knosp E, Wolfsberger S (2012) *Strong 5-aminolevulinic acid-induced fluorescence is a novel intraoperative marker for representative tissue samples in stereotactic brain tumor biopsies*. Neurosurgical review 35:381-391; discussion 391. doi:10.1007/s10143-012-0374-5
319. Kamp MA CJ, Steiger HJ, Sabel M (2019) *5-Aminolevulinic Acid and Brain Metastases*. In: CS H (ed) Fluorescence-Guided Neurosurgery: Neuro-oncology and Cerebrovascular Application. Thieme, USA,
320. Cornelius JF, Placke JM, Knipps J, Fischer I, Kamp M, Steiger HJ (2017) *Minispectrometer with handheld probe for 5-ALA based fluorescence-guided surgery of brain tumors: Preliminary study for clinical applications*. Photodiagnosis Photodyn Ther 17:147-153. doi:10.1016/j.pdpdt.2016.12.007
321. Salas S, Brulard C, Terrier P, Ranchere-Vince D, Neuville A, Guillou L, Lae M, Leroux A, Verola O, Jean-Emmanuel K, Bonvalot S, Blay JY, Le Cesne A, Aurias A, Coindre JM, Chibon F (2015) *Gene Expression Profiling of Desmoid Tumors by cDNA Microarrays and Correlation with Progression-Free Survival*. Clin Cancer Res 21:4194-4200. doi:10.1158/1078-0432.CCR-14-2910
322. Kemmner W, Wan K, Ruttinger S, Ebert B, Macdonald R, Klamm U, Moesta KT (2008) *Silencing of human ferrochelatase causes abundant protoporphyrin-IX accumulation in colon cancer*. FASEB J 22:500-509. doi:10.1096/fj.07-8888com
323. Sabel M, Knipps J, Neumann LM, Kieslich M, Steiger HJ, Rapp M, Kamp MA (2018) *Quantification of ALA-fluorescence induced by a modified commercially available head lamp and a surgical microscope*. Neurosurgical review 41:1079-1083. doi:10.1007/s10143-018-0997-2
324. DeAngelis LM (2001) *Brain tumors*. The New England journal of medicine 344:114-123. doi:10.1056/NEJM200101113440207
325. Caballero JA, Sneed PK, Lamborn KR, Ma L, Denduluri S, Nakamura JL, Barani IJ, McDermott MW (2012) *Prognostic factors for survival in patients treated with stereotactic radiosurgery for recurrent brain metastases after prior whole brain radiotherapy*. Int J Radiat Oncol Biol Phys 83:303-309. doi:10.1016/j.ijrobp.2011.06.1987
326. Kim DH, Schultheiss TE, Radany EH, Badie B, Pezner RD (2013) *Clinical outcomes of patients treated with a second course of stereotactic radiosurgery for locally or regionally recurrent brain metastases after prior stereotactic radiosurgery*. J Neurooncol 115:37-43. doi:10.1007/s11060-013-1191-6
327. Kondziolka D, Kano H, Harrison GL, Yang HC, Liew DN, Niranjan A, Brufsky AM, Flickinger JC, Lunsford LD (2011) *Stereotactic radiosurgery as primary and salvage*

treatment for brain metastases from breast cancer. Clinical article. Journal of neurosurgery 114:792-800. doi:10.3171/2010.8.JNS10461

328. Bhangoo SS, Linskey ME, Kalkanis SN, American Association of Neurologic S, Congress of Neurologic S (2011) *Evidence-based guidelines for the management of brain metastases*. Neurosurgery clinics of North America 22:97-104, viii. doi:10.1016/j.nec.2010.09.001
329. Mikkelsen T, Paleologos NA, Robinson PD, Ammirati M, Andrews DW, Asher AL, Burri SH, Cobbs CS, Gaspar LE, Kondziolka D, Linskey ME, Loeffler JS, McDermott M, Mehta MP, Olson JJ, Patchell RA, Ryken TC, Kalkanis SN (2010) *The role of prophylactic anticonvulsants in the management of brain metastases: a systematic review and evidence-based clinical practice guideline*. J Neurooncol 96:97-102. doi:10.1007/s11060-009-0056-5
330. Al-Shamy G, Sawaya R (2009) *Management of brain metastases: the indispensable role of surgery*. J Neurooncol 92:275-282. doi:10.1007/s11060-009-9839-y
331. Kennion O, Holliman D (2017) *Outcome after craniotomy for recurrent cranial metastases*. Br J Neurosurg:1-5. doi:10.1080/02688697.2017.1302072
332. Schackert G, Schmiedel K, Lindner C, Leimert M, Kirsch M (2013) *Surgery of recurrent brain metastases: retrospective analysis of 67 patients*. Acta neurochirurgica 155:1823-1832. doi:10.1007/s00701-013-1821-y
333. Stummer W, Novotny A, Stepp H, Goetz C, Bise K, Reulen HJ (2000) *Fluorescence-guided resection of glioblastoma multiforme by using 5-aminolevulinic acid-induced porphyrins: a prospective study in 52 consecutive patients*. Journal of neurosurgery 93:1003-1013. doi:10.3171/jns.2000.93.6.1003
334. Stummer W, Reulen HJ, Meinel T, Pichlmeier U, Schumacher W, Tonn JC, Rohde V, Oppel F, Turowski B, Woiciechowsky C, Franz K, Pietsch T, Group AL-GS (2008) *Extent of resection and survival in glioblastoma multiforme: identification of and adjustment for bias*. Neurosurgery 62:564-576; discussion 564-576. doi:10.1227/01.neu.0000317304.31579.17
335. Pessina F, Navarria P, Cozzi L, Ascolese AM, Maggi G, Rossi M, Riva M, Scorsetti M, Bello L (2016) *Role of Surgical Resection in Patients with Single Large Brain Metastases: Feasibility, Morbidity, and Local Control Evaluation*. World neurosurgery 94:6-12. doi:10.1016/j.wneu.2016.06.098
336. Ringel F, Pape H, Sabel M, Krex D, Bock HC, Misch M, Weyerbrock A, Westermaier T, Senft C, Schucht P, Meyer B, Simon M, group SNs (2016) *Clinical benefit from resection of recurrent glioblastomas: results of a multicenter study including 503 patients with recurrent glioblastomas undergoing surgical resection*. Neuro Oncol 18:96-104. doi:10.1093/neuonc/nov145
337. Duffau H (2015) *Resecting diffuse low-grade gliomas to the boundaries of brain functions: a new concept in surgical neuro-oncology*. Journal of neurosurgical sciences 59:361-371
338. Eyupoglu IY, Hore N, Fan Z, Buslei R, Merkel A, Buchfelder M, Savaskan NE (2015) *Intraoperative vascular DIVA surgery reveals angiogenic hotspots in tumor zones of malignant gliomas*. Sci Rep 5:7958. doi:10.1038/srep07958
339. Berghoff AS, Preusser M (2015) *The future of targeted therapies for brain metastases*. Future Oncol 11:2315-2327. doi:10.2217/fon.15.127
340. Berghoff AS, Preusser M (2017) *Targeted Therapies for Melanoma Brain Metastases*. Curr Treat Options Neurol 19:13. doi:10.1007/s11940-017-0449-2
341. Abusabha Y, Petridis AK, Kraus B, Kamp MA, Steiger HJ, Beseoglu K (2017) *Life-threatening posterior reversible encephalopathy syndrome in the cerebellum treated by posterior fossa decompression*. Acta neurochirurgica 159:1325-1328. doi:10.1007/s00701-017-3228-7

342. Lohmann P, Stoffels G, Ceccon G, Rapp M, Sabel M, Filss CP, Kamp MA, Stegmayr C, Neumaier B, Shah NJ, Langen KJ, Galldiks N (2017) *Radiation injury vs. recurrent brain metastasis: combining textural feature radiomics analysis and standard parameters may increase (18)F-FET PET accuracy without dynamic scans*. European radiology 27:2916-2927. doi:10.1007/s00330-016-4638-2
343. Sperduto PW, Chao ST, Sneed PK, Luo X, Suh J, Roberge D, Bhatt A, Jensen AW, Brown PD, Shih H, Kirkpatrick J, Schwer A, Gaspar LE, Fiveash JB, Chiang V, Knisely J, Sperduto CM, Mehta M (2010) *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 77:655-661. doi:10.1016/j.ijrobp.2009.08.025

Acknowledgements

An erster Stelle möchte ich Prof. Dr. Steiger danken, der mich richtungsweisend und mit Engagement während dieser Arbeit und meiner Facharztausbildung begleitet hat.

Des Weiteren möchte ich mich herzlich bei dem ganzen Neurochirurgischen-Team des Universitätsklinikums Düsseldorf bedanken, insbesonderes Prof. Dr. Sabel, Prof. Dr. Cornelius, Prof. Dr. Vesper und PD Dr. Slotty.

Danken möchte ich außerdem meinen Kollegen PD Dr. Beez und PD Dr. Beseoglu für die tägliche Unterstützung, Geduld und Engagement.

Der größte Dank gilt PD. Dr. Kamp! Ohne Seine Unterstützung wäre das Ganze nicht möglich gewesen.

Nicht minder aufreibend waren die vergangenen Jahre für meine Familie und Freunde, die diese "Fahrt" in allen Phasen mit jeder möglichen Unterstützung bedacht haben. Ihnen gilt mein spezieller Dank. Gracias, gracias y muchas gracias…

A Paty, Dr. Azmitia y Dr. Matheu: siempre estaré en deuda con Ustedes. Por siempre agradecido!

A la vieja… sin Usted todo ésto sería sólo un sueño. Nunca podré terminar de agradecerle…

"It is the mark of an educated mind to be able to entertain a thought without accepting it."

Aristotle