M.A. Hayat
Editor

Tumors of the Central Nervous System

Volume 11
Pineal, Pituitary, and Spinal Tumors

Springer

Tumors of the Central Nervous System
Volume 11

For further volumes:
http://www.springer.com/series/8812

Tumors of the Central Nervous System
Volume 11

Tumors of the Central Nervous System

Pineal, Pituitary, and Spinal Tumors

Edited by

M.A. Hayat
Distinguished Professor
Department of Biological Sciences,
Kean University, Union, NJ, USA

Springer

Editor
M.A. Hayat
Department of Biological Sciences
Kean University
Room 213, Library building
Morris Avenue 1000
Union, NJ 07083, USA

ISBN 978-94-007-7036-2 ISBN 978-94-007-7037-9 (eBook)
DOI 10.1007/978-94-007-7037-9
Springer Dordrecht Heidelberg New York London

Library of Congress Control Number: 2013945296

Printed on acid-free paper

Springer is part of Springer Science+Business Media (www.springer.com)

Although touched by technology, surgical pathology always has been, and remains, an art. Surgical pathologists, like all artists, depict in their artwork (surgical pathology reports) their interactions with nature: emotions, observations, and knowledge are all integrated. The resulting artwork is a poor record of complex phenomena.

Richard J. Reed, MD

One Point of View

All small tumors do not always keep growing, especially small breast tumors, testicular tumors, and prostate tumors. Some small tumors may even disappear without a treatment. Indeed, because prostate tumor grows slowly, it is not unusual that a patient may die at an advanced age of some other causes, but prostate tumor is discovered in an autopsy study. In some cases of prostate tumors, the patient should be offered the option of active surveillance followed by PSA test or biopsies. Similarly, every small kidney tumor may not change or may even regress. Another example of cancer or precancer reversal is cervical cancer. Precancerous cervical cells found with Pap test may revert to normal cells. Tumor shrinkage, regression, dormancy, senescence, reversal, or stabilization is not impossible. Can prosenescence therapy be an efficient alternative strategy to standard therapies for cancer prevention and treatment?

Another known example of cancer regression is found in pediatric neuroblastoma patients. Neuroblastoma shows one of the highest rates of spontaneous regression among malignant tumors. In addition to the well-known spontaneous regression in stage 4S disease, the high incidence of neuroblastoma remnants found during autopsy of newborns suggest that localized lesions may undergo a similar regression (Guin et al., 1969). Later studies also indicate that spontaneous regression is regularly seen in infants with localized neuroblastoma and is not limited to the first year of life (Hero et al., 2008). These and other studies justify the "wait and see" strategy, avoiding chemotherapy and radiotherapy in infants with localized neuroblastoma, unless MYCN gene is amplified. Infants with nonamplified MYCN and hyperdiploidy can be effectively treated with less intensive therapy. Infants with disseminated disease without MYCN have excellent survival with minimal or no treatment. Another example of spontaneous shrinkage and loss of tumors without any treatment is an intradural lipoma (Endoh et al., 1998).

Although cancers grow progressively, various lesions such as cysts and thyroid adenomas show self-limiting growth. Probably, cellular senescence occurs in many organ types following initial mutations. Cellular senescence, the growth arrest seen in normal mammalian cells after a limited number of divisions, is controlled by tumor suppressors, including p53 and p16, and so this phenomenon is believed to be a crucial barrier to tumor development. It is well-established that cell proliferation and transformation induced by oncogene activation are restrained by cellular senescence.

Metastasis is the main cause of death from cancer. Fortunately, metastasis is an inefficient process. Only a few of the many cancer cells detached from the primary tumor succeed in forming secondary tumors. Metastatic inefficiency varies depending on the location within an organ, but the malignancy may continue to grow preferentially in a specific tissue environment. Some of the cancer cells shed from the primary tumor are lost in the circulation due to hemodynamic forces or the immune system, macrophages, and natural killer cells.

Periodic rejection of a drug by FDA, which was previously approved by the FDA, is not uncommon. Most recently, the FDA ruled that Avastin should not be used to treat advanced breast cancer, although it remains on the market to treat other cancers, including colon and lung malignancies. Side-effects of Avastin include high blood pressure, massive bleeding, heart attack, and damage to the stomach and intestines.

Unwanted side effects of some drug excipients (e.g., propylene glycol, menthol) may also pose safety concerns in some patients. Excipients are defined as the constituents of the pharmaceutical formulation used to guarantee stability, and physicochemical, organoleptic and biopharmaceutical properties. Excipients frequently make up the majority of the volume of oral and parenteral drugs. Not all excipients are inert from the biological point of view. Although adverse drug reactions caused by the excipients are a minority of all adverse effects of medicinal products, the lack of awareness of the possible risk from excipients should be a concern for regulatory agencies, physicians, and patients (Ursino et al., 2011). Knowledge of the potential side effects of excipients is important in clinical practice.

It is known that chemotherapy can cause very serious side-effects. One most recent example of such side-effects was reported by Rubsam et al. (2011). Advanced hepatocellular carcinoma (HCC) induced by hepatitis C virus was treated with Sorafenib. It is an oral multikinase inhibitor that interferes with the serine/threonine kinases RAF-1 and B-Raf and the receptor tyrosine kinases of the vascular endothelial growth factor receptors and the platelet-derived growth factor receptor-beta. Although sorafenib is effective in regressing HCC, it shows serious side-effects including increasingly pruritic and painful skin changes (cutaneous eruption).

An example of unnecessary surgery is the removal of all the armpit lymph nodes after a biopsy when a sentinel node shows early stage breast cancer; removal of only the sentinel node may be needed. Limiting the surgery to the sentinel node avoids painful surgery of the armpit lymph nodes, which can have complications such as swelling and infection (such limited surgery is already being practiced at the Memorial Sloan-Kettering Cancer Research Center). Radiation-induced second cerebral tumors constitute a significant risk for persons undergoing radiotherapy for the management of cerebral neoplasms. High-grade gliomas are the most common radiation-induced tumors in children (Pettorini et al., 2008). The actual incidence of this complication is not known, although it is thought to be generally low.

Medical Radiation

Chromosome aberrations induced by ionizing radiation are well-known. Medical radiation-induced tumors are well-documented. For example, several types of tumors (sarcomas, meningiomas) can develop in the CNS after irradiation of the head and neck region (Parent, 1990). Tumorigenic mechanisms underlying the radiation therapy of the CNS are discussed by Amirjamshidi and Abbassioun (2000) (see below).

Radiation therapy is commonly used to treat, for example, patients with primary and secondary brain tumors. Unfortunately, ionizing radiation has limited tissue specificity and tends to damage both neoplastic and normal brain tissues. Radiation-induced brain injury, in fact, is a potential, insidious later cerebral side-effect of radiotherapy. Most commonly it consists of damage in small arteries and capillaries, resulting in secondary processes of ischemia.

After radiation therapy, imaging techniques (CT, MRI, SPECT) can be used to assess treatment response and detect radiation-induced lesions and recurrent tumors. Optical spectroscopy has also been used for detecting radiation damage (Lin et al., 2005). The F_{500} nm spectral peak allows accurate selection of tissues for biopsy in evaluating patients with new, contrast enhancing lesions in the setting of previous irradiation. This peak is highly correlated with a histological pattern of radiation injury. Deep lesions require a stereotactic biopsy to be conclusive. Also, much of the radiation effect is mediated by acute and chronic inflammatory cellular reactions. Biopsy samples supplement pathological differentiation of radiation effect from tumor progression. It should be noted that most of the biopsies show radionecrosis as well as scattered tumor cells.

Women treated with therapeutic chest radiation may develop cancer. This possibility becomes exceedingly serious considering that 50,000–55,000 women in the United States have been treated with moderate to high-dose chest radiation (~20 Gy). This possibility is much more serious for pediatric or young adult cancer patients, because these women are at a significantly increased risk of breast cancer and breast cancer mortality following cure of their primary malignancy (Mertens et al., 2008). A recent study also indicates that such young women develop breast cancer at a young age, which does not appear to plateau (Henderson et al., 2010). In this high risk population, ironically there is a benefit associated with early detection. In other words, young women with early stage breast cancer following chest radiation have a high likelihood for favorable outcome, although life-long surveillance is needed.

Presently, although approximately 80 % of the children with cancer are cured, the curative therapy could damage a child's developing organ system; for example, cognitive deficits following cranial radiotherapy are well known. Childhood survivors of malignant diseases are also at an increased risk of primary thyroid cancer (Sigurdson et al., 2005). The risk of this cancer increases with radiation doses up to 20–29 Gy. In fact, exposure to radiation therapy is the most important risk factor for the development of a new CNS tumor in survivors of childhood cancer, including leukemia and brain tumors. The higher risk of subsequent glioma in children subjected to medical radiation

at a very young age reflects greater susceptibility of the developing brain to radiation. The details of the dose-response relationships, the expression of excess risk over time, and the modifying effects of other host and treatment factors have not been well defined (Neglia et al., 2006).

A recent study indicates that childhood brain tumor survivors are at an increased risk of late endocrine effects, particularly the patients treated with cranial radiation and diagnosed at a younger age (Shalitin et al., 2011). Among children with cancer, the application of radiotherapy, therefore, should not be taken lightly, and it should be administered only when absolutely necessary to successfully treat the primary tumor. When radiotherapy is administered, use of the minimum effective dose tends to minimize the risk of second CNS neoplasms (late effect). Prolonged follow-up of childhood cancer survivors (particularly those treated with radiation) is necessary because of the long period between treatment and the development of malignancy. This practice should be a part of the effective therapy of the primary disease.

It is well established that radiation doses are related to risk for subsequent malignant neoplasms in children with Hodgkin's disease. It has been reported that increasing radiation dose was associated with increasing standardized incidence ratio ($p=0.0085$) in survivors of childhood Hodgkin's disease (Constine et al., 2008). Approximately, 75 % of subsequent malignancies occurred within the radiation field. Although subsequent malignancies occur, for example, in breast cancer survivors in the absence of radiotherapy, the rise increases with radiation dose.

The pertinent question is: Is it always necessary to practice tumor surgery, radiotherapy, chemotherapy or hormonal therapy or a combination of these therapies? Although the conventional belief is that cancer represents an "arrow that advances unidirectionally", it is becoming clear that for cancer to progress, it requires cooperative microenvironment (niche), including immune system and hormone levels. However, it is emphasized that advanced (malignant) cancers do not show regression, and require therapy. In the light of the inadequacy of standard treatments of malignancy, clinical applications of the stem cell technology need to be expedited.

Prostate Cancer

There were an estimated 217,730 new cases of prostate cancer in the United States in 2010 with 32,050 deaths, making it the second leading cause of cancer deaths in men. Currently, there are more than 2,000,000 men in the United States who have had radical or partial prostate surgery performed. Considering this huge number of prostate surgeries and the absence of a cumulative outcome data, it seems appropriate to carefully examine the benefits of radical surgery, especially in younger men.

Clinical prostate cancer is very rare in men of the ages younger than 40 years. In this age group the frequency of prostate malignancy is 1 in 10,000 individuals. Unfortunately, the incidence of malignancy increases over the ensuing decades, that is, the chance of prostate malignancy may reach to 1 in 7 in men between the ages of 60 and 79 years. Reactive or aging-related

alterations in the tumor microenvironment provide sufficient influence, promoting tumor cell invasion and metastasis. It has been shown that nontumorigenic prostate epithelial cells can become tumorigenic when cocultured with fibroblasts obtained from regions near tumors (Olumi et al., 1999).

Prostate cancer treatment is one of the worst examples of overtreatment. Serum prostate specific antigen (PSA) testing for the early detection of prostate cancer is in wide use. However, the benefit of this testing has become controversial. The normal cut-off for serum levels of PSA is 4 ng/ml, so a man presenting with a PSA above this level is likely to require a rectal biopsy, but only 25 % of men with serum levels of PSA between 4 ng and 10 ng/ml have cancer (Masters, 2007). The PSA threshold currently being used for biopsy ranges between 2.5 and 3.4 ng/ml. Up to 50 % of men presenting with prostate cancer have PSA levels within the normal range. It is apparent that screening of prostate cancer using PSA has a low specificity, resulting in many unnecessary biopsies, particularly for gray zone values (4–10 ng/ml). According to one point of view, the risks of prostate cancer overdetection are substantial. In this context, overdetection means treating a cancer that otherwise would not progress to clinically significant disease during the lifetime of the individual. Overdetection results in overtreatment. The advantages and limitations of PSA test in diagnosing prostate cancer were reviewed by Hayat (2005, 2008).

Androgen deprivation therapy (ADT) is an important treatment for patients with advanced stage prostate cancer. This therapy is carried out by blocking androgen receptor or medical or surgical castration. Although ADT is initially very effective, treated tumors inevitably progress to androgen-independent prostate cancer (AIPC), which is incurable. One possible mechanism responsible for the development of AIPC is modulation of the tissue microenvironment by neuroendocrine-like cancer cells, which emerge after ADT (Nelson et al., 2007).

Recently, Pernicova et al. (2011) have further clarified the role of androgen deprivation in promoting the clonal expansion of androgen-independent prostate cancer. They reported a novel linkage between the inhibition of the androgen receptor activity, down-regulation of S-phase kinase-associated protein 2, and the formation of secretory, senescent cells in prostate tumor cells. It is known that several components of the SASP secretome, such as IL-6, IL-8, KGH, and epidermal growth factor, are capable of transactivating androgen receptor under androgen-depleted conditions (Seaton et al., 2008). It needs to be pointed out that androgen deprivation therapy, used in high-risk patients with prostate cancer, may cause reduced libido, erectile dysfunction, fatigue, and muscle loss; osteoporosis is also a late complication. Therefore, periodic bone density scanning needs to be considered.

Recently, the FDA cleared the use of NADiA (nucleic acid detection immunoassay) ProsVue prognostic cancer test. This proprietary nucleic acid detection immunoassay technology identifies extremely low concentrations of proteins that have not been routinely used as a diagnostic or prognostic aid. It is an *in vitro* diagnostic assay for determining the rate of change of serum total PSA over a period of time. The assay can quantitate PSA at levels<1 ng/ml. This technique can be used as a prognostic marker, in conjunction with

clinical evaluation, to help identify patients at reduced risk for recurrence of prostate cancer for years following prostatectomy. It targets the early detection of proteins associated with cancer and infectious diseases. This technique combines immunoassay and real-time PCR methodologies with the potential to detect proteins with femtogram/ml sensitivity (10–15 g/ml). Additional clinical information is needed regarding its usefulness in predicting the recurrence.

A significant decrease in the risk of prostate cancer-specific mortality is observed in men with few or no comorbidities. Indeed, active surveillance in lieu of immediate treatment (surgery or radiation, or both) is gaining acceptance. Most men with prostate cancer, even those with high-risk disease, ultimately die as a result of other causes (Lu-Yao et al., 2009). Debate on this controversy is welcome, but narrow opinions and facile guidelines will not lead to facts and new information; men worldwide deserve it (Carroll et al., 2011). Automatic linking positive diagnosis with treatment, unfortunately, is a common clinical practice. Unfortunately, even men who are excellent candidates for active surveillance in the United States often undergo some treatment. Deferment of treatment is advised in men with low-risk disease, especially of a younger age.

Active surveillance is proposed for patients with low-risk prostate cancer in order to reduce the undesirable effects of overdiagnosis. Prostate specific antigen serum level lower than 10 ng/l and Gleason score lower than 7 are the main criteria to select patients for active surveillance. The correct use of these two criteria is essential to differentiate between aggressive and nonaggressive prostate cancer. Autopsy studies indicate that approximately one out of three men older than 50 years show histological evidence of prostate cancer (Klotz, 2008). Thus, a large proportion of prostate cancers are latent, never destined to progress, or affect the life of the patient. It is estimated that the percentage of low-risk prostate cancer is between 50 and 60 % of newly diagnosed cases. A large number of patients die having prostate cancer, but not because of this cancer (Filella et al., 2011).

First whole genome sequences of prostate tumors were recently published online in *Nature* journal (vol. 470: 214–220, 2011). This study revealed that rather than single spelling errors, the tumor has long "paragraphs" of DNA that seem to have broken off and moved to another part of the genome (rearrangement of genes), where they are most active. These portions of DNA contain genes that help drive cancer progression. The mutated genes involved include *PTEN, CADM2, MAG12, SPOP*, and *SPTA1*. This information may lead to the development of more efficient, less invasive ways to diagnose and treat this cancer. Such information, in addition, should lead to personalized therapeutics according to sequencing results of different gene mutations or chromosomal rearrangements. The urgent need of such studies becomes apparent considering the huge number of new cases of prostate problems reported every year.

In contrast to prostate cancer, cardiovascular disorders take the heavier toll of life. In other words, the risk of death for men in the United States between the ages of 55 and 74 years due to cardiovascular disease surpasses that of prostate cancer. Cardiovascular disease is the most common of the chronic non-communicable diseases that impact global mortality. Approximately, 30 % of all deaths worldwide and 10 % of all healthy life lost to disease are accounted for by cardiovascular disease alone.

In conclusion, initial treatment with standard surgery, irradiation, chemotherapy, or hormonal therapy, or combination of these protocols can result in both local and systemic sequalae. Therefore, surveillance for late recurrence and secondary primary malignancies is recommended for most cancer patients. Patients with breast, lung, prostate, colorectal, and head and neck cancers constitute the largest groups requiring long-term monitoring and follow-up care.

Eric Hayat

References

Amirjamshidi A, Abbassioun K (2000) Radiation-induced tumors of the central nervous system occurring in childhood and adolescence. Child Nerv Syst 16:390–397

Carroll PR, Whitson JH, Cooperberg MR (2011) Serum prostate-specific antigen for the early detection of prostate cancer; always, never, or only sometimes? J Clin Oncol 29:345–346

Constine LS, Tarbell N, Hudson MM et al (2008) Subsequent malignancies in children treated for Hodgkin's disease; associations with gender and radiation dose. Int J Rad Oncol Biol Physol 72:24–33

Endoh M, Iwasaki Y, Koyanagi I, Hida K, Abe H (1998) Spontaneous shrinkage of lumbosacral lipoma in conjunction with a general decrease in body fat: case report. Neurosurgery 43(1):150–151; discussion 151–152

Filella X, Alcover J, Molina R (2011) Active surveillance in prostate cancer: the need to standardize. Tumor Biol 32:839–843

Guin P, Gilbert E, Jones B (1969) Incidental neuroblastoma in infants. Am J Clin Pathol 51:126–136

Hayat MA (2005) Prostate carcinoma: an introduction. In: Immunohistochemistry and in situ hybridization of human carcinomas, vol 2. Elsevier, San Francisco, pp 279–297

Hayat MA (2008) Prostate carcinoma. In: Methods of cancer diagnosis, therapy, and prognosis, vol 2. Springer, New York, pp 391–396

Henderson TO, Amsterdam A et al (2010) Surveillance for breast cancer in women treated with chest radiation for a childhood, adolescent or young adult cancer: a report from Children's Oncology Group. Ann Int Med 152:1–22

Hero S, Simon T, Spitz R, Ernestus K, Gnekow A, Scheel-Walter H, Schwabe D, Schilling F, Benz-Bohm G, Berthold F (2008) Localized infant neuroblastomas often show spontaneous regression: results of the prospective trials NB95-S and NB 97. J Clin Oncol 26:1504–1510

Klotz L (2008) Low-risk prostate cancer can and should often be managed with active surveillance and selective delayed intervention. Nat Clin Pract Urol 5:2–3

Lin W-C, Mahadevan-Jansen A, Johnson MD, Weil R, Toms SA (2005) *In vivo* optical spectroscopy detects radiation damage in brain tissue. Neurosurgery 57:518–525

Lu-Yao GL, Albertsen PC, Moore DF et al (2009) Outcomes of localized prostate cancer following conservative management. JAMA 302:1202–1209

Masters JR (2007) Clinical applications of expression profiling and proteomics in prostate cancer. Anticancer Res 27:1273–1276

Mertens AC, Liu Q, Neglia JP et al (2008) Cause-specific late mortality among 5-year survivors of childhood cancer: the Childhood Cancer Survivor Study. J Natl Cancer Inst 100:1368–1379

Neglia JP, Robison LL, Stovall M, Liu Y, Packer RJ et al (2006) New primary neoplasms of the central nervous system in survivors of childhood cancer: a report from the childhood cancer survivor study. J Natl Cancer Inst 98:1528–1537

Nelson EC, Cambio AJ, Ok JH, Lara PN Jr, Evans CP (2007) Clinical implications of nueroendocrine differentiation in prostate cancer. Prostate Cancer Prostatic Dis 10:6–14

Olumi AF, Grossfeld GD, Hayward SW, Carroll PR, Tlsty TD, Cunha GR (1999) Carcinoma-associated fibroblasts direct tumor progression of initiated human prostatic epithelium. Cancer Res 59:5002–5011

Parent AD (1990) Late complications of radiation-induced neoplasms. Neurosurgery 26:1090–1091

Pernicova Z, Slabakova E, Kharaishvill G, Bouchal J, Kral M, Kunicka Z, Machalam M, Kozubik A, Soucek K (2011) Androgen depletion induces senescence in prostate cancer cells through down-regulation of SKp2. Neoplasia 13:526–536

Pettorini BL, Park Y-S, Caldarelli M, Massimi L, Tamburrini G, DiRocco C (2008) Radiation induced brain tumors after central nervous system irradiation in childhood: a review. Child's Nervous Syst 24:793–805

Rubsam K, Flaig MJ, Ruzicka T, Prinz JC (2011) Erythema marginatum hemorrhagicum: a unique cutaneous side effect of sorafenib. J Am Acad Dermatol 64:1194–1196

Seaton A, Scullin P, Maxwell PJ, Wilson C, Pettigrew J, Gallagher R, O'Sullivan JM, Johnston PG, Waugh DJ (2008) Interleukin-8 signaling promotes androgen-independent proliferation of prostate cancer cells via induction of androgen receptor expression and activation. Carcinogenesis 6:1148–1156

Shalitin S, Gal M, Goshen Y, Cohen I, Yaniv I, Philip M (2011) Endocrine outcome in long-term survivors of childhood brain tumors. Horm Res Paediatr 76:113–122

Sigurdson AJ, Ronckers CM, Mertens AC et al (2005) Primary thyroid cancer after a first tumor in childhood (the childhood cancer survivor study): a nested case-control study. Lancet 365:2014–2023

Ursino MG, Poluzzi E, Caramella C, DePonti F (2011) Excipients in medicinal products used in gastroenterology as a possible cause of side effects. Regul Toxicol 60:93–105

Preface

It is recognized that scientific journals and books not only provide current information but also facilitate exchange of information, resulting in rapid progress in the medical field. In this endeavor, the main role of scientific books is to present current information in more details after careful additional evaluation of the investigational results, especially those of new or relatively new therapeutic methods and their potential toxic side-effects.

Although subjects of diagnosis, drug development, therapy and its assessment, and prognosis of tumors of the central nervous system, cancer recurrence, and resistance to chemotherapy are scattered in a vast number of journals and books, there is need of combining these subjects in single volumes. An attempt will be made to accomplish this goal in the projected fourteen-volume series of handbooks.

In the era of cost-effectiveness, my opinion may be minority perspective, but it needs to be recognized that the potential for false-positive or false-negative interpretation on the basis of a single laboratory test in clinical pathology does exist. Interobservor or intraobservor variability in the interpretation of results in pathology is not uncommon. Interpretative differences often are related to the relative importance of the criteria being used.

Generally, no test always performs perfectly. Although there is no perfect remedy to this problem, standardized classifications with written definitions and guidelines will help. Standardization of methods to achieve objectivity is imperative in this effort. The validity of a test should be based on the careful, objective interpretation of the tomographic images, photo-micrographs, and other tests. The interpretation of the results should be explicit rather than implicit. To achieve accurate diagnosis and correct prognosis, the use of molecular criteria and targeted medicine is important. Equally important are the translation of molecular genetics into clinical practice and evidence-based therapy. Translation of medicine from the laboratory to clinical application needs to be carefully expedited. Indeed, molecular medicine has arrived.

This is the eleventh volume in the series, Tumors of the Central Nervous System. As in the case of the ten previously published volumes, this volume mainly contains information on the diagnosis, therapy, and prognosis of brain tumors. Various aspects of four types of tumors (Glioblastoma, Meningioma, Schwannoma, and Spinal Tumors) are discussed. Various types of brain imaging methods, including molecular imaging and PET are explained in detail. The application of stereotactic radiosurgery for treating

high risk patients with brain metastasis is presented. Tumor seeding following stereotactic brain surgery is included.

Introduction to new technologies and their applications to tumor diagnosis, treatment, and therapy assessment are explained. Molecular profiling of brain tumors to select therapy in clinical trials of brain tumors is included. Several surgical treatments, including resection and radiosurgery, are discussed. The remaining volumes in this series will provide additional recent information on this and other aspects of CNS malignancies.

By bringing together a large number of experts (oncologists, neurosurgeons, physicians, research scientists, and pathologists) in various aspects of this medical field, it is my hope that substantial progress will be made against this terrible disease. It would be difficult for a single author to discuss effectively the complexity of diagnosis, therapy, and prognosis of any type of tumor in one volume. Another advantage of involving more than one author is to present different points of view on a specific controversial aspect of the CNS cancer. I hope these goals will be fulfilled in this and other volumes of this series. This volume was written by 93 contributors representing 8 countries. I am grateful to them for their promptness in accepting my suggestions. Their practical experience highlights their writings, which should build and further the endeavors of the reader in this important area of disease. I respect and appreciate the hard work and exceptional insight into the nature of cancer provided by these contributors. The contents of the volume are divided into three subheadings: Pineal Tumors, Pituitary Tumors, and Spinal Tumors for the convenience of the reader.

It is my hope that the current volume will join the preceding volumes of the series for assisting in the more complete understanding of globally relevant cancer syndromes. There exists a tremendous, urgent demand by the public and the scientific community to address to cancer diagnosis, treatment, cure, and hopefully prevention. In the light of existing cancer calamity, financial funding by governments must give priority to eradicating this deadly malignancy over military superiority.

I am thankful to Dr. Dawood Farahi and Philip Connelly for recognizing the importance of medical research and publishing through an institution of higher education. I am also thankful to my students for their contribution to the preparation of this volume.

Union, NJ, USA M.A. Hayat
April, 2013

Contents

Contents of Volume 1

Contents of Volume 2

Contents of Volume 3

Contents of Volume 4

Contents of Volume 5

Contents of Volume 6

Contents of Volume 7

Contents of Volume 8

Contents of Volume 9

Contents of Volume 10

Contributors

Manish K. Aghi UCSF Neurosurgery, San Francisco, USA

Johnny Akers UCSD Neurosurgery, San Diego, CA, USA

Jun Amano Department of Surgery, Shinshu University School of Medicine, Matsumoto, Japan

Chiazo Amene Department of Neurosurgery, University of California, San Diego, Rady Children's Hospital, La Jolla, CA, USA

Christopher J. Anker Department of Radiation Oncology, Huntsman Cancer Hospital, University of Utah, Salt Lake City, UT, USA

Susan Biffl Children's Hospital Colorado Rehabilitation Medicine, Aurora, CO, USA

Amy Lee Bredlau Division of Pediatric Neuro-Oncology, University of Medical University of South Carolina, Charleston, SC, USA

Wilfried Budach Department of Radiation Oncology, Heinrich Heine University, Düsseldorf, Germany

Manuela Caroli Neurosurgery Unit, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milano, Italy

Bob Carter UCSD Neurosurgery, San Diego, CA, USA

Brandyn A. Castro Department of Neurological Surgery and Hellen Diller Family Comprehensive Cancer Center, University of California, San Francisco, CA, USA

Steven D. Chang Department of Neurosurgery, Robert C. and Jeannette Powell Professor in the Neurosciences, Stanford University, Stanford, CA, USA

Michael A. Chappell Institute of Biomedical Engineering, University of Oxford, Oxford, UK

Clark Chen UCSD Neurosurgery, San Diego, CA, USA

Varun Kumar Chowdhry Department of Radiation Oncology, SUNY Upstate Medical University, Syracuse, NY, USA

John Crawford Department of Neurosciences and Pediatrics, Division of Child Neurology and Hematology-Oncology, University of California, San Diego, Rady Children's Hospital, La Jolla, CA, USA

Andrea Di Cristofori Neurosurgery Unit, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milano, Italy

Takashi Eguchi Department of Thoracic Surgery, Shinshu University School of Medicine, Matsumoto, Japan

D. Gareth R. Evans Department of Genetic Medicine, St. Mary's Hospital, Manchester Academic Health Sciences Center, University of Manchester, Manchester, UK

Emmanouil Fokas Department of Radiation Therapy and Oncology, Johann Wolfgang Goethe University, Frankfurt, Germany

Masayuki Fujiwara Department of Pathology, Ina Central Hospital, Ina, Japan

Takanori Fukushima Division of Neurosurgery, Duke University Medical Center, Durham, NC, USA

Carolina Neuroscience Institute, International Neurosurgery Education and Research Foundation, Raleigh, NC, USA

Frederik L. Giesel Department of Nuclear Medicine, University Hospital Heidelberg, Heidelberg, Germany

John G. Golfinos Department of Neurosurgery, NYU Langone Medical Center, New York, NY, USA

David Gonda UCSD Neurosurgery, San Diego, CA, USA

Amit Goyal UCSD Neurosurgery, San Diego, CA, USA

Gordan Grahovac Department of Neurosurgery, University Hospital "Dubrava", Zagreb, Croatia

Wiesława Grajkowska Department of Experimental and Clinical Neuropathology, Mossakowski Medical Research Centre, Polish Academy of Sciences, Warsaw, Poland

Steven J. Greco UMDNJ-New Jersey Medical School, Newark, NJ, USA

Seung Shin Hahn Department of Radiation Oncology, SUNY Upstate Medical University, Syracuse, NY, USA

Christian Hartmann Clinical Cooperation Unit Neuropathology, German Cancer Center and Department of Neuropathology, Institute of Pathology, Ruprecht-Karls University Heidelberg, Heidelberg, Germany

Toshinori Hasegawa Department of Neurosurgery, Gamma Knife Center, Komaki City Hospital, Komaki, Aichi Prefecture, Japan

M.A. Hayat Department of Biological Sciences, Kean University, Union, NJ, USA

Yohei Hidai Department of Orthopedics, Ina Central Hospital, Ina, Japan

Howard Hsu Department of Radiation Oncology, NYU Langone Medical Center, New York, NY, USA

Motoki Inaji Research Team for Neuroimaging, Tokyo Metropolitan Institute of Gerontology, Tokyo, Japan

Bowen Jiang Department of Neurosurgery, Stanford University Medical Center, Stanford, CA, USA

Marcel A. Kamp Department of Neurosurgery, Heinrich Heine University, Düsseldorf, Germany

Philipp Kickingereder Department of Stereotaxy and Functional Neurosurgery, University Hospital of Cologne, Cologne, Germany

Shohei Kohno Department of Neurosurgery, Ehime University Graduate School of Medicine, Shitsukawa, Toon, Ehime, Japan

Ricardo J. Komotar Department of Neurosurgery, University of Virginia Health System, Charlottesville, VA, USA

Department of Neurosurgery, University of Miami, Miami, FL, USA

David N. Korones Division of Pediatric Hematology/Oncology and Division of Palliative Care, University of Rochester Medical Center, Rochester, NY

Yoshiaki Kumon Department of Neurosurgery, Ehime University Graduate School of Medicine, Shitsukawa, Toon, Ehime, Japan

Michael Levy Department of Neurosurgery, University of California, San Diego, Rady Children's Hospital, La Jolla, CA, USA

Francesca Lucarella Neurosurgery Unit, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milano, Italy

Cassie Ludwig Department of Neurosurgery, Stanford University Medical Center, Stanford, CA, USA

Nicole Ludwig Department of Human Genetics, Medical Faculty, Saarland University, Homburg, Saar, Germany

David Ly Department of Radiation Oncology, Huntsman Cancer Hospital, University of Utah, Salt Lake City, UT, USA

Emmanuel Mandonnet Department of Neurosurgery, Lariboisière Hospital, Paris, France

Makoto Matsubara Department of Radiology, Ina Central Hospital, Ina, Japan

Ewa Matyja Department of Experimental and Clinical Neuropathology, Mossakowski Medical Research Centre, Polish Academy of Sciences, Warsaw, Poland

Amit Mehndiratta Keble College, University of Oxford, Oxford, UK

Douglas C. Miller Department of Pathology and Anatomical Sciences, University of Missouri School of Medicine, Columbia, MO, USA

Christine Min Department of Radiation Oncology, NYU Langone Medical Center, New York, NY, USA

Zaman Mirzadeh Division of Neurological Surgery, Barrow Neurological Institute, St. Joseph's Hospital and Medical Center, Phoenix, AZ, USA

Jessian Munoz UMDNJ-New Jersey Medical School, Newark, NJ, USA

Tadashi Nariai Research Team for Neuroimaging, Tokyo Metropolitan Institute of Gerontology, Tokyo, Japan

Yoichi Nonaka Division of Neurosurgery, Duke University Medical Center, Durham, NC, USA

International Neurosurgery Education and Research Foundation, Raleigh, NC, USA

Jamie L. Odem Department of Pathology and Anatomical Sciences, University of Missouri School of Medicine, Columbia, MO, USA

Takanori Ohnishi Department of Neurosurgery, Ehime University Graduate School of Medicine, Shitsukawa, Toon, Ehime, Japan

Shiro Ohue Department of Neurosurgery, Ehime University Graduate School of Medicine, Shitsukawa, Toon, Ehime, Japan

Johan Pallud Department of Neurosurgery, University Paris Descartes – Sainte-Anne Hospital Center, Paris cedex 14, France

Stephen J. Payne Institute of Biomedical Engineering, University of Oxford, Oxford, UK

Pranela Rameshwar UMDNJ-New Jersey Medical School, Newark, NJ, USA

Daniel M.S. Raper Department of Neurosurgery, University of Virginia Health System, Charlottesville, VA, USA

Jean Regis Department of Stereotactic and Functional Neurosurgery CHU Timone, Public Assistance of the Hospitals of Marseilles, Aix Marseille University, Timone University Hospital, Marseilles, France

Maximilian I. Ruge Department of Stereotaxy and Functional Neurosurgery, University Hospital of Cologne, Cologne, Germany

Stephen Rush The NYU Gamma Knife Center, NYU Langone Medical Center, New York, NY, USA

Muneyuki Sakata Research Team for Neuroimaging, Tokyo Metropolitan Institute of Gerontology, Tokyo, Japan

Nora Sandu Department of Neurosurgery, University of Paris, Paris, France

Antonio Santacroce Departments of Neurosurgery and Radiation Oncology, Heinrich Heine University Düsseldorf, Düsseldorf, Germany

Atsushi Sato Department of Neurosurgery, Ina Central Hospital, Ina, Japan

Bernhard Schaller Department of Neurosurgery, University of Paris, Paris, France

Meic H. Schmidt Department of Neurosurgery, Huntsman Cancer Institute, University of Utah, Salt Lake City, UT, USA

Marcel Seiz Clinical Cooperation Unit Neuropathology, German Cancer Center and Department of Neuropathology, Institute of Pathology, Ruprecht-Karls University Heidelberg, Heidelberg, Germany

Yusaku Shimizu Department of Neurology, Ina Central Hospital, Ina, Japan

Atsunori Shinoda Department of Radiology, Ina Central Hospital, Ina, Japan

Ioannis Simiantonakis Department of Radiation Oncology, Heinrich Heine University, Düsseldorf, Germany

Miriam J. Smith Department of Genetic Medicine, St. Mary's Hospital, Manchester Academic Health Sciences Center, University of Manchester, Manchester, UK

Robert F. Spetzler Division of Neurological Surgery, Barrow Neurological Institute, St. Joseph's Hospital and Medical Center, Phoenix, AZ, USA

Toma Spiriev Department of Neurosurgery, University of Paris, Paris, France

Robert M. Starke Department of Neurosurgery, University of Virginia Health System, Charlottesville, VA, USA

Hans Jakob Steiger Department of Neurosurgery, Heinrich Heine University, Düsseldorf, Germany

Keiichiro Takasuna Departments of Thoracic Surgery, Ina Central Hospital, Ina, Japan

Yee Kai Tee Wolfson College, University of Oxford, Oxford, UK

Jun Toyohara Research Team for Neuroimaging, Tokyo Metropolitan Institute of Gerontology, Tokyo, Japan

Harald Treuer Department of Stereotaxy and Functional Neurosurgery, University Hospital of Cologne, Cologne, Germany

Anand Veeravagu Department of Neurosurgery, Stanford University Medical Center, Stanford, CA, USA

Kazuo Yoshida Department of Thoracic Surgery, Shinshu University School of Medicine, Matsumoto, Japan

Barbara Zarino Neurosurgery Unit, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milano, Italy

Samis Zella Neurosurgery Unit, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milano, Italy

Leonardo Zottarelli Neurosurgery Unit, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milano, Italy

Part I

Imaging

An Introduction to Brain Tumor Imaging

1

Amit Mehndiratta, Yee Kai Tee, Stephen J. Payne, Michael A. Chappell, and Frederik L. Giesel

Contents

A. Mehndiratta (✉)
Keble College, University of Oxford, Parks Road, Oxford, OX1 3PG, UK
e-mail: amit.mehndiratta@keble.ox.ac.uk

Y.K. Tee
Wolfson College, University of Oxford, Linton Road, Oxford, OX2 6UD, UK

S.J. Payne • M.A. Chappell
Institute of Biomedical Engineering, University of Oxford, Old Road Campus Research Building, Headington, Oxford, OX3 7DQ, UK

F.L. Giesel
Department of Nuclear Medicine, University Hospital Heidelberg, Heidelberg, Germany

Abstract

Brain tumors are among the leading causes of tumor-related deaths globally; hence considerable research effort is being expended to improve the patient outcome. There are now multiple imaging techniques available for the diagnosis and management of brain tumors in clinical practice, as well as different contrast agents. All these coupled with amino acid tracers newly available in positron emission tomography can offer more accurate tumor diagnosis. The evaluation of tumors using multiple imaging modalities is now one of the trends in neuroradiology, where computed tomography (CT), magnetic resonance imaging (MRI) and molecular imaging all play a vital role in the brain tumor assessment.

In this chapter, we will cover the clinical applications of computed tomography, magnetic resonance imaging with and without gadolinium contrast agents including perfusion weighted imaging, amide proton transfer imaging and magnetic resonance spectroscopy, and positron emission tomography (PET) for the evaluation of brain tumors. The advantages and limitations of each modality, as well as how they perform with respect to certain specific clinical questions.

M.A. Hayat (ed.), *Tumors of the Central Nervous System, Volume 11*,
DOI 10.1007/978-94-007-7037-9_1,

Introduction

Brain tumors are among the leading causes of tumor related deaths globally, with 10–15 out of every 100,000 people diagnosed in Europe and USA alone every year (Essig, 2003). There are a number of imaging techniques used in diagnosis and therapy for brain tumors, such as Computed Tomography (CT), Magnetic Resonance Imaging (MRI) and Positron Emission Tomography (PET). Variety of MRI sequences and contrast agents have enhanced the range of diagnostic imaging to a new level. Furthermore, the addition of amino acids tracers for use in PET has taken this imaging modality to a molecular level which enables the radiologist to target and measure tumor progression with much greater accuracy.

CT along with MRI (perfusion MRI and dynamic contrast enhanced (DCE) MRI) now play a pivotal role in brain tumor assessment. In this chapter, the latest brain tumor assessment protocols using CT, MRI with and without gadolinium contrast and PET imaging will be discussed and compared. This includes the more recent developments in the field such as amino acid tracer for PET, amide proton transfer imaging and MR spectroscopy. These new imaging methods have shown promising results in research and are now being used concurrently with the conventional imaging techniques to improve the evaluation of brain tumors.

Role of Diagnostic Imaging in Brain Tumor Assessment

Brain tumors can be categorized into primary or secondary tumors based on its originating tissue and intraaxial or extraaxial depending on its origin of growth. The most common primary intraaxial tumors are neuroepithelial tumors including astrocytoma, oligodendroglioma, glioblastoma multiforme and mixed glioma, whereas the most common primary extraaxial tumors are meningioma, pituitary adenoma, acoustic neuroma, schwannoma and caraniopharyngioma. Glioblastoma multiforme is the most common primary intraaxial brain tumor while meningioma is the most common extraaxial tumor accounting for 20 % of all brain tumors. Secondary metastatic brain lesions from systemic cancers are the most common brain tumors in general.

From the time when a patient comes to a radiologist with an intracranial mass (suspected as intracranial tumor) to the management and the post therapeutic prognosis, imaging plays an important role at each step. Although there are many different stages in diagnosis and management of intracranial tumor, they are often closely integrated with each other in practice and imaging can be of great use in some of the following steps (Kandel and Schavinsky, 1972; Mehndiratta and Giesel, 2011):

1. Detection and confirmation of the structural abnormality.
2. Localization and assessment of the extent of the pathological structure (lesion).
3. Grading the tumor: as neoplastic or non-neoplastic mass, if is neoplastic then further classify it as either malignant or benign.
4. Staging of the tumor: lymphatic and vascular spread or spread to other organs (Metastases).
5. Looking for involvement of any vital brain areas which might be of immediate concern for therapeutic planning.
6. Facilitate surgical planning (if required) by reviewing non-invasively the vital structures around tumor.
7. Intraoperative support during the surgical procedure.
8. Prognostic monitoring and follow up.

CT is often the first imaging technique used in brain tumor assessment because of its wide availability, low cost and minimally invasiveness. It is also considered to be a very good screening tool for the detection of a supratentorial abnormality, but MRI with more sophisticated sequences are required to provide accurate anatomical distinction for surgical planning. There are various structural features which are of key interest to a

radiologist for the evaluation of brain tumor (Mehndiratta and Giesel, 2011):

1. Signal contrast of tumor with respect to the normal brain parenchyma in vicinity.
2. Degree of contrast enhancement.
3. Tumor structure, margins, size and extent.
4. Associated perifocal edema.
5. Tumor signs (compression syndrome, midline shift etc.).
6. Tumor vascularity, especially the main vessel supplying the tumor and its course.

MR imaging can provide critical information for accurate diagnosis and surgical intervention beyond that is available from CT. Contrast enhanced MR imaging using gadolinium (Gd) contrast agents can depict blood brain barrier (BBB) disruption and if there has been an increase in the extracellular-extravascular space (EES). MR angiography can reveal the blood vessels in the vicinity of tumor which need to be protected during any surgical procedure, as well as the main artery supplying the tumor mass which have to be ligated before surgical removal of the tumor. Simple contrast enhanced morphological imaging is limited in its accuracy for predicting tumor aggressiveness, hence DCE and DSC imaging, which can provide additional information such as hemodynamics and neo-angeiogenic status along with lesion morphology, are often performed. T1w (T1-weighted) and T2* perfusion imaging for a follow up scan are also important as they can differentiate between tumor recurrence and radiation necrosis (Giesel et al., 2010; Mehndiratta and Giesel, 2011) (discussed later in detail).

Table 1.1 summarizes some of the key advantages and limitations of CT, MR and PET imaging in brain tumor assessment (Mehndiratta and Giesel, 2011).

Computed Tomography Imaging in Brain Tumor Assessment

Computed tomography is the mathematical reconstruction of a cross-sectional image of the body from measurement of x-ray transmission through a thin slice of patient tissue. A narrow well-collimated beam of x-rays is generated from one side of the patient and as the beam passes through patients body it fans out. During the course of its transit the x-ray beam is attenuated by absorption and scatter through body tissue. A sensitive x-ray detector array on the opposite side of the patient measures the x-ray transmission. These measurements are repeated systematically from multiple directions as x-ray tube is pulsed while the gantry rotates 360º around the patient. CT values are assigned to each voxel in the image by a back-projection algorithm based on the attenuation of the measured x-ray beam. These values are measured in Hounsfield Units (HU), named after Sir Godfrey N. Hounsfield; the inventor of CT. HU is not an absolute scale but is proportional to the difference in x-ray attenuation of the tissue and of water. Thus, water is normally assigned as a reference having 0 HU, with the HU scale ranging from −1,024 HU for air to +3,000 HU for dense bone. Soft tissue like brain has HU in the range of +20 to +50 HU.

The key advantages of CT compared with MR are rapid image acquisition, superior bone details, and demonstration of calcifications in soft tissue. CT scan is usually limited to the axial plane; however, images may be reformatted in sagittal, coronal or oblique planes and also as three-dimensional images. If image acquisition is anisotropic, the 3D reformatting is usually not very good and thus axial plane images are normally used to perform the assessment. Helical CT, Multi Detector CT (MDCT) and flat panel Volumetric CT (fpVCT) are some of the CT acquisition types which differ in either dimensions of the x-ray detector or the patient table motion during image acquisition.

CT is usually the first imaging to be performed on a patient presented with signs and symptoms of any central nervous system disorder because of its wider availability and low cost. CT is considered to be a very good screening tool for the detection of any supratentorial abnormality or extraaxial brain tumors. Intracranial space occupying lesion presenting with a mass effect can be easily picked by a midline shift in the axial slice of brain CT. CT is the imaging of choice for bone abnormalities like destruction, skull erosion, permeation or hyperostosis. Beside that, CT is used for detection of calcification within an intracranial

Table 1.1 Comparison of CT, MRI and PET in the assessment of brain tumors (Mehndiratta and Giesel, 2011)

Imaging modality	Advantages	Limitations
Computed Tomography	• Shorter image acquisition time • Low cost of scanning • Better spatial resolution • Good for extra-axial brain tumor assessment • Superior in detection of calcifications, skull erosion, penetration and destruction	• Poor definition of edema • Most of the time anisotropic image • X-ray radiation risk • Poor tissue characterization • Imaging of posterior fossa is limited due to bone artifacts
Magnetic Resonance Imaging	• Good in demonstration of parenchymal edema (an early sign for tumor detection) • Accurate delineation of edema and compression effects • Better detection of mass effects and atrophy • High neuroanatomical definition (tissue contrast) • Accurate detection of vascularity of tumor (multiplane acquisition)	• Poor detection of calcification and bone erosions • Not possible in intraoperative assessment • Lower spatial fidelity • Some of the special sequences are time consuming leading to long scanning time and discomfort to the patient
Positron Emission Tomography	• Good in demonstration of cellular metabolic activity • Can pick up early changes of tumor activity even before morphological changes appear	• Expensive • Poor spatial resolution • Small tumors can be easily missed because of poor spatial resolution Slow growing, less active tumors might not absorb much tracer to be detected

space occupying lesion. A big unilateral hemorrhage can be identified by CT easily but not subtle bilateral hemorrhage which can be missed sometimes as it easily blend with the brain soft tissue. Calcification within an intracranial lesion might indicate a slow growing mass whereas hemorrhage within an intracranial mass is a sign of malignancy.

CT does not have much role in brain tumor imaging assessment other than the ones mentioned above but is usually the first line of diagnostic imaging in all cases. PET-CT is very common nowadays and could be performed with a hybrid machine. The benefit of this simultaneous PET-CT acquisition is that co-registration of images is not required in the post processing and CT could provide morphological information while acquiring the PET imaging data.

Multi-energy CT (MECT) is a new innovation in the CT technology. MECT at present is performed with two x-ray energies. The methodology is commonly referred to as Dual Energy CT (DECT). DECT employ two X-ray sources and two detector arrays fixed orthogonal to each other equipped for simultaneous acquisition operated at different energy levels for atomic characterization, whereas in traditional CT there is only one x-ray source and one detector array.

DECT is based on the principle that x-ray attenuation is energy dependant. X-ray absorption depends on the atomic number and the density but is independent of its chemical bonding. The peak tube voltage (kVp) determines the energy spectrum of the x-ray beam. Therefore, a change in kVp leads to an alteration of average photon energy. Since the beam attenuation caused by different materials is energy dependent, one can differentiate the different tissue types based on their attenuation characteristics at two different energy levels. For example, iodine has high attenuation at low kVp which changes to half its value at high photon energies. Unlike iodine, the attenuation of calcium changes much less when the kVp of the tube is changed. The strength of DECT is its post processing algorithms that can analyze the acquired data sets simultaneously to extract the material specific differences in attenuation.

Recently, DECT has been proposed (Mehndiratta et al., 2011) as a new tool for the characterization of intracranial neoplastic disease (primary or metastatic) in three essential ways:

1. The internal density and composition of the tumor can be readily studied using CT. For example, DECT is very sensitive in detecting as well as quantitatively measuring internal calcifications, necrosis, foci of haemorrhage, and fatty deposits.
2. The presence and extent of bone erosion or skull base involvement is better depicted by CT than MRI.
3. The presence of neo-vascularity can be evaluated by DECT perfusion studies.

Brain tumor under assessment can be imaged with one iodine contrast enhanced DECT scan (Mehndiratta et al., 2011). The contrast enhanced dual energy images can thus generate an iodine map of the tumor in which the iodine load might be related to the tumor vascularity and hence its malignant potentials (Pharmacokinetic analysis of malignant pleural mesothelioma-initial results of tumor microcirculation and its correlation to microvessel density (CD-34), Acad Radiol. 2008 May; 15(5):563–70. doi: 10.1016/j.acra.2007.12.014). Iodine mapping of brain might also be used in grading the tumor or radiotherapy planning. In addition the contrast enhanced DECT imaging scanning might be beneficial in the follow up scans after chemo-radiotherapy, where the recurrent or remnant tumor might show iodine uptake but not at the region of radiation necrosis due to lack of vascularity after the treatment. The DECT application in brain tumor assessment is yet in its neonatal phase and need to be validated for its clinical utility.

Magnetic Resonance Imaging in Brain Tumor Assessment

Magnetic Resonance Imaging (MRI) is a powerful imaging tool that is based on the resonance phenomenon of body protons with an externally applied magnetic field. Because of each atomic nucleus spin motion there is a induced local magnetic moment (μ). When nuclei are exposed to an external magnetic field (B_0, measured in Tesla), the interaction with local magnetic moment

causes the nuclei to precess. The frequency at which precession occurs is called the Larmor frequency (ω_0), defined by Larmor equation, $\omega_0 = B_0 \cdot \gamma$, where γ is the gyro-magnetic ratio (measured in mega Hertz per Tesla) which is an atom specific property defined at a particular magnetic field strength (e.g., for ^1H, $\gamma/2\pi = 42.57$ MHz/T) (Pooley, 2005). Free magnetic moments of protons are randomly oriented in body in the absence of an external magnetic source. When the external source is present, all the protons will align along the direction of the magnetic field, B_0. This equilibrium can be disturbed by an application of an electromagnetic gradient in the form of radio frequency (RF) pulse having radiation energy (Erf). The radiation energy is atom specific, $Erf = \hbar \cdot \omega_0$; where $\hbar = h/2\pi$, h being the Planck's constant (Pooley, 2005). The RF pulse causes the net magnetization to flip by a certain angle (called flip angle), and thus produces two magnetization vector components, longitudinal and transverse. Due to the resonant irradiation, the spin system takes up additional energy which can be dissipated to surrounding by corresponding relaxation (dephasing) of spinning protons.

When the RF energy is switched off, the net magnetization vector tends to realign with the axis of B_0 through the process of T1 recovery, during which longitudinal magnetization recovers. Simultaneously the transverse magnetization decays through the process called T2 decay. Different body tissues have specific T1, T2 and T2* values. As the transverse magnetization precesses in axis of the receivers coil, it induces a current in that coil which is read as the MR signal. In MR imaging, differences in T1, T2 (T2*) and proton density in various tissues create differences in tissue contrast on images (Pooley, 2005). Repetition time (TR), echo time (TE) an flip angle are some commonly used MR sequence parameters to alter the tissue contrast of an image.

MRI is an important diagnostic technique in the evaluation of intracranial tumors. It is highly sensitive to the pathological changes in the brain parenchyma water content, as demonstrated by abnormal high or low signal intensity on T2- or T1-weighted images, respectively. Compared to other imaging modalities, MRI allows more accurate determination of lesion location, extent and subtle mass effects or atrophy especially those along the cerebral convexities. MRI is also very effective in depicting subacute and chronic hemorrhages, permitting more accurate distinction between vascular structure and adjacent parenchyma. When compared to CT which is superior in depicting the presence of calcifications and bone anomalies, MRI is better in soft tissue contrast that is for differentiating between tumor and perifocal edema, for defining the extent of the tumor and showing the relationship of the tumor to critical adjacent structures. Heavily T2-weighted sequences are most sensitive for the detection of tumor and edema extent (Mehndiratta and Giesel, 2011), while T1-weighted sequences following contrast enhancement generally provide better localization of the tumor nidus and improved diagnostic information relating to tumor grade, BBB breakdown, hemorrhage, edema and tissue necrosis (Mehndiratta and Giesel, 2011). Contrast enhanced T1-weighted images can elaborate small focal lesions such as metastases, minimal tumor recurrence and ependymal or leptomeningeal tumor spread because of improved signal contrast. Proton density images are more useful in distinguishing tumor and edema from adjacent cerebrospinal fluid, which may have a similar appearance as high-signal zone on heavily T2-weightd image. All these information are essential for surgical planning purposes.

It has been shown in the literature that imaging findings in MR studies correlate well with the histological grading of cerebral gliomas (Mehndiratta and Giesel, 2011). Generally, a tumor with sharp margins, homogenous in signal intensity and with little contrast enhancement is a low grade glioma. Tumors with indistinct margins which are inhomogeneous in signal and demonstrate intense, irregular contrast enhancement tend to be high-grade gliomas. These are some generalizations, but for diagnostic and therapeutic purposes, imaging findings and contrast-enhancing patterns must be considered all together. Additionally, each case is unique and tumor presentation varies from case

to case due to high population variability. Some of the low grade Astrocytomas are primarily infiltrating and histologically benign, but they might demonstrate a poor margination with the surrounding brain, where some of the rapidly growing malignant gliomas may show sharp margins (Mehndiratta and Giesel, 2011).

Dean et al. (1990) found that the degree of mass effect and incidence of cyst formation or necrosis are statistically significant positive predictors of tumor grade. A central non-enhancing area within a highly enhanced tumor mass usually suggests the area is necrosis as a result of the rapidly growing tumor that outstrips the vascular supply. This is a common presentation of malignant behavior and might suggest the diagnosis of Glioblastoma multiforme. Similarly, hemorrhage within a tumor also favors the diagnosis of a malignancy mostly associated with Glioblastoma or secondary metastases. An incredibly large zone of edema surrounding a contrast enhancing intra-axial tumor is also a sign of malignancy which contribute to the mass effect associated with these tumors. A notable exception to this is meningioma, which is a benign tumor often associated with high amount of adjacent edema and mass effect (Mehndiratta and Giesel, 2011). This can be easily distinguished from malignant gliomas by its extra-axial location. Low grade gliomas tend to present with an infiltrating pattern which might appear as edema on imaging but it lacks the contrast enhancement and mass effect which are the key factors associated only with cerebral edema. A slow growing neoplasm can show calcifications; this is a classical feature of oligodendroglioma and ganglioglioma. Occasionally, calcification might also be observed in tumors like Astrocytoma and ependymoma.

There are few limitations associated with the present MR techniques including:

1. There exists a considerable overlap among different intracranial tumors for respective morphological characteristics. This makes the histological diagnostic confirmation almost mandatory for definitive therapy planning.
2. An MR image is a spatial map of the difference in water proton relaxivity characteristics (T1 or T2 relaxation). Though significant intracranial pathological anomalies alter these characteristics, which make their effect visible on an image, but sometimes the changes might be very subtle compared to the surrounding normal tissue. Also, with infiltrative gliomas and small tumors the visible changes are minimal, frequently they are asymptomatic and thus go undiagnosed before they present with a large mass effect distorting the normal anatomy.
3. The well-defined enhancing tumor nidus is easily detectable on MR image, but infiltrating tumor or isolated tumor cells might extend far beyond tumor nidus into the surrounding edematous zone. These abnormalities could be easily overlooked by inexperienced eyes.
4. Large amount of calcification could blur the MR signal, making classification of the tumor almost impossible using MR imaging.
5. Artifacts might degrade the diagnostic image quality so much that normal tissue could be misinterpreted as a pathological mass. Motion artifacts are known for introducing ‘bright’ and ‘dark’ zones in the normal brain which might be misdiagnosed as a lesion.
6. Image spatial resolution is very sensitive to magnetic field inhomogeneity. Poor shimming could alter magnetic field inhomogeneity and distort an image.

Brain Tumor Imaging Using Contrast Enhanced MRI

Contrast enhanced MR neuroimaging (CE-MRI) is widely used in the evaluation of primary and secondary brain tumors. Conventional MRI is very sensitive in tumor detection and delineation which is important for diagnosis and tumor grading, whereas CE-MRI enables the radiologist to localize the vital surrounding structure around the tumor to facilitate appropriate intervention. Contrast agents help to localize surrounding vessels and nerves to aid surgical and radiotherapeutic planning. CE-MRI is also used during post-intervention to monitor the treatment response. An early identification of treatment failure could facilitate alternative therapeutic measures, hence improve patient outcome.

A common imaging protocols for brain tumor evaluation is: (1) T1 weighted, (2) T2 weighted and (3) T2* perfusion imaging sequence followed by T1 post contrast image acquisition. T1 and T2 weighted imaging give good anatomical and morphological information whereas contrast-enhanced images provide well defined tumor margins. The T1w image is also useful for selecting a region of interest (ROI) including the tumor for further perfusion analysis. DSC-MRI could provide information on tumor vascularity and hot spots (areas of high vascularity) which might be potentially useful for tumor grading and therapeutic planning (Essig, 2003).

Given the usefulness of Gd based contrast agents in MRI imaging for brain tumors, it is important to note that excessive use of Gd contrast can cause nephrogenic systemic fibrosis (NHS) particularly in the case of patients with compromised kidney function (Broome et al., 2007). Recent research has shown that contrast agents like gadobenate, gadoxetate and gadofosveset have a transient protein-binding capability that is capable of doubling or more the R1 and R2 relaxivity (1/T1 and 1/T2) (Giesel et al., 2010), enabling the use of a lower dosage of this kind of agents to achieve equivalent image contrast in the cohort of patients with compromised kidney function.

The dosage of gadolinium contrast agent for CE imaging is a topic of considerable research interest, but for clinical practice a dose of 0.1 mmol/kg bodyweight is considered to be safe (Essig, 2003). Many studies have demonstrated the diagnostic benefit of double and triple dose (0.2–0.3 mmol/kg bodyweight) in MR imaging (Giesel et al., 2010; Sze et al., 1998) but recent concerns of NSF has limited the higher Gd contrast dosage protocols to only research studies (Broome et al., 2007). Even though a higher dosage is very sensitive in determining the extent of primary tumor spread, it increases the cost of the MR examination and might produce a higher false positive rate (Giesel et al., 2010; Sze et al., 1998). Most of the currently available Gd-contrast are 0.5 % molarity except gadobutrol (Gadovist®) which is the only high molarity (1 %) contrast agent (Giesel et al., 2010) available for clinical use. Gadobutrol has been demonstrated to be highly sensitive to tumor activity (Giesel et al., 2009) (Fig. 1.1), which could potentially enable intensity-modulated radiotherapy to be used more efficiently based on the underlying tumor activity. Essig et al. (2006) compared single and double dose of gadobutrol and gadobenate dimeglumine at 1.5 T in a healthy control volunteer study where it was found that a double dose of contrast could give a large peak signal drop but there was no statistical difference between agents or dose for its clinical utility. As gadobutrol is double the molarity of other contrast agents, it could be given as half the volume of injection to deliver the same Gd- dose, which has been demonstrated to have a better bolus profile (Giesel et al., 2009). Nevertheless, the study of Essig et al. (2006) showed that the bolus width achieved by gadobutrol and gadobenate dimeglumine were sharp and comparable but the reduced injection time of gadobutrol did not produce any added benefit in perfusion quantification.

Diagnostic accuracy could be improved by the use of high relaxivity Gd- contrast agents (Giesel et al., 2010) without actually increasing the Gd-dose. Dosing studies have demonstrated the beneficial effects of gadobenate dimeglumine in improving the sensitivity for brain tumor detection, but an incremental triple dose did not have any advantage even for high relaxivity contrast agents (Giesel et al., 2010; Mehndiratta and Giesel, 2011). Later significant evidence supporting improved diagnostic performance of high relaxivity contrast agents came from intra-individual crossover studies directly comparing gadobenate dimeglumine with gadopentetate dimeglumine (Colosimo et al., 2004; Kuhn et al., 2007; Maravilla et al., 2006; Rumboldt et al., 2009), gadoterate meglumine (Colosimo et al., 2001, 2004), gadodiamide (Colosimo et al., 2001; Rowley et al., 2008) and gadofosveset trisodium (Giesel et al., 2010). The first such crossover study, performed in 2001, demonstrated that in patients with metastatic central nervous system disease, the sensitivity for lesion detection with gadobenate dimeglumine (93–100 %) was much higher than that with an equal dose of a comparable agent (65–73 %), like gadopentetate dimeglumine (N = 13), gadodiamide (N = 4), or gadoterate meglumine

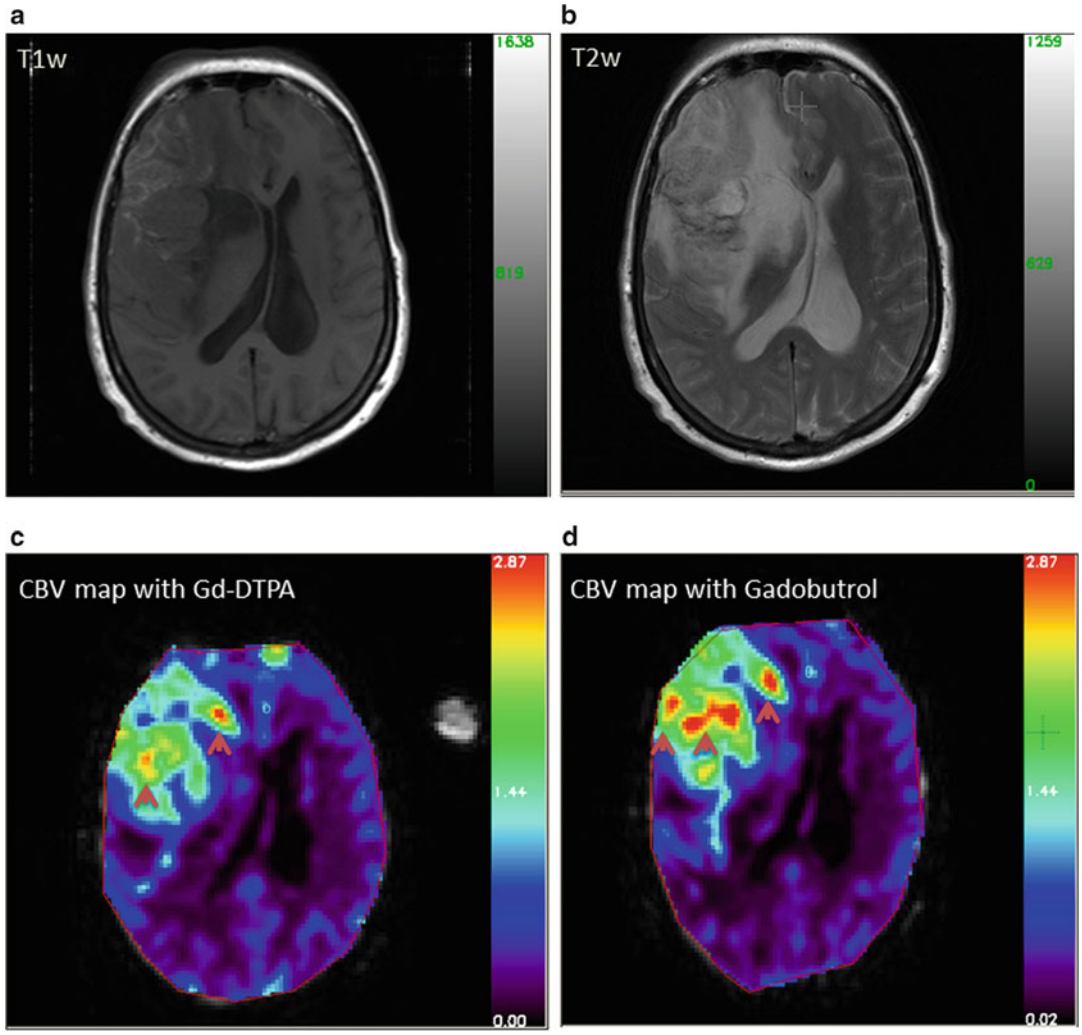

Fig. 1.1 (**a**) T1-weighted; (**b**) T2-weighted MRI image of patient with tumor in the right frontal lobe; (**c**) T2* weighted parametric CBV map with Gd-DTPA contrast; (**d**) T2* weighted parametric CBV map with Gadobutrol contrast. Gadobutrol is shown to be more sensitive to tumor activity (*arrow heads*) and show more number of hyperactive lesions in tumor with high blood volume

(N = 5) (Colosimo et al., 2001). In addition, tissue contrast in the main lesion-to-normal brain parenchyma was consistently greater for gadobenate dimeglumine (143 %) than for an equal dose comparable agent (127 %) as compared to unenhanced images (Colosimo et al., 2001). Since then a total of five large population randomized crossover studies have been performed, demonstrating the benefits and limitations of gadobenate dimeglumine compared to non-protein binding Gd-contrast agents (Colosimo et al., 2004; Maravilla et al., 2006; Rowley et al., 2008; Rumboldt et al., 2009). Recently, a specific study on cohort of intra-axial brain tumors (N = 158) has demonstrated the significant ($p < 0.01$) diagnostic improvement using gadobenate dimeglumine both qualitatively and quantitatively (Kuhn et al., 2007).

T1 weighted (T1w) CE-MRI is important in brain tumor imaging as the BBB within tumor is often found to be damaged leading to leakage of the contrast into the extravascular space. T1w

contrast enhancement is often due to BBB damage associated with either neovascular angiogenesis or capillary damage in region of active tumor growth. Angiogenesis is an important marker of active tumor growth and might correlate with tumor aggressiveness (Mehndiratta and Giesel, 2011). As angiogenesis increases microvascular blood volume, perfusion imaging will show a higher CBV (cerebral blood volume) and CBF (cerebral blood flow) that gives a unique insight into tumor physiology and could be used as a metric to monitor therapeutic response. PET has been used in the past for similar measurements but both these techniques are very much dependent on a perfect bolus injection of contrast and require computationally expensive post-processing algorithms.

MRI for the Microvascular Assessment of Brain Tumor

With the raising concern of Gd-contrast related complication in the patients, research efforts have been directed toward non-invasive methodologies for vascular imaging using MRI. The idea is to either magnetically label the blood itself (as in Arterial Spin Labeling, ASL) or to null the blood signal and use it as a negative contrast, measuring blood volume indirectly (Vascular Space Occupancy, VASO) by vascular imaging.

Recently, a new T1 weighted sequence has been developed called Vascular Space Occupancy (VASO) that offers a non-invasive method for detecting CBV (Donahue et al., 2008). The VASO technique uses the difference in the T1 relaxivity of tissue and blood to nullify the intravascular blood signal and thus providing a measure of intravascular volume indirectly by measuring the remaining signal from the tissue. The technique has been used to measure CBV changes during neuronal activity and more recently the methods have been developed to quantify blood volume at rest, but these have not yet been extensively validated for tumor imaging. Studies have also demonstrated that VASO and MPRAGE (Magnetization Prepared Rapid Gradient Echo) MRI could provide soft tissue contrast complementary to Gd-T1w and FLAIR (fluid attenuation inversion recovery) MRI for tumor imaging (Donahue et al., 2008). FLAIR, VASO and MPRAGE are all inversion-based MRI sequences. However, they each offer a range of T1w contrasts, a collective analysis of which provides information not otherwise evident from each alone (Donahue et al., 2008).

Another non-invasive methodology for microvascular imaging is Arterial Spin Labeling (ASL). In ASL, the magnetically labeled water in blood is used as an endogenous contrast to directly measure blood flow and blood volume in the tissue of interest. At the level of the supplying artery for the tissue, a 180° radiofrequency pulse is applied to invert the magnetization of the water protons in the arterial blood. Once this magnetically labeled blood reaches the tissue an image of the tissue is acquired. A second image is subsequently acquired without the application of the inversion pulse (thus in the absence of labeled blood). Upon the subtraction of the two acquired datasets, the difference image provide a measure of blood supply to the tissue. Further images may be acquired varying the delay between labeling and imaging, this time series data can be analyzed in similar manner of perfusion MRI methods. The information provided by ASL is similar to that of DSC MRI, but the method is completely non-invasive (do not require exogenous contrast agents). Additionally, since it is water in blood that is acting as the contrast agent ASL provides a more direct measure of perfusion, the delivery to the tissue, as would be expected from positron labeled water PET. ASL has been used in stroke and other vascular pathologies but it remains to be tested and validated for brain tumor assessment.

Brain Tumor Imaging Using Amide Proton Transfer (APT) Contrast

Although the MR imaging protocols discussed above are the standard of care for assessing the brain tumors before, during and after therapy, it still has limited diagnostic specificity in identifying tumor grade or separating the mass of solid

tumor from the surrounding edema. For example, hyperintensities on T2w and FLAIR images may be caused by either solid tumor mass or peritumoral edema. Surgical resection normally targets the bulk of the T1w contrast enhancing tumor with or without a margin clearance of the surrounding tissue with abnormal T2w or FLAIR signal. The motivation is to minimize the resection of the brain tissue that is affected primarily by edema because these tissues may recover to normal function after the surgical treatment of the nearby tumor (Zhou et al., 2008). Therefore, new imaging approaches which can precisely delineate the volume of tumor tissues for resection or can identify the ideal region for biopsy that is able to aid treatment recommendations are still highly desirable.

APT imaging is a new non-invasive cellular and molecular imaging technique for MRI. Through the process of chemical exchange saturation transfer (CEST), APT imaging provides an indirect way to detect endogenous mobile proteins and peptides which would otherwise be undetectable due to their low concentration. During an APT imaging acquisition, radiofrequency irradiation is applied to saturate (decrease the signal) the amide protons of the proteins and peptides that resonance at 3.5 ppm downfield from the water resonance. The saturated amide protons then interact with the unsaturated water protons via chemical exchange, leading to a transfer of magnetization and subsequently a decrease in the measured water intensity at the resonance frequency of amide protons. This chemical exchange led reduction in the intensity of measured water signal allows the detection of these low concentration proteins (milli-molar range). Quantitative *in vivo* MRI measurement has found that these mobile protein concentrations are generally higher in brain tumors than normal white matter and it increases with the tumor grade (Howe et al., 2003).

The APT ratio (APTR) is a common metric used in the APT imaging to differentiate the tumor from healthy tissues. It is an asymmetric analysis with respect to the water signal and is calculated by normalizing the difference between the measured intensity after saturation at ±3.5 ppm with the unsaturated signal (in the absence of radiofrequency irradiation) (van Zijl and Yadav, 2011). The calculated APTR of viable tumor tissue has been found to be positive and statistically higher than necrotic tissue, surrounding peripheral edema and healthy tissues (Wen et al., 2010). This allows a clear differentiation of solid tumor masses from peritumoral edema which was previously indistinguishable on T2w and FLAIR. In addition, the higher APTR of the active tumor core facilitates the identification of the highly malignant zone of tumor for biopsy. This is useful clinically because some high-grade gliomas are known to demonstrate no contrast enhancement in CE-MRI (Wen et al., 2010).

Although T1w and T2* perfusion imaging together can differentiate the tumor recurrence and radiation necrosis, the latter is an invasive approach which requires the administration of contrast agents. APT imaging on the other hand is a completely non-invasive technique and could assess the tumor response to therapy based on its unique capability of detecting the endogenous mobile proteins and peptides that are markers of functionally active tissue. After radiation therapy, viable glioma would show a hyperintensity on an APT image whereas hypointensity or isointensity would be observed in the necrotic region. This difference is probably caused by the absence of mobile cytosolic proteins and peptides in the necrosis region due to the loss of cytoplasm after cell depolarization (Zhou et al., 2011).

Although APT imaging can be used for detecting brain tumor activity without the need of an exogenous contrast agent and can potentially distinguish the heterogeneity of high grade tumors through the change of concentration of the endogenous mobile proteins, the obtained APTR for the brain at 3 T is small, only about 2–4 % of the water intensity (van Zijl and Yadav, 2011). Current research is, therefore, focused on more optimal strategies for acquisition of the data that in particular may correct for various artifacts including field inhomgeneities and the effects of patient movement. Artifacts are often observed near the surface of brain and ventricles on APT images due to patient movement during the scan (Wen et al., 2010). APT imaging is still a relatively new method for brain tumor imaging and

has only been used on a small cohort of patients with high grade gliomas, but its unique capabilities can potentially provide valuable complimentary information to the existing brain tumor diagnostic imaging.

Brain Tumor Imaging Using MR Spectroscopy (MRS)

MR spectroscopy can provide information on tumor biochemical composition which is complimentary to other imaging modalities. Standard proton MRS (1H-MRS) is the most widely explored MRS technique with its application in tumor neuroimaging (Howe and Opstad, 2003).

Brain tumor spectroscopy can be performed in a single- or multi voxel form. The most widely used methods of volume selection are (i) Stimulated Echo Acquisition Mode (STEAM) and (ii) Point-Resolved Spectroscopy Sequence (PRESS). STEAM works best at short echo times (TE) which makes it highly susceptible to motion artifacts. Theoretically for a similar TE, PRESS could achieve almost double the signal to noise ratio than STEAM and would comparatively be less sensitive to motion artifacts (Castillo et al., 1996), but PRESS requires high computational power with sophisticated algorithm design for the analysis. With the advancement of computational analysis nowadays, PRESS is gaining wider acceptance in clinical routine.

Single voxel MRS has been applied for characterizing the metabolic signatures of brain tumors as it has high signal to noise ratio, shorter acquisition time and is easier to be processed. Single voxel MRS faces the limitation of poor spatial resolution and hence lacks the regional mapping of metabolic variations in the tissue. Furthermore, poor spatial resolution makes the single voxel MRS results highly susceptible to partial volume error. Brain tumors are highly heterogeneous in metabolic activity and aggressiveness, hence single voxel MRS is not an optimal solution to perform or assist tumor grading. Multivoxel MRS may be more suitable to study the brain tumor metabolic heterogeneity which is particularly important for planning focal treatments of tumor such as radiation and surgical resection and for following response to therapy.

For the most commonly used clinical MRS sequences, the spectrum is sensitive to five metabolites: Choline (Cho), N-Acetyl Aspartate (NAA), Creatine (Cr), Lactate and Lipid (Law et al., 2002; Shino et al., 1999; Usenius et al., 1994). The NAA peak is exclusive to neuronal cell, Creatine is a marker of energy synthesis and Choline reflects cell membrane turnover in MRS of brain. Lactate reflects the presence of anaerobic metabolism which is not a common finding in healthy tissue but is frequently found elevated in necrotic or infarcted brain tumor (Usenius et al., 1994). Primary brain tumors are notorious for showing a specific pattern in the elevation of Choline and loss of NAA peaks (Usenius et al., 1994).

MRS could aid in detailed evaluation of brain tumor and its grading along with morphological MRI. An elevated Cho/Cr and Cho/NAA ratio has been found to be associated to high grade gliomas (Law et al., 2002). MRS is very sensitive in differentiation of tumor recurrence and necrosis where both appear to be contrast enhancing on T1w MRI. MRS also play a useful role in assessing the therapeutic response as the Cho peak would decrease and lactate or lipids may increase over time during the treatment course (Shino et al., 1999). This is particularly important for early detection of treatment failure so that it can be modified prior to a significant progression of the disease.

In addition, MRS is equally sensitive in differentiation of non-enhancing tumor from edema or other causes of T2 prolongation. Presently, MR spectroscopy is being optimized by different research groups in assessing the treatment response of primary brain tumors or metastases. MR spectroscopy can noninvasively differentiate a solitary metastasis and high-grade gliomas, when used alongside with perfusion MR imaging (Law et al., 2002). The study showed that measurement of Cho and mean CBV in the peri-enhancing region can be used as a good marker for differentiating solitary metastases from high grade glioma, where elevated levels of Cho and mean CBV surrounding a peripherally enhancing

mass are more likely to be associated with an infiltrating glioma.

Positron Emission Tomography and Molecular Imaging of Brain Tumors

Positron emission tomography is a form of molecular imaging that requires an injection of a radioactive tracer into the blood stream. Radionuclide tracers are prepared using a cyclotron device and a wide variety of molecules can be labeled by this means, including metabolically active substances. Tracers are often characterized by their half-life, which refers to the length of time it takes for the radioactivity of a radioisotope to decrease by a factor of two. Some of the radionuclides have a relatively short half-life and often tend to be used for medical diagnostic purposes because they do not remain radioactive for long following administration and hence result in a relatively low radiation dose. But isotopes with a relatively long half-life have been used in the past for therapeutic applications in medicine too. Table 1.2 shows the half-life of some commonly used radioisotopes.

Table 1.2 Commonly used radioisotopes and their half-life

Radioisotope	Half life (approx.)
^{81m}Kr	13 s
^{99m}Tc	6 h
^{131}I	8 days
^{51}Cr	1 month
^{137}Cs	30 years
^{241}Am	462 years
^{226}Ra	1,620 years

Table 1.3 Organ specific radiotracers used in PET imaging

Body organ	Radiotracer
Brain	^{99m}Tc-Ceretec
Thyroid	Na^{99m}TcO4
Lung (ventilation)	^{133}Xe gas
Lung (perfusion)	^{99m}Tc-MAA
Liver	^{99m}Tc-Tin Colloid
Spleen	^{99m}Tc-Damaged Red Blood Cells
Pancreas	^{75}Se-Selenomethionine
Kidneys	^{99m}Tc-DMSA
Neuroendocrine tumors (SSR2 specific)	^{68}Ga-DOTATOC

The radionuclide is generally administered to the patient in the form of a radiopharmaceutical agent or radiotracer. This follows some physiological pathway to accumulate for a short period of time in some specific organ of the body (Table 1.3). A good example is ^{99m}Tc-tin colloid which following intravenous injection accumulates mainly in the liver. The radiopharmaceutical emits gamma-rays and the images are obtained by mapping the distribution of an administered radiopharmaceutical within the body. The radiation is emitted from within the patient and subsequently detected in the imaging device, unlike CT which requires an external X-ray source. Specific organ function is determined by the biological behaviour of the radiopharmaceutical. Conventional imaging achieved using a gamma camera (used to image gamma radiation emitted by radioisotopes) is referred to as Planar Imaging. A more recent variant is Single Photon Emission Computed Tomography (SPECT) which produce axial slice imaging through the body. SPECT uses a gamma camera to record images at a series of angles around the patient, in a similar manner to CT acquisitions, with the resultant data being processed using Filtered Back Projection Iterative Reconstruction algorithms. The more advanced version of the molecular imaging is Positron Emission Tomography (PET) that is also an axial projection acquisition based technique. PET exploits the positron annihilation process where two 0.51 MeV back-to-back gamma-rays are produced. When these gamma-rays are detected, their origin will lie on a line joining two of the detectors on the ring of detectors which encircles the patient. More recently, the limited anatomical definition of radionuclide imaging has been addressed to some degree by the development of hybrid imaging techniques in which radionuclide imaging devices are combined with computed

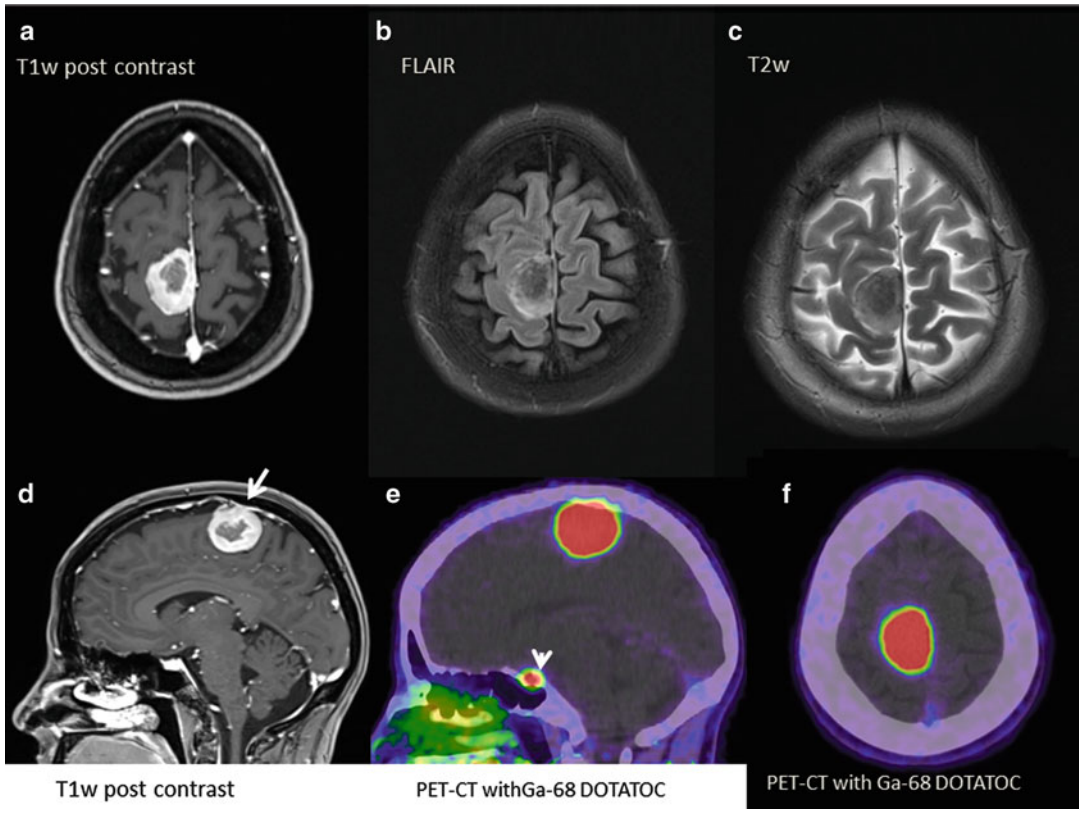

Fig. 1.2 A brain tumor seen in T1w post contrast (**a**), FLAIR (**b**) and T2w (**c**) axial plane. It could either be a primary or a secondary metastasis tumor of the brain. In sagittal plane of T1w post contrast MRI (**d**) the tumor showed growth from meninges (*arrow*). In the PET-CT (**e**, **f**) using Ga-68 DOTATOC, the tumor showed positive uptake confirming it as a meningioma shown here in sagittal and axial plane. Meningioma has a high uptake of Ga-68 DOTATOC because of high expression of somatostatin-receptors subtype 2. The sagittal slice (**e**) also shows high uptake in pituitary (*arrow head*) which is a normal finding as pituitary also has high expression of SSR2

tomography in a single imaging system. The resulting images display the functional data obtained from the radionuclide distribution (in color), overlaid on the anatomical information from CT (in grey scale). As the two image data sets are acquired almost simultaneously using the same imaging device, the two data sets can be co-registered very accurately (Fig. 1.2). Not only do these hybrid systems allow abnormalities seen on radionuclide images to be assigned to the precise anatomical structures, they also enable the morphological appearances of disease processes depicted by CT to be assimilated into the interpretation of the findings on radionuclide images. For example, such combined interpretation can aid the distinction of malignant and inflammatory causes of uptake of the positron emitting radiopharmaceutical ^{18}F-fluorodeoxyglucose (FDG). Further advantages of hybrid systems include the use of the CT data to correct radionuclide images for artifacts resulting from attenuation of photons within the body and the ability to incorporate radionuclide image data into CT-based radiotherapy planning systems.

PET is a metabolic imaging technique that is capable of differentiating benign and malignant tumors more accurately. PET has been used extensively in staging of brain tumors as it can produce a visual mapping of biochemical changes caused by the metabolic activity of the brain tumor.

Fluorodeoxyglucose PET (FDG-PET) produces high background intensity in normal gray matter but still has been shown to provide useful information in management of patient with brain

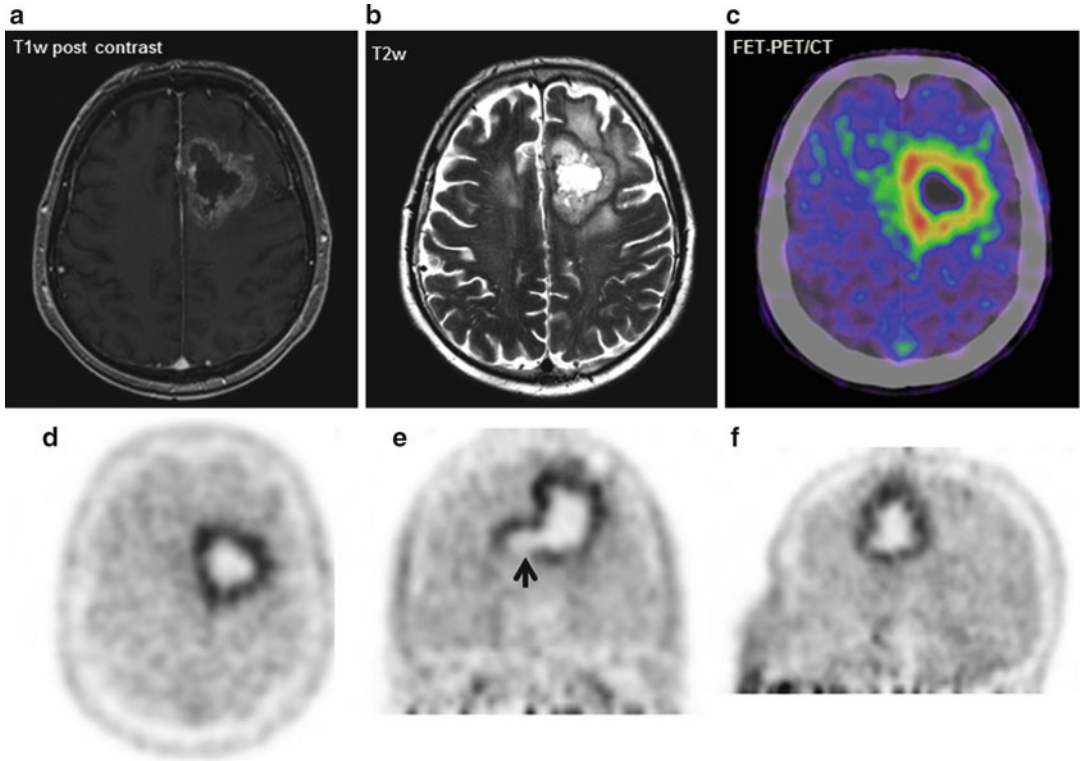

Fig. 1.3 Patient with a high grade Glioma tumor showing T1w post contrast (**a**) enhancing margins with the central area of necrosis in the tumor, T2w image (**b**) confirming the findings. The combined PET-CT using FET tracer (**c**) shows the tumor clearly with infiltrations to the cerebral cortex and infiltration to the contralateral hemisphere. The *bottom row* shows the PET image in axial (**d**), coronal (**e**) and sagittal (**f**) plane confirming infiltration to contralateral hemisphere in the coronal plane (*arrow*)

tumors. PET can provide information on global location of high activity tumor zone, hence can be used to guide appropriate biopsy sampling. Besides providing information on the metabolic activity, a PET image represents the tumor aggressiveness thereby enhancing the ability to provide a prognostic indication. PET can also help in the differentiation of post-surgery tumor recurrence and radiation necrosis. In this scenario, the aggressive tumor responds with a bright signal because of its high uptake of FDG whereas radiation necrosis might show no uptake. In addition, FDG-PET has been used in differentiating lymphoma from infectious toxoplasmosis in patients with acquired immune deficiency syndrome with almost 100 % accuracy, and is the investigation of choice in that settings (Basu and Alavi, 2009).

Gallium-68 DOTATOC (DOTA-[Tyr3]-Octreotide) is one specific radiopharmaceutical which is highly sensitive to somatostatin-receptors subtype 2 (SSR2) that is expressed in neuroendocrine tumors and in the brain tumor like meningioma (Fig. 1.2). Other than the FDG and Ga-68 DOTATOC, research has been done in amino acid tracers for PET imaging of brain tumors (Fig. 1.3). The novel tracers which have been employed include positron labeled methionine, thymidine, tyrosine, choline and fluoromisonidazole (Basu and Alavi, 2009). One of the key advantages of these new radiotracers over FDG is a significant reduction in background activity from gray matter which allows the detection of small tumors with high precision (Basu and Alavi, 2009). The emphasis has also being placed on investigating amino acid tracers which are sensitive to recurrent tumor particularly the low-grade ones because they are difficult to be detected. O-(2-[18F]fluoroethyl)-L-tyrosine (FET) is a

novel amino acid PET tracer (Fig. 1.3) that has been shown to have better differentiation capabilities for tumor tissue from inflammation. 18F-FET is being investigated for monitoring post therapeutics of Squamous Cell Carcinoma (SCC) because the tumor tissue reaction can now be specifically detected by FET, in which the surrounding inflammatory tissue will not show any uptake (Pauleit et al., 2006).

Hypoxia imaging tracers (such as fluoromisonidazole or more recently EF5) have a promising future in radiotherapy planning and the prediction of treatment response (Basu and Alavi, 2009) because these tracers could play an important role in directing and monitoring targeted hypoxic therapy for tumors with hypoxia. New PET radiotracers have thus shown a great potential to image important aspects of tumor activity which were only speculative in the past.

Future of Brain Tumor Imaging

Brain tumor imaging has progressed a long way from radiography to the advanced multi-modality imaging of CT, MRI and PET today. In MRI, high relaxivity contrast agents can now provide vital information on tumor vascular supply and high field strength scanners offering better SNR are becoming the norm. In future it remains to be validated how brain tumor diagnostics can be improved with the combination of better contrast agents on high field strength MRI. Another advancement in brain tumor imaging is greater exploitation of multi-modality hybrid imaging, including their coregistration.

Multi-modality imaging is gaining more focus for diagnostic imaging nowadays. This approach might be computationally challenging and expensive but the clinical benefit of it is immensely high. Healthcare providers have shown great interest in using multi-modality information simultaneously for the benefit of patient care. The time in patient journey for diagnostic imaging is very much shortened by using a hybrid multi-modality imaging when compared to using them independently. This is particularly important in trauma and medical emergencies, where an accurate and quick diagnostic technique could aid appropriate management that might be lifesaving. The diagnostic efficiency has also shown to be improved by implementation of such hybrid devices. PET-CT is a very valuable addition to this hybrid imaging technology. It has been used widely for tumor diagnostics as CT could provide simultaneous morphological information that can be coupled with functional information from the PET. PET-MRI is now feasible and has come into clinical practice recently. MR is very good in producing distinctive contrast of soft tissue in the brain and now coupled with functional imaging provided by PET, they have shown promising future prospects. Further advancement in combining PET-MR image acquisition at same time would advance the brain tumor imaging to a new platform of diagnostics.

The newly available CT technique – Multi-Energy CT (MECT), serves on multi-energy x-ray spectrum. It is capable with material characterization of the tissue and is also a promising tool for high resolution anatomical and tumor activity imaging (Mehndiratta et al., 2011). More works need to be done to reveal its real potential in brain tumor assessment.

ASL and VASO imaging are other non-invasive MRI techniques for neurovascular imaging. Both these are being used for stroke and other neurovascular disorders, it will be interesting to know how well it can blend into brain tumor diagnosis and management.

Novel amino acid PET tracers have recently begun to be used for brain tumor diagnosis, together with the development of the exciting PET tracers such as hypoxia imaging tracer, PET will be one of the important imaging tools for brain tumor management in the future.

In conclusion, brain tumor imaging typically requires a high resolution anatomical imaging with computed tomography or magnetic resonance imaging and functional tumor activity with PET. Clinicians rely on both anatomical and functional information to design an appropriate treatment planning for the patient. The future of brain tumor imaging lies in developing optimal image registration and segmentation strategies for the multi-modal imaging as well as novel PET tracers. The development would also

be useful for intensity-modulated radiotherapy, and is likely to have important clinical and research applications in radiotherapy planning for patients with brain tumors.

References

Basu S, Alavi A (2009) Molecular imaging (PET) of brain tumors. Neuroimaging Clin N Am 19(4):625–646

Broome DR, Girguis MS, Baron PW, Cottrell AC, Kjellin I, Kirk GA (2007) Gadodiamide-associated nephrogenic systemic fibrosis: why radiologists should be concerned. AJR Am J Roentgenol 188(2):586–592

Castillo M, Kwock L, Mukherji SK (1996) Clinical applications of proton MR spectroscopy. AJR Am J Roentgenol 17(1):1–15

Colosimo C, Ruscalleda J, Korves M, La Ferla R, Wool C, Pianezzola P, Kirchin MA (2001) Detection of intracranial metastases: a multicenter, intrapatient comparison of gadobenate dimeglumine-enhanced MRI with routinely used contrast agents at equal dosage. Invest Radiol 36(2):72–81

Colosimo C, Knopp MV, Barreau X, Gérardin E, Kirchin MA, Guézénoc F, Lodemann KP (2004) A comparison of Gd-BOPTA and Gd-DOTA for contrast-enhanced MRI of intracranial tumours. Neuroradiology 46(8): 655–665

Dean BL, Drayer BP, Bird CR, Flom RA, Hodak JA, Coons SW, Carey RG (1990) Gliomas: classification with MR imaging. Radiology 174(2):411–415

Donahue MJ, Blakeley JO, Zhou J, Pomper MG, Laterra J, van Zijl PCM (2008) Evaluation of human brain tumor heterogeneity using multiple T1-based MRI signal weighting approaches. Magn Reson Med 59(2):336–344

Essig M (2003) Clinical experience with MultiHance in CNS imaging. Eur Radiol 13(Suppl 3):N3–N10

Essig M, Lodemann K-P, Le-Huu M, Brüning R, Kirchin M, Reith W (2006) Intraindividual comparison of gadobenate dimeglumine and gadobutrol for cerebral magnetic resonance perfusion imaging at 1.5 T. Invest Radiol 41(3):256–263

Giesel FL, Mehndiratta A, Risse F, Rius M, Zechmann CM, von Tengg-Kobligk H, Gerigk L, Kauczor HU, Politi M, Essig M, Griffiths PD, Wilkinson ID (2009) Intraindividual comparison between gadopentetate dimeglumine and gadobutrol for magnetic resonance perfusion in normal brain and intracranial tumors at 3 Tesla. Acta Radiol 50(5):521–530

Giesel FL, Mehndiratta A, Essig M (2010) High-relaxivity contrast-enhanced magnetic resonance neuroimaging: a review. Eur Radiol 20(10):2461–2474

Howe FA, Opstad KS (2003) 1H MR spectroscopy of brain tumours and masses. NMR Biomed 16(3): 123–131

Howe FA, Barton SJ, Cudlip SA, Stubbs M, Saunders DE, Murphy M, Wilkins P, Opstad KS, Doyle VL, McLean MA, Bell BA, Griffiths JR (2003) Metabolic profiles of human brain tumors using quantitative in vivo 1H magnetic resonance spectroscopy. Magn Reson Med 49(2):223–232

Kandel EI, Schavinsky YV (1972) Stereotaxic apparatus and operations in Russia in the 19th century. J Neurosurg 37(4):407–411

Kuhn MJ, Picozzi P, Maldjian JA, Schmalfuss IM, Maravilla KR, Bowen BC, Wippold FJ, Runge VM, Knopp MV, Wolansky LJ, Gustafsson L, Essig M, Anzalone N (2007) Evaluation of intraaxial enhancing brain tumors on magnetic resonance imaging: intraindividual crossover comparison of gadobenate dimeglumine and gadopentetate dimeglumine for visualization and assessment, and implications for surgical intervention. J Neurosurg 106(4):557–566

Law M, Cha S, Knopp EA, Johnson G, Arnett J, Litt AW (2002) High-grade gliomas and solitary metastases: differentiation by using perfusion and proton spectroscopic MR imaging. Radiology 222(3):715–721

Maravilla KR, Maldjian JA, Schmalfuss IM, Kuhn MJ, Bowen BC, Wippold FJ, Runge VM, Knopp MV, Kremer S (2006) Contrast enhancement of central nervous system lesions: multicenter intraindividual crossover comparative study of two MR contrast agents. Radiology 240(2):389–400

Mehndiratta A, Giesel FL (2011) Brain tumor imaging. In: Abujamra AL (ed) Diagnostic techniques and surgical management of brain tumors. InTech, ISBN 978-953-307-589-1

Mehndiratta A, Kapal JM, Prabu A (2011) Iodine mapping in brain tumor imaging using dual-energy computed tomography. Med Hypotheses 76(5):764

Pauleit D, Zimmermann A, Stoffels G, Bauer D, Risse J, Flüss MO, Hamacher K, Coenen HH, Langen KJ (2006) 18F-FET PET compared with 18F-FDG PET and CT in patients with head and neck cancer. J Nucl Med 47(2):256–261

Pooley RA (2005) AAPM/RSNA physics tutorial for residents: fundamental physics of MR imaging. Radiographics 25(4):1087–1099

Rowley HA, Scialfa G, Gao PY, Maldjian JA, Hassell D, Kuhn MJ, Wippold FJ, Gallucci MB, Bowen BC, Schmalfuss IM, Ruscalleda J, Bastianello S, Colosimo C (2008) Contrast-enhanced MR imaging of brain lesions: a large-scale intraindividual crossover comparison of gadobenate dimeglumine versus gadodiamide. AJNR Am J Neuroradiol 29(9):1684–1691

Rumboldt Z, Rowley HA, Steinberg F, Maldjian JA, Ruscalleda J, Gustafsson L, Bastianello S (2009) Multicenter, double-blind, randomized, intraindividual crossover comparison of gadobenate dimeglumine and gadopentetate dimeglumine in MRI of brain tumors at 3 tesla. J Magn Reson Imaging 29(4):760–767

Shino A, Nakasu S, Matsuda M, Handa J, Morikawa S, Inubushi T (1999) Noninvasive evaluation of the malignant potential of intracranial meningiomas performed using proton magnetic resonance spectroscopy. J Neurosurg 91(6):928–934

Sze G, Johnson C, Kawamura Y, Goldberg SN, Lange R, Friedland RJ, Wolf RJ (1998) Comparison of

single- and triple-dose contrast material in the MR screening of brain metastases. AJNR Am J Neuroradiol 19(5):821–828

Usenius JP, Kauppinen RA, Vainio PA, Hernesniemi JA, Vapalahti MP, Paljärvi LA, Soimakallio S (1994) Quantitative metabolite patterns of human brain tumors: detection by 1H NMR spectroscopy in vivo and in vitro. J Comput Assist Tomogr 18(5):705–713

van Zijl PCM, Yadav NN (2011) Chemical exchange saturation transfer (CEST): what is in a name and what isn't? Magn Reson Med 65(4):927–948

Wen Z, Hu S, Huang F, Wang X, Guo L, Quan X, Wang S, Zhou J (2010) MR imaging of high-grade brain tumors using endogenous protein and peptide-based contrast. Neuroimage 51(2):616–622

Zhou J, Blakeley JO, Hua J, Kim M, Laterra J, Pomper MG, Van Zijl PCM (2008) Practical data acquisition method for human brain tumor amide proton transfer (APT) imaging. Magn Reson Med 60(4):842–849, Prometheus Books

Zhou J, Tryggestad E, Wen Z, Lal B, Zhou T, Grossman R, Wang S, Yan K, Fu DX, Ford E, Tyler B, Blakeley J, Laterra J, van Zijl PCM (2011) Differentiation between glioma and radiation necrosis using molecular magnetic resonance imaging of endogenous proteins and peptides. Nat Med 17(1):130–134

Molecular Imaging of Brain Tumors

2

Nora Sandu, Toma Spiriev, and Bernhard Schaller

Contents

N. Sandu • T. Spiriev • B. Schaller (✉)
Department of Neurosurgery,
University of Paris, Paris, France
e-mail: bernhardjschaller@gmail.com

Abstract

Non-invasive energy metabolism measurements in brain tumors in vivo are now performed widely as molecular imaging by positron emission tomography. This capability has developed from a large number of basis and clinical science investigations, which have cross- fertilized one another. Apart from precise anatomical localization and quantification, the most intriguing advantage of such imaging is the opportunity to investigate the time course (dynamics) of disease-specific molecular events in the intact organism. Most importantly, molecular imaging represents a key technology in translational research, helping to develop experimental protocols that may later be applied to human patients. Common clinical indications for molecular imaging of primary brain tumors, therefore, contain (1) primary brain tumor diagnosis,

M.A. Hayat (ed.), *Tumors of the Central Nervous System, Volume 11*,
DOI 10.1007/978-94-007-7037-9_2, © Springer Science+Business Media Dordrecht 2014

(2) identification of metabolically most active brain tumor reactions (differentiation of viable tumor tissue from necrosis), and (3) prediction of treatment response by measurement of tumor perfusion or ischemia. The key question remains whether the magnitude of biochemical alterations demonstrated by molecular imaging reveals prognostic value with respect to survival. Molecular imaging may identify early disease and differentiate benign from malignant lesions. Moreover, an early identification of treatment effectiveness could influence patient management by providing objective criteria for evaluation of therapeutic strategies for primary brain tumors. Its novel potential to visualize metabolism and signal transduction to gene expression is used in reporter gene assays to trace the location and temporal level of expression of therapeutic and endogenous genes. Currently, molecular imaging probes are developed to image the function of targets without disturbing them or as a drug in order to modify the target's function. In this new context, the microenvironment of malignant brain tumor and the blood-brain barrier shows increased interest. The objective is transfer gene therapy's experimental knowledge into clinical applications. Molecular imaging closes the gap between in vitro to in vivo integrative biology of disease.

Introduction

Despite increasing experimental research regarding pathophysiological mechanism of primary brain tumors in the recent years, the underlying molecular changes both in the tumor area and its surrounding brain tissue remain only partially understood (Schaller, 2003, 2005; Schaller and Buchfelder, 2006). For this reason, much experimental attention has been directed toward understanding the cellular and molecular mechanism of the glial tumor genesis and the development of noninvasive, high-resolution in vivo imaging technology, especially in vivo molecular imaging (Weissleder and Mahmood, 2001).

Glial Tumor Genesis

A complex series of molecular changes occur in the development of primary brain tumors, which results in (1) dysregulation of the cell cycle (e.g., hypermethylasation of TP53), (2) alterations of apoptosis and cell differentiation (amplification of oncogenes and growth factors and/or their receptors (e.g., MDMD2)), epidermal growth factor receptor (EGFR), vascular endothelial growth factor (VEGF), PDGFR (platelet-derived growth factor (PDGF) and its receptor), (3) neovascularization and (4) tumor cell migration and invasion into the brain parenchyma (Weissleder and Mahmood, 2001; Schaller, 2004). For instance, during progression from low-grade astrocytoma (WHO grade II) to anaplastic astrocytoma (WHO grade III) and to glioblastoma multiforme (WHO grade IV) a step-wise accumulation of genetic alterations occurs (Weissleder and Mahmood, 2001; Schaller, 2004): TP53 mutation and PDGF and PDGFR-α overexpression represent early changes during low-grade glioma development. Further progression to anaplastic astrocytoma is associated with pRB alteration and loss of heterozygosis (LOH) of 19q. Finally, malignant progression to glioblastoma multiforme includes LOH 10q and mutations of the PTEN gene (Schaller, 2004). These secondary glioblastomas, which develop from better-differentiated astrocytomas, can be distinguished from de novo glioblastomas on the basis of molecular genetic findings (Schaller, 2004). Amplifications and/or overexpression of the EGFR, p16 deletion, PTEN mutation, pRB alteration, and LOH 10p and 10q are associated with primary glioblastoma.

A clinically most interesting consequence of this research is that molecular alterations have been identified that indicate different therapeutic response of a tumor type to a given drug, which is prognostically relevant. For example, anaplastic oligodendrogliomas with LOH 1p and/or LOH 19q are characteristically sensitive to PCV (procarbazine, lomustine, and vincristine) chemotherapy, and patients' survival is significantly prolonged (DeAngelis et al., 1998).

Molecular Imaging

Intratumoral heterogeneity of brain tumors is not adequately reflected in conventional magnetic resonance imaging (MRI) and evaluation of a contrast enhancing lesion may either under- or over-estimate the presence of active tumor tissue (Levivier et al., 1996). Molecular imaging by positron emission tomography (PET) is therefore performed to gain additional information on metabolic and molecular tumor markers. PET measures and visualizes cellular biochemical processes non-invasively and quantitatively by pattern of in vivo uptake of molecular probes into the brain tissue (Levivier et al., 1996). Because biochemical changes may be related to the growth rate of tumor cells (Levivier et al., 1996) they can be thought as markers of tumor cell proliferation.

In primary brain tumors, molecular imaging allows (1) earlier detection of tumor genesis at pre-disease states, (2) evaluation of the pharmacodynamic and neurotoxicity of chemotherapeutic agents, (3) evaluation of the response to treatment, (4) differentiation between iatrogenic lesions and residual or recurrent tumor tissue (Weissleder and Mahmood, 2001; Jasanoff, 2005).

This chapter reviews the potential of the molecular neuroimaging, particularly PET, in brain tumors, giving an overview regarding the current possibilities and giving additionally link to molecular biological features of brain tumors.

The Microenvironment of Brain Tumors

Pathological characteristics of malignant brain tumors are exemplified by active invasiveness, necrosis, and a specialized form of angiogenesis, known as microvascular hyperplasia. Such pathological features are thought to be due to tissue hypoxia. Therefore, hypoxia is a critical aspect of the surrounding microenvironment of brain tumors, and is generally associated with unfavorable clinical outcomes. Cells that are under hypoxic stress can develop an adaptive response that includes increased rates of glycolysis and angiogenesis or undergo cell death by promoting apoptosis and/or necrosis. The ability of tumor cells to maintain a balance between adaption to hypoxia and cell death is regulated by hypoxia-inducing factors, a family of transcription factors that are essential for the regulation of the expression of a large number of hypoxia-responsive genes. Tumor hypoxia is hypothesized to facilitate metastases, tumor recurrence, invasive potential, resistance to chemotherapy and radiotherapy, which culminate in decreased patient survival. For this reason, effective targeting of hypoxic areas in brain tumors remains a significant therapeutic challenge. New therapeutic options for tumor-targeted drug delivery show promise in treatment of brain tumors that are refractory to traditional therapies. However, the molecular mechanism of targeting to (hypoxic) tumor areas is not well understood. The unique ability, for example, of stem cells, to "home in" on tumor cells and then deliver a desired gene product makes such methods a promising option in brain tumor therapy. Cytolytic viruses and genes coding for anti-tumor cytokines, prodrug-converting enzymes and various neurotrophic factors have been engineered into such options. Novel brain tumor treatment strategies that involved transplantation or infusion of cells that seek out invading tumor cells demand thorough in vivo monitoring. In particular, such treatment methods have attracted great interest because they have demonstrated tropism to tumor cells and even long-distance migration to single tumor cells. However, little is known regarding how these cells exert their beneficial effects in vivo.

Principles of Molecular Imaging in Neurological Sciences

The design of molecular probes for PET studies is usually based on either fundamental biochemical principles or on known pharmacological properties of particular classes of drugs. In reality, it is often difficult to draw a clear distinction between the two, because most modern drugs are designed to interact with predetermined molecular targets that have been identified through pharmacological study as clinically relevant.

Molecular imaging of the central nervous system (CNS) has enabled scientists and researchers to better understand the basic biology of brain function and the way in which various disease processes affect the brain. Unlike other organs, the brain is not easily accessible, and it has a highly selective barrier in that specialized cerebral microvascular endothelium interacts with the cellular milieu of the brain and extracellular matrix to form a neurovascular unit known as the blood-brain barrier (BBB) (Schaller, 2004). BBB dysfunction is a complication of high-grade brain tumors, but it also prevents many therapeutic molecules from entering the CNS (Schaller, 2004). Furthermore, genetic and/or epigenetic abnormalities in the constituents of the BBB may be significant contributing factors in disease etiology.

At present, molecular imaging is able to quantify permeability measurements across the brain endothelium. Malignant primary brain tumors, such as glioblastoma, are characterized by extensive angiogenesis and permeability of the BBB (Schaller, 2004). To date, BBB permeability data have been shown to be useful in preoperative brain tumor grading and potentially also in determining the effectiveness of selective types of therapy in primary brain tumors (Schaller, 2004). For this reason, explorative studies are evaluating new strategies for safe and effective alteration of the BBB permeability to improve local drug delivery into primary brain tumors (Schaller, 2004). As new anti-angiogenesis drugs become available, BBB permeability imaging may also become critical as a surrogate angiogenesis marker to monitor tumor response to these agents.

Characterization of molecular agents at the level of individual cells is crucial if molecular neuroimaging techniques are to be correctly interpreted and trusted as direct measures of physiological or pathophysiological brain function (Schaller, 2004). Determination of delivery methods, subcellular localization patterns, sensor response properties, toxic effects, and in vivo kinetics in simple systems will facilitate application of labeled-agent-based imaging (Jacobs et al., 2003a, b). At the present time, several groups have developed reduced preparations (some are of biological interest in themselves), in which many physiological variables have been minimized, and the effects of contrast agents has been possible with true-cellular or near-cellular resolution (Jacobs et al., 2003a, b). An example of this molecular level characterization is the current possibility to determine P-gp-based drug interactions at the human BBB by PET (Jacobs et al., 2003a, b). From this knowledge to visualize cellular or subcellular functions, the application of molecular neuroimaging techniques has evolved now into the clinical practice of humans.

Before new and potentially more effective treatment strategies, such as gene- and cell-based therapies, can be effectively implemented in the clinical application, certain prerequisites have to be established. First, the exact localization, extent, and metabolic activity of the brain tumors have to be determined to identify the biologically active target tissue for a biological treatment regimen. This necessary prerequisite is usually performed by imaging the expression of up-regulated endogenous genes (Schaller, 2004). Second, neuronal function and functional changes within the surrounding brain tissue have to be assessed in order to save this tissue from therapy-induced damage (Weissleder and Mahmood, 2001). Third, pathognomonic genetic changes leading to disease have to be explored at the molecular level to serve as specific molecular therapeutic targets for patient-tailored therapies (Jacobs et al., 2003a, b). Finally, a concerted noninvasive analysis of both endogenous and exogenous gene expression in animal models as well as the clinical setting is desirable to effectively translate new treatment strategies from experimental into clinical application (Schaller et al., 2007). Non-invasive imaging of endogenous gene expression by means of PET may reveal insight into the molecular basis of pathogenesis, metabolic activity of the glioma, and the extent of treatment response (Schaller, 2004). When exogenous genes are introduced to serve for a therapeutic function, PET imaging techniques may additionally reveal the assessment of the location, magnitude and duration of therapeutic gene expression, and its relation to the therapeutic effect (Schaller et al., 2007). All of these issues can be addressed by multi-modal

molecular imaging techniques and may therefore reveal insight into the molecular basis of pathogenesis and metabolic activity of the brain tumors and the extent of treatment response (Schaller, 2004).

Molecular Imaging Strategies

The biochemistry of life involves a complex series of interdependent interactions that comprise homeostasis. These interactions can be envisaged as the interaction of the genome and the "functional" molecules it encodes through bioenergetically driven chemical interactions (Paulmurugan et al., 2004). Such so-called "split reporter system" can be used to efficiently screen small molecule drugs that modulate protein-protein interactions, and also to assess drugs in living animals or even humans. Both represent essential steps in the preclinical evaluation of candidate pharmaceutical agents targeting protein-protein interactions, including signaling pathways in brain tumor cells (Paulmurugan et al., 2004). Such simplified models are comprised of three key interactive groups of molecules:

- Those related to the genome, including nucleosides and nucleotides, nucleic acids, aptamers, and oligonucleotides.
- Those arising from expression of the genome, namely, the proteins, including enzymes, receptors, structural elements, and antibodies.
- Those providing energy to drive these systems, specially glucose, acetate, and fatty acids, and compounds that reflect oxygen-dependent processes.

There is great interdependency among these groups, involving highly complex pathways that are integral components of the cell and the organism (Paulmurugan et al., 2004). Image-based study of these components with true substrates (e.g., (^{11}C) glucose) may be difficult because the accumulated radioactivity in tissue will reflect the totality of their biochemical reactions. Because PET radiopharmaceuticals can be prepared at highly specific activities it is possible to use PET to study virtually all processes at sub-physiological concentrations, thereby avoiding biochemical perturbations of the processes under investigation (Paulmurugan et al., 2004). But, full validation of false substrates and natural substrates alike is necessary to ensure that images and parametric image data can be used in support of a clinical diagnosis (Blasberg and Tjuvajev, 2003). The study of these small molecule-mediated protein-protein interactions is important in understanding abnormal signal transduction pathways in a variety of neurological disorders including primary brain tumors, and well as in optimizing the process of drug development and validation (Blasberg and Tjuvajev, 2003).

The three most widely used molecular imaging strategies are (1) direct, (2) indirect, and (3) surrogate. Direct molecular imaging generally involves direct probe-target interactions, whereby the resultant image of probe localization and image intensity is directly related to its interaction with the target epitope or enzyme (Schaller, 2004; Blasberg and Tjuvajev, 2003). This strategy is based on imaging the target directly, for example, the receptor, usually with a target-specific probe. Indirect molecular imaging is more complex in that it may involve multiple components (Levivier et al., 1996; Schaller, 2004). Indirect evaluation may be achieved by using specific substrate probes for a target enzyme. One type of indirect imaging that is now being widely used, is reporter imaging, which involves a reporter gene and a reporter probe (Blasberg and Tjuvajev, 2003). These components must be complementary; the reporter gene product is frequently an enzyme that converts a reporter probe to a metabolite that is selectively trapped within transduced cells (Weissleder and Mahmood, 2001; Blasberg and Tjuvajev, 2003). Alternatively, the reporter gene product can be a receptor or transporter that irreversibly traps the probe in transduced cells during the period of image acquisition. Indirect molecular imaging is currently being more widely used than direct molecular imaging, particularly in preclinical animal studies. Surrogate or biomarker molecular imaging strategies reflect downstream affects of one or more endogenous molecular-genetic processes. This latter approach is particularly attractive for potential translation

into clinical studies in the near term because it uses established radiopharmaceuticals and clinical imaging protocols already in use in clinical medicine (or soon to be implemented) (Blasberg and Tjuvajev, 2003). Molecular imaging could provide information on in vivo distribution of biological markers in response to targeted therapy and could improve for example the selection of patients before therapies.

In brain tumors, tumor cell growth and proliferation with the consecutive recurrence attract the greatest interest both for diagnosis and therapy. For this reason, the molecular imaging is also focused on these pathophysiological changes. Clearly, metabolism, genome, and protein expression inseparably manifest in the tumor phenotype, underpinning all biochemically based diagnostics and therapeutics for brain tumors and representing, therefore, potential targets for molecular imaging (Weissleder and Mahmood, 2001).

Principles of Positron Emission Tomography

The general principles of nuclear medicine imaging also apply to molecular imaging. These include knowledge of the normal distribution of a tumor tracer that determines in what regions of the body the method may be successful. For example, high background uptake in an organ may interfere with tumor visualization in that organ. Another main factor is the level of uptake. Visualization depends on the detecting system (PET camera, gamma camera), but also strongly on the amount of tracer that is present at or in the target. In theory, a sub-millimeter lesion can be detected as long as tracer uptake is high enough. On the other hand, a large lesion may be missed when the uptake level is too low. In contrast with radiological methods, it is, therefore, in principle not possible to determine a detection threshold, although in daily practice this threshold is generally around 0.5–1 cm for the best methods.

Imaging of brain tumors with (^{18}F)-FDG was the first oncologic application of PET (Blasberg and Tjuvajev, 2003). (^{18}F)-FDG is actively transported across the BBB into the cell, where it is phosphorylated. PET, therefore, allows the quantitative localization of expression of endogenous or exogenous genes coding for enzymes or receptors by measuring the accumulation or binding of the respective enzyme substrates or receptor binding compounds (Tjuvajev et al., 2002). Depending on the radiotracer, various molecular processes can be visualized in primary brain tumors by PET, most of them related to an increased cell proliferation with astrocytoma. Radiolabeled 2-deoxy-2-(^{18}F)fluoro-D-glucose (FDG) (41), methyl-(11C)-L-methionine ((^{11}C)-MET) and 3′-deoxy-3′-(^{18}F)fluoro-L-thymidine ((^{18}-F)-thymidine) are taken up by proliferating gliomas depending on their tumor grades as a reflection of increased activity of membrane transporters for glucose ((^{18}F)-FDG), amino acids ((^{11}C)-MET), and nucleosides ((^{18}F)-thymidine) as well as increased expression of cellular hexokinase FDG and thymidine kinase ((^{18}F)-thymidine) genes, which specifically phosphorylate FDG and ^{18}F-thymidine, respectively (Schaller et al., 2007; Paulmurugan et al., 2004; Blasberg and Tjuvajev, 2003; Tjuvajev et al., 2002).

Positron Emission Tomography Imaging and Its Relationship to Brain Tumors in Experimental Research

On the Way to Gene Therapy: The Reporter Gene Concept

Imaging reporter gene is a new method to noninvasively and repetitively visualize the location, duration, and magnitude of transgene expression in living animals. Because the radionuclide approach has sufficient sensitivity to measure gene expression in vivo, the approach of using imaging reporter genes with high-resolution PET scanning in brain tumors has been increasingly investigated during the last years (Schaller, 2004; Schaller et al., 2007). Reporter gene imaging is an indirect approach of visualizing the expression of exogenous and endogenous genes, as well as specific intracellular protein-protein interactions (Schaller et al., 2007). Reporter gene imaging can

also be used for monitoring brain tumors cells or neural stem cells (Schaller et al., 2007).

An enormous gap exists between rapidly increasing theoretical knowledge regarding pathophysiological and genetic mechanisms of brain tumors and current lack of its clinical application (Schaller et al., 2007). Therefore, there is a need for animal models to shed more light on the complexity of varying molecular genetic aspects and to have a critical impact on the safety and efficacy of specific treatment modalities, such as gene therapy, in its clinical application (Schaller et al., 2007). In the effort to transfer genes into animals, a safe vector and expression system has to be developed to achieve efficient target and regulated alteration of specific (therapeutic) gene expression (Schaller et al., 2007). In the recent years, animal models of various glial cell lines have been established using different retrovirus or adenovirus mediated reporter genes (Tjuvajev et al., 2002) and radiolabeled tracers as reporter probes (Tjuvajev et al., 2002). Reporter genes can be used (1) to image vector targeting and the level of suicide gene (HSV1-tk) expression (Tjuvajev et al., 2002), (2) to image the regulation of endogenous genes and signal-transduction pathways (Tjuvajev et al., 2002), and (3) to monitor and quantitatively assess the expression of a second transgene that is cis-linked to the reporter gene by an internal ribosome entry site sequence (Schaller et al., 2006). By providing in vivo biochemical and physiological data in quantitative and tomographical terms, PET tracer methods can serve as an interface lining in vitro with in vivo findings of brain tumors. From the scientific point of view, three main research areas appear to be of current interest to study biological relevant mechanisms of primary brain tumor non-invasively by PET; (1) measuring biologically relevant tumor cell mechanisms (e.g., proliferation, angiogenesis, hypoxia, and apoptosis); (2) localizing of magnitude and duration of gene expression; and (3) verifying treatment efficacy on tumor cell metabolism (Tjuvajev et al., 2002). In the context of gene therapy, it is assumed that specific biochemical mechanisms of brain tumor cells, which can be measured with PET, determine individual treatment response (Schaller et al., 2006). Consequently, different radiolabeled probes for non-invasive imaging reporter gene expression have been developed: the quantification of herpes simples virus type 1 thymidine kinase (HSV-1-tk) and cellular thymidine kinase (ctk) gene expression relies on determination of accumulation rates of specific marker substrates such as 2′-fluoro-2′-deoxy-1β-D-arabinofuranosyl-5-(^{124}I)iodo-uracil (^{124}I) FIAU) or 9-(4-(^{18}F)fluoro-3-(hydroxymethyl) butyl)guanine ((^{18}F)FHBG) for HSV-1-tk and 3′-deoxy-3′(^{18}F)fluoro-L-thymidine (^{18}F)FLT for ctk expression, respectively (DeAngelis et al., 1998; Schaller et al., 2007; Tjuvajev et al., 2002). For example, glial RG2 cell cultures, accumulation rate of (^{14}C)FIAU normalized to that of (^{3}H) TdR was proportional to HSV-1-tk mRNA expression (Tjuvajev et al., 2002).

Experimental Attempts of the Reporter Gene Concept

Strategies for non-invasive and quantitative imaging of gene expression in vivo have been developed over the past decade. Non-invasive assessment of the dynamics of gene regulation is of interest for the detection of endogenous disease-specific biological alterations (e.g., signal transduction) and for monitoring the induction and regulation of therapeutic genes (e.g., gene therapy) (Schaller et al., 2006). Several radiolabeled probes have been developed and used to image viral or cellular TK expression in experimental animal brain tumors; these probes can be conveniently separated into pyrimidine nucleoside, acycloguanosine, and thymidine nucleoside derivates (Tjuvajev et al., 2002). A major problem with comparing different radiolabeled markers in experimental studies lies in the fact that until present times, there was (1) no paired comparison between transduced and wild-type glioma cells in the same animal tissue and (2) no comparison to a standard tracer in the same animal tissue to test the probes efficacy (Schaller et al., 2006).

To develop efficient and safe gene therapy approaches, the herpes simplex virus type 1 thymidine kinase gene (HSV-1-tk) has been shown

to function as a marker gene for the direct noninvasive in vivo localization of thymidine kinase (TK) expression by PET using radiolabeled nucleoside analogues as specific TK substrates (Schaller et al., 2006). Moreover, the gene encoding dopamine type 2 receptor (d2r) could be used as a PET marker gene using specific radiolabeled receptor binding compounds (Jacobs et al., 2001; Schaller et al., 2006). The sensitivity of (^{18}F) FHBG in visualizing cells expressing TK-GFP gene has not yet been determined in animal models of glioma cell lines. Our in vivo studies revealed a much higher accumulation of (^{18}F) FHBG with time in transduced cell lines compared with that in non-transduced control cell lines, consistent with monophosphorylation of the tracer by TK-GFP (Jacobs et al., 2001). Cellular accumulation of (^{18}F)FHBG may be unrelated to cell growth rate in wild-type cells (doubling time, 24) compared with that in transduced cells (doubling time 48). Thus, higher uptake in transduced cells supports the hypothesis that the tracer is selectively phosphorylated by TK-GFP only and not by native thymidine kinase suggesting a significant time-dependent difference in the distribution and magnitude of (^{18}F) FHBG (Jacobs et al., 2001). Moreover, (^{18}F) FHBG does not penetrate the intact BBB and can serve only as a marker substrate for HSV-1-TK expression in the brain when the BBB is disrupted (Jacobs et al., 2001). In addition, the PET images provide important spatial information that identifies the viable portion of transduced tissue at a given "imaging time window" (Jacobs et al., 2001). Therefore, it should be possible to infer the biodistribution of a therapeutic gene's expression, delivered by an appropriate TK-vector and regulated by an appropriate promoter in an animal model of F-98 glioma cell lines by imaging with (^{18}F)FHBG, respectively.

Positron Emission Tomography Imaging and Its Relationship to Brain Tumors in Clinical Medicine

Techniques for human brain imaging have undergone rapid developments in recent years. Technological progress has enabled the assessment of many physiological parameters in vivo that are highly relevant for primary brain tumor grading, tissue characterization, definition of the extent and infiltration of tumors, and planning and monitoring of therapy.

Table 2.1 Indication for use of positron emission tomography studies in brain tumors related to (patho) physiological factors

^{18}F-FDG-PET
1. Ninety percent accurate for tumor grading and prognosis
2. Can be used for grading and monitoring for progression to a higher degree of malignancy and for differentiating radionecrosis and recurrence. Recurrence may be undetectable due to high glucose consumption in surrounding normal brain tissues.
3. ^{18}F-FDG accumulation dependent on
(i) glucose transport blood/brain or brain/blood
(ii) phosphorylation of glucose
L-Amino acids PET
1. Only partly accurate for tumor grading and prognosis
2. Good separation of brain tumor from surrounding normal brain tissue
3. Monitoring for progression to a higher degree of malignancy
4. Differentiating stable disease from tumor regrowth
5. Amino acid accumulation dependent on (i) increased affinity and (ii) increased amount of carriers (V_{max})
Thymidine analogs PET
1. Accurate for cell proliferation imaging providing reliable estimation of cellular proliferation by measuring thymidine flux from the blood into DNA of tumors
2. Good estimation of therapeutic efficacy, early detection of recurrence and of malignant transformation

Adapted with Permission from Jacobs et al. (2003a, b)
Legend: *FDG* (18F)fluoro-2-deoxy-D-glucose, *PET* positron emission tomography

Brain Tumor Detection

Generally, a high sensitivity is reported for primary brain tumor detection with PET (Table 2.1). Initial FDG-PET studies could identify elevated FDG uptake in primary brain tumors (Jacobs et al., 2001) with good correlation of the grade of malignancy (Table 2.2). Thus, low-grade astrocytomas are not easily identified or appear as hypometabolic areas surrounded by normal high FDG uptake within the cerebral cortex hindering a clear definition of exact tumor extension. However, amino

Table 2.2 ^{18}F-FDG positron emission tomography with a gold standard of biopsy or radiographic follow-up

	FDG-PET diagnosis		FDG-PET diagnosis in brain metastasis patients only		FDG-PET diagnosis in primary tumor patients only		Magnetic resonance imaging diagnosis	
Gold Standard	Tumor (%)	Necrosis (%)	Tumor (%)	Necrosis (%)	Tumor (%)	Necrosis (%)	Tumor (%)	Necrosis (%)
Tumor	47	16	42	17	75	13		
Necrosis	7	3	8	33	0	13	36	9
Sensitivity	75	0	71	0	86	0	94	0
Specificity	81	0	80	0	100	0	50	0

Adapted with Permission from Jacobs et al. (2003a, b)
Legend: *FDG* (18F)-fluoro-2-deoxy-D-glucose, *PET* positron emission tomography

acid transport is generally increased in malignant transformation (Schaller, 2004; Jacobs et al., 2001). In animal models, upregulation of the amino acid transporter in the supporting vasculature of brain tumor tissue has been shown responsible for increased facilitation of amino acid transport into the tumor cell (Jacobs et al., 2001). Factors involved in this active transport have been reviewed: flux of the amino acid to the tissue, the intrinsic activity of the amino acid transporter, and the rate of intracellular amino acid metabolism (Jacobs et al., 2001). Many clinical studies have demonstrated that (^{11}C)-MET-PET imaging, (amino acid tracer studies) is highly accurate in defining of tumor boundaries both in primary or recurrent brain tumors, regardless of their histological grading (Jacobs et al., 2001). For example, it is demonstrated an excellent 97 % sensitivity for (^{11}C)-MET-PET in 32 patients with high-grade astrocytomas but only a 61 % sensitivity in low-grade astrocytomas have been demonstrated (Jacobs et al., 2001). Other present a patient-based sensitivity of 84 % using stereotactic biopsies from primary brain tumors and normal brain tissue areas, indicating that tumor specificity of (^{11}C)-MET contains a certain rate of false-positive results (Jacobs et al., 2001). In another large series of astrocytomas, 95 % of 37 lesions are clearly visualized in (^{11}C)-MET-PET studies, whereas (^{18}F)-FDG shows 41 % as hypermetabolic, of which most are high-graded astrocytomas; and 49 % as hypometabolic lesions, while 10 % are difficult to distinguish from surrounding normal brain tissue (Jacobs et al., 2001). The reported advantage of (^{11}C)-MET over (^{18}F)-FDG in delineating astrocytomas is probably not relevant in CNS lymphoma, where (^{18}F)-FDG uptake is much higher in tumor than normal brain tissue (Jacobs et al., 2001).

Experience with (^{18}F)-tyrosine as radiolabeled liganding for PET studies in primary brain tumors is more limited. (^{18}F)-tyrosine PET imaging for both primary and recurrent brain tumors (including metastases and cerebral lymphomas) found 91 % of 22 tumors positive for uptake (cited in Jacobs et al., 2001 and Giese et al., 1998). Others could demonstrate increased uptake and transport rates of (^{18}F)-tyrosine in primary brain tumors (n = 15) (cited in Jacobs et al., 2001). Such an uptake appears more related to amino acid transport than to protein synthesis.

Molecular Signaling Pathways, Changes in Vascular Permeability and Angiogenic Potential of Brain Tumors

Within the brain, dissemination of glioma cells follows myelinated fiber tracts and extracellular matrix containing structures such as the basement membranes of blood vessels (Giese et al., 1998; Schaller et al., 2008). These patterns represent the two major routes of invasion frequently observed in clinical disease. For this reason, much of the interest in angiogenesis and hypoxia has led to investigating diagnostic imaging methodologies and developing efficacious agents against angiogenesis in primary brain tumors. In many ways, because of the cytostatic effects of these agents on tumor growth and tumor-associated endothelial cells, the effects of therapy are not immediately evident. Hence, finding clinically applicable

imaging tools and pathologic surrogate markers is an important step in translating glioma biology to therapeutics. There is a variety of strategies in the approach to experimental therapeutics that target the hypoxia-inducible factor pathway, the endogenous antiangiogenic and proangiogenic factors and their receptors, adhesion molecules, matrix proteases and cytokines, and the existing vasculature.

While PET imaging provides more information regarding the metabolic and molecular events of primary brain tumor activity, limited resolution prevents anatomical surgical planning and hinders the understanding of its vascular status. Currently, Dynamic Contrast-Enhanced (DCE)-MRI, and general contrast MRI are, therefore, the best techniques to assess the (micro)vascular status of malignant primary brain tumors (Giese et al., 1998; Schaller et al., 2008). However, promising studies may open some new indications for PET in primary brain tumors. This reveals the complexity of tumor vasculature and heterogeneity that may aid in therapeutic management especially in non-enhancing high-grade gliomas (Giese et al., 1998; Schaller et al., 2008).

Many low-grade gliomas respond to chemotherapy. Cerebral blood flow (CBF) and microvessel density may be critical for drug delivery. Low-grade gliomas are heterogenous tumors with regard to the distribution of amino acid uptake and CBF (Giese et al., 1998; Schaller et al., 2008). In the tumor center, both are coupled, whereas in the tumor periphery, where tumor infiltration of surrounding brain occurs, CBF may be low irrespective of increased (^{18}F)-FET uptake (Giese et al., 1998; Schaller et al., 2008).

However, blood volume and blood flow are independent of different biomarkers of brain tumor perfusion. Therefore, both should be measured when characterizing the efficacy of antiangiogenic therapies (Giese et al., 1998; Schaller et al., 2008). A promising approach for the diagnosis of primary brain tumor is targeting extracellular structures that are involved in angiogenic processes, such as the extra domain B (ED-B) of fibronectin (^{76}Br)-L19-SIP (ED-B fibronectin-binding human antibody derivate (L19-SIP)) specifically accumulates at the target site, enabling detailed PET of tumor neovasculature (Jacobs et al., 2001; Schaller et al., 2008).

Hypoxia is a critical event in tumor progression and angiogenesis. Proteins important for tumor angiogenesis and invasion have been detected in hypoxic brain foci. It was shown that HIF-1 alpha, VEGF-A, and VEGFR2 (Flk-1) protein and mRNA expression levels were significantly higher and MMP-9 was significantly upregulated in brain tumor tissues compared to normal brain (Herholz et al., 2007; Schaller et al., 2008). Together, these results suggest the critical role of hypoxia in tumor angiogenesis and invasion (Schaller et al., 2008). However, underexpression of VEGF-A does not result in complete inhibition of angiogenesis. Moreover, these tumors have a different perfusion phenotype, suggesting that angiogenesis is mediated by an alternative pathway (Herholz et al., 2007). Current results indicate that VEGF-D is an alternative mediator of this angiogenesis (Herholz et al., 2007; Schaller et al., 2008). Nevertheless, (^{18}F)-FMISO PET provides a noninvasive assessment of hypoxia in glioma and is prognostic for treatment outcomes in the majority of patients: (1) an uptake is observed in all high-grade gliomas but not in low grade gliomas and (2) a significant relationship is found between (^{18}F)-FDG or (^{18}F)-FMISO uptake and expression of VEGF-R1 and Ki67 expression (Schaller et al., 2008).

Brain Tumor Grading

PET imaging with (^{18}F)-FDG is considered useful in the diagnostic workup of suspected primary brain tumors or metastases, as it may identify focal hypermetabolic brain areas. Different molecular imaging studies have related the grade of malignancy of astrocytomas to the rate of (^{18}F)-FDG uptake in PET. It was shown that low-grade astrocytomas had low and glioblastoma multiforme had elevated uptake (Schaller et al., 2008). (^{18}F) FDG-PET imagines are also a useful tool to assess the tumor grade in oligodendrogliomas and gangliogliomas (Schaller et al., 2008).

Nearly all PET studies on tumor detection also address the feasibility of tumor characterization

and grading. The uptake is compared between benign and malignant processes and between various grades of malignancy. This clinically useful aspect is supported by in vitro proliferation markers (Schaller et al., 2008). Positive correlation was demonstrated between proliferation cell nuclear antigen index and (^{11}C)-MET uptake, indicating that (^{11}C)-MET is taken up more rapidly and accumulated in highly proliferative tissue (Schaller et al., 2008). Somewhat surprising is that this relationship was not confirmed for (^{18}F)-tyrosine uptake (n=20) (Schaller et al., 2008). Different (^{11}C)-MET accumulations in vivo have shown an uptake corresponding to the background uptake in low-grade astrocytomas, but a high uptake in oligodendrogliomas (cited in Schaller et al., 2008). It has been suggested that this difference could be clinically useful (Schaller et al., 2008). In this context, differentiation between skull base meningiomas and benign neuromas was demonstrated by Nyberg et al. with good specificity (Schaller et al., 2008). The largest study performed by Herholz et al., (2007), found 79 % accuracy in distinguishing astrocytomas from nonneoplastic lesions in 196 patients with a suspected primary brain tumor. Therefore, transport across the BBB is not the rate-limiting step for (^{18}F)-FDG, whereas transport across the BBB does appear to be the rate liming step for amino acid tracers such as (^{11}C)-MET. Transport of the (^{18}F)-amino acid analog (^{3}O)-methyl-6-(^{18}F)-fluoro-L-DOPA via sodium-independent, high-capacity amino acid transport systems has been demonstrated in tumor cell lines (Schaller et al., 2008).

Cerebral A_1 adenosine receptor (A_1ARs) represents a potential indicator of the cerebral response of glioma invasion. With molecular imaging, A_1AR signal intensity was increased in a zone surrounding experimental tumor in a rat glioma model (Schaller et al., 2008). The results of the first-8-cyclopentyl-3-(3-(^{18}F)fluoropropyl)-1-propylxanthine ((^{18}F)-CPFPX)-PET study on a patient with recurrent glioblastoma multiform confirmed the finding of animal models (Schaller et al., 2008). Molecular imaging with (^{18}F)-CPFPX-PET may open novel possibilities for experimental and clinical insights into the cerebral response to tumor invasion.

Brain Tumor Delineation

Many studies have demonstrated that the margins of primary brain tumors, as assessed by (^{11}C)-MET-uptake, are frequently wider than the anatomic boundaries, as demonstrated by MRI (Giese et al., 1998; Schaller et al., 2008). This is explained by the lack of contrast enhancement in MRI in intratumoral areas with an intact BBB. In low-grade tumors and in diffuse gliomatosis, this phenomenon may be even more pronounced (Schaller et al., 2008). In comparison with (^{18}F)-FDG-PET, a better tumor delineation has been reported both for (^{11}C)-MET and (^{18}F)-tyrosine-PET (4). (^{11}C)-MET of (^{18}F)-FDG scanning is combined with activation studies using radiolabeled with ($H_2{}^{15}O$) to depict tumor extension in relation to functional brain areas (Schaller et al., 2008), with the aim to permit a more aggressive surgical resection with a reduced risk of neurological impairment.

(^{18}F)-thymidine PET is useful for evaluating the histological grade and cellular proliferation of brain tumors, as well as for the detection and delineation of brain tumors that show decreased or similar uptake compared with normal gray matter of (^{18}F)-FEG-PET (Schaller et al., 2008). (^{18}F)-thymidine PET, however, does not appear sufficiently useful for differentiating tumors from non-tumor lesions.

Biopsy Localization

Stereotactic biopsies should be taken from the most malignant part of the tumor, which can be identified by changes in microvascular structure and metabolic activity (Schaller et al., 2008). But primary brain tumors are histologically heterogeneous. Accurate grading and diagnosis are especially important for directing the therapeutic approach and providing the prognosis in patients with nonresectable tumors. Stereotactic biopsies of localizations that are based on either methionine or (^{18}F)-FDG-PET seem to be more successful to find accurate brain tumor tissue than are biopsy trajectories based on CT only (Table 2.2) (Herholz et al., 2007; Schaller et al., 2008).

Especially strong uptake reduction of (^{11}C)-MET in necrotic parts or high uptake in anaplastic parts of the tumor tissue may influence the surgical planning and subsequent results of brain tumor biopsies. Methionine is better in detection of nonanaplastic tumor zones and brain tissue with infiltrating neoplastic cells than (^{18}F)-FDG (Schaller et al., 2008). Planning of biopsy trajectories may be improved by tyrosine, particularly in low-grade astrocytomas (Schaller et al., 2008).

Positron Emission Tomography Guided Treatment

Because PET activity reflects tumor metabolic activity, using PET to guide treatment seems to be a logical approach. Studies using PET to delineated tumor volumes for radiation therapy have been reported. In a study of 27 patients with glioblastoma, does escalation using an (^{18}F)-FDG PET-defined volume was investigated (Schaller et al., 2008), demonstrating that (^{18}F)-FDG PET uptake was the only parameter significant for predicting survival and time to tumor progression. However, in a subsequent report of 40 patients, such radiation dose escalation based on (^{18}F)-FEG PET volume did not result in improved survival or time to tumor progression, compared with historical controls (Schaller et al., 2008).

Differential Diagnosis

MRI usually establishes the differential diagnosis between "normal" brain tissue and malignant or nonmalignant lesions. However, AIDS related lesions are difficult to distinguish. Here (^{18}F)-FDG-PET has been used to differentiate between toxoplasmosis and lymphoma (Schaller et al., 2008): High grade uptake of (^{18}F)-FDG is strongly suggestive of a malignant lymphoma presenting as an extremely metabolically active tumor, while a toxoplasmosis presents as hypometabolic lesion (Table 2.3). The problem of specificity, however, may limit the usefulness of (^{18}F)-FDG-PET as a routine method, as inflammatory lesions are able to also accumulate (^{18}F)-FDG (Schaller et al., 2008).

Positron Emission Tomography in Pediatric Brain Tumors

Less is known regarding PET for pediatric brain tumors. Approximately, 10 years ago, clinical studies suggested that PET technology might gain widespread clinical application in pediatric brain tumors. The first (^{18}F)-FDG-PET studies of isolated case showed a relationship between (^{18}F)-FDG uptake and the degree of tumor malignancy (Schaller et al., 2008), the response to chemotherapy and highlighted the heterogeneity of (^{18}F)-FDG uptake in pediatric brain tumors. Still, the literature remains scant and indication for PET application in pediatric brain tumors is not clearly defined (Schaller et al., 2008). A recent study on (^{18}F)-FDG and (^{11}C)-MET-PET in 27 untreated primary pediatric brain tumors found that both (^{18}F)-FDG and (^{11}C)-MET uptake is associated with malignancy grade and may give valuable additional information on clinical aggressiveness (Schaller et al., 2008).

Positron Emission Tomography in Experimental Brain Tumors Models

Molecular imaging studies in experimental brain tumor models over the past 10 years aimed toward (1) the development of new radiotracers for cellular proliferation and protein synthesis, (2) characterization of these tracers with respect to their ability to detect responses to radio- and chemotherapy at a relatively early stage, (3) strategies for imaging transcriptional regulation and migration of tumor cells, and (4) imaging the expression of exogenous genes carrying a marker or therapeutic function and introduced into experimental gliomas for the purpose of developing improved gene therapeutic vectors. These experimental strategies have been previously reviewed in detail (Schaller et al., 2008).

New developments aim toward (1) the detection of tumor cell migration in vivo (Schaller et al., 2008), (2) the establishment of in vivo assays for direct imaging of tumor-specific signal transduction pathways (e.g. p53-, E2F-1 and HIF-1-α regulated pathways (Schaller et al., 2008)),

Table 2.3 Overview of brain tumors and its imaging by positron emission tomography

Tumor entities (% of all primary brain tumors)	Positron emission tomography study	
	FDG[a]	Methionine[b]
1. Gliomas		
Pilocytic astrocytoma WHO I° (<3 %)	Variable, focally increased	Up to 2-fold
Astrocytoma WHO II° (<5 %)	Decreased	1- to 2–fold
Anaplastic astrocytoma WHO III° (<5 %)	Variable	2- to 3-fold
Glioblastoma multiforme WHO IV° (<20–25 %)	Increased	>2.5-fold
Oligodendroglioma WHO II°/III° (<5 %)	Decreased/increased	>2.5-fold
Oligoastrocytoma WHO II°/III° (<5 %)	Decreased/increased	2- to 3-fold
Ependymomas (2–3 %)	Decreased	1.3- to 2.7 fold
2. Neuronal and glioneuronal tumors		
Dysembryoplastic neuroepithelial tumor (<1 %)	Decreased benzodiazepine receptor	Density as possible reason for epileptogenicity
Dysplastic gangliocytoma (<1 %)	Increased	Increased
Ganglioglioma (<1 %)	Variable, depending on WHO grade	NA
Central neurocytoma (<1 %)	Increased, depending on proliferative activity	Increased
3. Tumor of the pineal gland (<1 %)		
Pineoblastoma	Increased	NA
4. Embryogenic tumors		
Medulloblastoma (20–25 % <15 y.o.: 1 % > 20 y.o.)	Strongly increased	Increased
Primitive neuroectodermal tumors (PNET)	Decreased; relatively increased in spinal localization	NA
5. Meningeal tumors		
Meningiomas (25–30 %)	Variable (0.2- to 1.8-fold)	Increased (1.3- to 3.6 fold)
	(^{68}GA)DOTATOC-PET detects somatostatin receptor expression in meningiomas	
Hemangiopericytoma (<0.5 %)	Decreased	Increased
6. Tumors of the region of the sella		
Craniopharyngioma (<2 %)	Variable depending on histological type	NA
Adenomas of the hypophysis (5–8 %)	Specific binding to D2-receptors on adenomas of hypophysis from perisellar meningiomas and craniopharyngiomas specific increases in monoaminooxidase activity on ^{11}C-Deprenyl-PET differentiates adenomas of hypophysis from perisellar meningiomas by specific increased monoaminooxidase activity	^{18}F-FESP-PET differentiates
7. Tumors of cranial nerves		
Neurinoma (6–8 %)	Iso–or hypometabolic	Only slight increase
8. Lymphomas		
Primary CNS lymphoma (2–5 %)	Increased; allows differential diagnosis from toxoplasmosis	Increased
9. Metastatic tumors (20 % of all brain tumors)		
Lung, breast melanoma, gastrointestinal, hypernephroma	Variable, screening for metastasis with ^{18}F-FDG is not recommended	NA
	(^{66}GA)-DOTATOC-PET details somatostatin receptor positive metastasis of carcinoid tumors	

Adapted with Permission from Jacobs et al. (2003a, b)

Legend: *NA* not available, *18F-FESP* (18F) fluoro-ethyl-spiperone, *68GA-DOTATOC* 68-GA-1,4,7,10-tetraazacyclododecan-N,N′,N″, N‴-tetraaceticacid-D-Phe-Try-octreoid, *PET* positron emission tomography

[a]18F-FDG in comparison to cortical cerebral metabolic rate of glucose (CMRGlc)

[b]11C-methionine in comparison to contralateral control region

(3) the design of labeled peptides binding specifically to the cell adhesion receptor integrin α(v)β (Weissleder and Mahmood, 2001) or other tumor-specific antigens and of labeled bone marrow-derived endothelial precursor cells to allow highly specific tumor visualization and the study of glioma angiogenesis and neovascularization (Haubner et al., 2001; Sundaresan et al., 2003; Schaller et al., 2008), (4) the generation and in vivo characterization of transgenic mice with gliomas induced by signaling through Ras and Akt pathways (Schaller et al., 2008), and (5) the construction of bifunctional imaging marker and therapeutic genes to allow direct assessment of therapeutic gene expression in culture and in vivo models by directly corresponding assays (Jacobs et al., 2003a, b; Schaller et al., 2008). Especially, the design of small tumor-specific antibody fragments is an attractive way for specific detection of tumor cells by imaging in vivo as well as for targeted therapy by radioimmunotherapy.

Many of the current experimental protocols investigating new drug and treatment strategies for experimental gliomas included MRI, optical or PET imaging of either the distribution of therapeutic agents (Jacobs et al., 2003a, b), or therapy-induced tumor-changes (Jacobs et al., 2003a, b; Voges et al., 2003; Schmidt et al., 2004), with the overall attempt of designing image-guided treatments (Voges et al., 2003; Schaller et al., 2008). Most intriguing for clinical application is the design of multifunctional nanoparticles that can be detected both by MRI and fluorescence imaging, allowing for noninvasive preoperative assessment of the tumor and for intraoperative visualization of tumor margins by optical imaging (Schaller et al., 2008).

PET receptor ligand studies have generated a wealth of knowledge regarding disease pathogenesis and potential therapeutic targets for novel pharmaceutical agents. PET offers the opportunity to use an in vivo technique to study the pharmacodynamics and biodistribution of new agents and to ensure they target the organs or compartments of interest, for example, in case of neuropharmacology, the ability of drug to cross the BBB and bind to specific receptors in the brain (Schaller, 2004; Schaller et al., 2008). The study of drug occupancy can provide information regarding the occupancy of the binding sites for a particular dose of the drug and its pharmacokinetics (Schaller et al., 2008). This will help determine optima drug dosing regimens.

Evaluation of Therapy by Positron Emission Tomography

The development and clinical testing of targeted biological therapies for brain tumors present new opportunities and new challenges. The efficacy of traditional cytotoxic agents, which may produce detectable tumor regression, is typically measured by response rate or survival (Schaller et al., 2008). However, new biologic therapies have led to targeted molecular therapies that may permit improvement in therapeutic efficacy and reduced toxicity; thus, requiring new measures of activity (Schaller et al., 2008): For example, signal transduction pathways that are inappropriately regulated in brain tumors include growth factors and their receptors (e.g. EGFR, VEGFR or PEDGR), which regulate cellular interactions with the microenvironment and intracellular oncogenic pathways. Improved functional neuropathology and molecular imaging may, therefore, permit identification of patient subgroups for which clinical responses may be enriched (Table 2.4).

In the early postoperative period, (^{18}F)-FDG-PET can be used to differentiate residual tumor tissue from postoperative surgical effects (Schaller et al., 2008). It seems clear that a decline in tumor tissue uptake of (^{18}F)-FDG weeks or months after therapy is suggestive of a good response to treatment, indicating either a reduced number of viable cells or reduced metabolism of damaged cells (Schaller et al., 2008).

After intensive irradiation or chemotherapy for malignant brain tumors, MRI is not able to distinguish tumor progression from radiation damage or necrosis. Some PET methods appear promising as relatively specific indices of therapeutic response. (^{18}F)-FDG uptake suggests the presence of viable brain tumor tissue (at least when high tumor uptake of (^{18}F)-FDG was

Table 2.4 New findings in brain tumors with possible relation to molecular imaging in human primary brain tumors

1. Experimental
Signal transduction pathways
Growth factors and their receptors: e.g. epidermal growth factor receptor, vascular endothelial growth factor receptor and platelet-derived growth factor), which regulate cellular interactions with the microenvironment and intracellular oncogenic pathways
Low-molecular-weight inhibitors
To target many kinases and may have advantages in terms of delivery. Monoclonal antibodies may have greater specificity, but face delivery restrictions
2. Clinical
18F-FLT PET
Potential to monitor treatment response and to serve as a prognostic marker?
18F-Fluoromisonidazole PET
A role in directing and monitoring targeted hypoxic therapy?
68Ga-DOTA-TOC PET
Potential?

Adapted with Permission from Schaller et al. (2008)
Legend: *DOTATOC* 68-GA-1,4,7,10-tetraazacyclododecan-N,N′,N″, N‴-tetraaceticacid-D-Phe-Try-octreoid, *FLT* 3′-deoxy-3′-[^{18}F] fluorothymidine, *PET* positron emission tomography

noted before therapy), while absence of (^{18}F)-FDG uptake suggests that necrosis may be present (Schaller et al., 2008). An increase in brain tumor metabolism compared to studies before therapy predicts longer survival (Schaller et al., 2008). This is explained by predominant killing of low energy-consuming cells or stimulation of quiescent cells, either tumor or normal, to become metabolically more active. In other terms, the increased regional metabolism means that within a certain volume of a specific tissue, the ratio and density of normal cells to tumor cells improved.

Changes in proliferation pattern can be assessed by monitoring (^{18}F)-thymidine uptake (reflecting protein synthesis). A novel strategy directly images apoptosis based on detection of the associated increased phosphatidylserine expression. Agents that are trapped when reduced can be used to assess tumor hypoxia, a cause of failure of chemotherapy or radiotherapy treatments. Defining these brain tumors regions that are likely to be refractory to noninvasive treatments could allow more selective targeting or cell kill therapies or surgical excision.

Detection of recurrent or residual viable brain tumor tissue can be troublesome in brain tumors treated by surgery or irradiation. In vitro evidence is somewhat conflicting, but it can be demonstrated that (^{11}C)-MET-PET is suitable for follow-up of the treatment effects (Woesler et al., 1997; Schaller et al., 2008). For example, a dose-dependent reduction in uptake of (^{11}C)-MET in low-grade astrocytomas up to 1 year after brachytherapy has been demonstrated, whereas (^{18}F)-FDG uptake is unchanged (cited in Schaller et al., 2008). Others have found no (^{11}C)-MET uptake in six of seven cases of radionecrosis that are difficult to assess using MRI or CT (cited in Schaller et al., 2008). (^{11}C)-MET-PET had a sensitivity of 77.8 % and specificity of 100 % for differentiation recurrence of metastatic brain tumors from post-radiotherapy changes (cited in Schaller et al., 2008). However, (^{11}C)-MET-uptake may also be elevated in other conditions where there is a disruption of the BBB, such as cerebral hematoma or even necrotic areas caused by radiotherapy (Voges et al., 1997; Schaller et al., 2008). Glucose metabolism may be normal or low in lower grade tumors compared with surrounding cortex. Combined use of (^{11}C)-MET- and (^{18}F)-FDG-PET enhances the discrimination between recurrent tumor and post radiotherapy changes. Remarkably, the protein synthesis rate, determined by using (^{18}F)-tyrosine-PET, remains unchanged in 80 % of patients after radiotherapy (Schaller et al., 2008). Four hours after irradiation, the increase in tumor (^{18}F)-FDG uptake compared to the preirradiation study is significantly assessed with MRI. For malignant astrocytomas, this relationship has not been assessed yet. Voges et al. (1997) report on a series of 46 patients who underwent serial (^{11}C)-MET- and (^{18}F)-FDG-PET studies following interstitial brachytherapy: (^{11}C)-MET is superior to (^{18}F)-FDG in delineating residual of recurrent tumor tissue. This finding confirms earlier data on the comparison of (^{18}F)-FDG and amino acid in visualization of untreated low- and high-grade astrocytomas.

Several PET studies have tried to establish a relationship between metabolic response and prognosis after initiation of chemotherapy in patients with glioblastoma multiforme. The change of (^{18}F)-FDG uptake induced by chemotherapy can be correlated with survival. Both positive and inverse correlation can be found between metabolic responses and survival, making these data inconclusive. In a more recent study, methionine is found to be superior to (^{18}F)-FDG in monitoring the treatment effects in low-grade astrocytomas (Schaller et al., 2008).

Prognosis

(^{18}F)-FDG-PET is used to predict the survival of untreated patients and to confirm suspected recurrence of high-grade astrocytomas. It was shown that (^{18}F)-FDG may differentiate recurrence from other therapy-related changes. Further tumor (^{18}F)-FDG uptake lower than adjacent cortical tissue is associated with a longer survival time than observed in tumor (^{18}F)-FDG uptake higher than in the adjacent cortex (Schaller et al., 2008). A relationship between glucose metabolism as assessed by (^{18}F)-FDG uptake as risk of malignant evolution in low-grade astrocytomas. It has also been shown the presence of areas of increased (^{18}F)-FDG uptake in a histologically proven low-grade astrocytoma predicts an adverse clinical course patients with hypermetabolic tumors demonstrated a median survival of 7 months after (^{18}F)-FDG-PET compared with 33 months for those with hypometabolic tumor. It has been demonstrated PET can be used to separate high-grade astrocytomas into subgroups (hypometabolic 78 % 1 year survival) (cited in Schaller et al., 2008; Schaller, 2008). Residual or recurrent high-grade astrocytomas showed high glucose utilization present with a mean survival period of 5 months, whereas in those tumors showing lower utilization, mean survival was 19 months (Schaller, 2008).

Presently, the experience with other tracers than (^{18}F)-FDG is limited, but in a quantitative evaluation of (^{11}C)-MET-uptake with low-grade astrocytomas, the patients with a low tumor uptake in the baseline study demonstrated a significantly better prognosis than those with a high uptake (Stockhammer et al., 2007). The prognostic information by amino acid PET studies has been provided by the presence, but not by the intensity, of uptake (Schaller et al., 2008). The current data suggest caution in relating high amino acid uptake values to poor prognosis despite the capability of amino acid imaging to help determine the presence and extent of astrocytomas.

Advances in Molecular Analysis and Characterization

Innovative techniques using complementary DNA and oligonucleotide microarrays (gene chips), tissue microarrays (tissue chips), and differential immunoabsorption have provided high throughput and potentially comprehensive approaches for the molecular characterization of human gliomas. Alterations of several tumor suppressor genes and oncogenes have already been identified as being critical to glioma transformation and progression. These approaches have led, for example, to the subclassification of glioblastoma multiforme into distinct subtypes based on the molecular signatures of the tumors. Improved and efficient molecular profiling of primary brain tumors is advancing diagnosis/prognosis. Identifying targets for novel and rational therapeutic approaches opens the window for clinical routine use of molecular imaging for primary brain tumors in the near future.

Oligodendroglial tumors harboring combined 1p and 19q loss 81p/19q LOH are characterized by a favorable prognosis and response to chemotherapy and radiotherapy, but detection of 1p/19q LOH relies on postoperative procedures. (^{18}F)-FDG-PET has the potential to predict 1p/19q LOH in WHO grade II gliomas preoperatively in tumors whose appearance on initial magnetic resonance images is consistent with that of low-grade glioma (Schaller et al., 2003a, b, c, d, 2008).

Although cell division is the most distinguishing function of growth in primary brain tumors, probing membrane biosynthesis with PET and 1-(^{11}C)acetate or a choline tracer may yield information as helpful as protein or DNA synthesis. Because astrocytic gliomas frequently carry epidermal growth factor receptor (EGFR) mutations at a frequency that is related to grade; a PET tracer that is specific for this mutated receptor could be useful for grading and prognosis. Methods for imaging angiogenesis are being developed (Schaller et al., 2003a, b, c, d, 2008); (^{18}F)-labeling of a cyclic RGD-containing glycopeptides, cyclo(-Arg-Gly-Asp-D-Phe-Lys(sugar amino acid)-), with 4-nitro-phenyl 2-(^{18}F)fluoropropionate has been reported. (^{18}F)-labeled annexin V is being tested as a new PET agent for quantization tumor cell death and predicting response to therapy. Annexin V binds to surface membranes that have exposed phosphatidyl serine residues resulting from programmed cell destruction.

Pharmacoselective Potential of Molecular Imaging in Neurooncology Drug Development

Novel targeted drugs such as small molecular inhibitors of receptors and signaling pathways in the biology of primary brain tumors are showing some activity in initial studies. As we learn more about these drugs and how to optimize their use as single agents and in combination with radiation, chemotherapy, and other targeted molecular agents, they will likely play an increasing role in the management of this devastating disease. Such molecules can be labeled with positron emitting isotopes and the emitted radiation is detected using sensitive PET cameras.

It is now possible to measure in vivo and normal tissue pharmacokinetics of anti-cancer drugs and investigate their mechanism of action. Radiolabelling of tracers can be used to measure specific pharmacodynamic endpoints and target identification (Schaller et al., 2008; Sandu and Schaller, 2010; Sandu et al., 2011a, b). Increasing evidence shows how these technologies, when added to early drug development, can rapidly reduce the time for entry into humans and early identification of mechanisms of action. With the move towards more segmented markets and identification of specific subgroups, PET's use for noninvasive biomarkers will become increasingly important.

Conclusion

Energy metabolism and amino acid transport and incorporation are important components of the pathophysiology of gliomas. Molecular imaging is providing such regional biologic information. Imaging brain tumors is straightforward and proliferation imaging with PET is very promising. However, neither has been exploited thoroughly enough to allow judgment of their potential benefit to the practice of neurooncology. Although protein and DNA based cell division is the most distinguishing feature of tumor growth, probing membrane biosynthesis with PET may also yield helpful information. Because astrocytic gliomas frequently carry EGFR mutations at a frequency that is related to grade, a PET racer, like (^{18}F)-fluoromisonidazole, that is specific for this mutated receptor, could be useful for grading and prognosis. Methods for imaging angiogenesis are being developed. As molecular pathways leading to and sustaining neoplasia become well understood, so will our capacity to measure them in vivo and intervene to the patient's advantage. Against the background of a thorough molecular imaging assessment of brain tumors, developments of novel therapeutic approaches based on gene therapy will involve the continued monitoring of therapy.

Not every patient can be studied with molecular imaging, and it is not necessary to do so; but molecular imaging technologies should be used in selected patients to advance our understanding of the complex pathophysiology of astrocytoma formation. This will allow the development and assessment of new therapeutic modalities including molecular target and gene therapies ("imaging-guided therapies").

References

Blasberg RG, Tjuvajev JG (2003) Molecular-genetic imaging: current and future perspectives. J Clin Invest 111:1620–1629

DeAngelis LM, Burger PC, Green SB, Cairncross JG (1998) Malignant glioma: who benefits from adjuvant chemotherapy? Ann Neurol 44:691–695

Giese A, Laube B, Zapf S, Mangold U, Westphal M (1998) Glioma cell adhesion and migration on human brain sections. Anticancer Res 18:2435–2447

Haubner R, Wester HJ, Weber WA, Mang C, Ziegler SI, Goodman SL, Senekowitsch Schmidtke R, Kessler H, Schwaiger M (2001) Noninvasive imaging of alpha(v) beta3 integrin expression using 18F-labeled RGD-containing gylcopeptide and positron emission tomography. Cancer Res 61:1781–1785

Herholz K, Coope D, Jackson A (2007) Metabolic and molecular imaging in neuro-oncology. Lancet Neurol 6:711–724

Jacobs A, Voges J, Reszka R, Lercher M, Gossmann A, Kracht L, Kaestle C, Wagner R, Wienhard K, Heiss WD (2001) Positron-emission tomography of vector-mediated gene expression in gene therapy for gliomas. Lancet 358:727–729

Jacobs AH, Li H, Winkeler A, Hilker R, Knoess C, Rüger A, Galldiks N, Schaller B, Sobesky J, Kracht L, Monfared P, Klein M, Vollmar S, Bauer B, Wagner R, Graf R, Wienhard K, Herholz K, Heiss WD (2003a) PET-based molecular imaging in neuroscience. Eur J Nucl Med Mol Imaging 30:1051–1065

Jacobs AH, Winkeler A, Hartung M, Slack M, Dittmar C, Kummer C, Knoess C, Galldiks N, Vollmar S, Wienhard K, Heiss WD (2003b) Improved herpes simplex virus type 1 amplicon vectors for proportional coexpression of positron emission tomography marker and therapeutic genes. Hum Gene Ther 14:277–297

Jasanoff A (2005) Functional MRI using molecular imaging agents. Trends Neurosci 28:120–126

Levivier M, Becerra A, De Witte O, Brotchi J, Goldman S (1996) Radiation necrosis or recurrence. J Neurosurg 84:148–149

Paulmurugan R, Massoud TF, Huang J, Gambhir SS (2004) Molecular imaging of drug-modulated protein-protein interactions in living subjects. Cancer Res 64:2113–2119

Sandu N, Schaller B (2010) Stem cell transplantation in brain tumors: a new field for molecular imaging? Mol Med 16:433–437

Sandu N, Pöpperl G, Toubert ME, Arasho B, Spiriev T, Orabi M, Schaller BJ (2011a) Molecular imaging of potential bone metastasis from differentiated thyroid cancer: a case report. J Med Case Rep 5:522

Sandu N, Pöpperl G, Toubert ME, Spiriev T, Arasho B, Orabi M, Schaller B (2011b) Current molecular imaging of spinal tumors in clinical practice. Mol Med 17:308–316

Schaller B (2003) Neuroprotection in brain tumors-pathophysiological sense or nonsense? Nervenarzt 74:1134–1136

Schaller B (2004) Usefulness of positron emission tomography in diagnosis and treatment follow-up of brain tumors. Neurobiol Dis 15:437–448

Schaller B (2005) Influences of brain tumor- associated pH changes and hypoxia on epileptogenesis. Acta Neurol Scand 111:75–83

Schaller B (2008) Strategies for molecular imaging dementia and neurodegenerative diseases. Neuropsychiatr Dis Treat 4:585–612

Schaller BJ, Buchfelder M (2006) Neuroprotection in primary brain tumors: sense or nonsense? Expert Rev Neurother 6:723–730

Schaller B, Graf R, Sanada Y, Tolnay M, Rosner G, Wienhard K, Heiss WD (2003a) Hemodynamic changes after occlusion of the posterior superior sagittal sinus: an experimental PET study in cats. AJNR Am J Neuroradiol 24:1876–1880

Schaller B, Graf R, Sanada Y, Rosner G, Wienhard K, Heiss WD (2003b) Hemodynamic and metabolic effects of decompressive hemicraniectomy in normal brain: an experimental PET-study in cats. Brain Res 982:31–37

Schaller B, Graf R, Wienhard K, Heiss WD (2003c) A new animal model of cerebral venous infarction: ligation of the posterior part of the superior sagittal sinus in the cat. Swiss Med Wkly 133:412–418

Schaller B, Graf R, Jacobs AH (2003d) Ischaemic tolerance: a window to endogenous neuroprotection? Lancet 362:1007–1008

Schaller B, Buchfelder M, Knauth M (2006) Trigeminocardiac reflex during skull base surgery: a new entity of ischaemic preconditioning? The potential role of imaging. Eur J Nucl Med Mol Imaging 33:384–385

Schaller BJ, Modo M, Buchfelder M (2007) Molecular imaging of brain tumors: a bridge between clinical and molecular medicine? Mol Imaging Biol 9:60–71

Schaller BJ, Cornelius JF, Sandu N, Buchfelder M (2008) Molecular imaging of brain tumors: personal experience and review of the literature. Curr Mol Med 8:711–726

Schmidt KF, Ziu M, Schmidt NO, Vaghasia P, Cargioli TG, Doshi S, Albert MS, Black PM, Carroll RS, Sun Y (2004) Volume reconstruction technique improve the correlation between histological and in vivo tumor volume measurements in mouse models of human gliomas. J Neurooncol 68:207–215

Stockhammer F, Thomale UW, Plotkin M, Hartmann C, Von Deimling A (2007) Association between fluorine-18-labeled fluorodeoxyglucose uptake and 1′ and 19q loss of heterozygosity in World Health Organization Grade II gliomas. J Neurosurg 106:633–637

Sundaresan G, Yazaki PJ, Shively JE, Finn RD, Larson SM, Raubitschek AA, Williams LE, Chatziioannou AF, Gambhir SS, Wu AM (2003) 124I-labeled engineered anti-CEA minibodies and diabodies allow high-contrast, antigen-specific small-animal PET

imaging of xenografts in athymic mice. J Nucl Med 44:1962–1969

Tjuvajev JG, Doubrovin M, Akhurst T, Cai S, Balatoni J, Alauddin MM, Finn R, Bommann W, Thaler H, Conti PS, Blasberg RG (2002) Comparison of radiolabeled nucleoside probes (FIAU, FHBG, and FHPG) for PET imaging of HSV1-tk gene expression. J Nucl Med 43:1072–1083

Voges J, Herholz K, Hölzer T, Würker M, Bauer B, Pietrzyk U, Treuer H, Schröder R, Sturm V, Heiss WD (1997) 11C-methionine and 18-F-2-fluorodeoxyglucose positron emission tomography: a tool for diagnosis of cerebral glioma and monitoring after brachytherapy with 125I seeds. Stereotact Funct Neurosurg 69:129–135

Voges J, Reszka R, Gossmann A, Dittmar C, Richter R, Garlip G, Kracht L, Coenen HH, Sturm V, Wienhard K, Heiss WD, Jacobs AH (2003) Imaging guided convection-enhanced delivery and gene therapy of glioblastoma. Ann Neurol 54:479–487

Weissleder R, Mahmood U (2001) Molecular imaging. Radiology 219:316–333

Woesler B, Kuwert T, Morgenroth C, Matheja P, Palkovic S, Schäfers M, Vollet B, Schäfers K, Lerch H, Brandau W, Samnick S, Wassmann H, Schober O (1997) Non-invasive grading of primary brain tumours: results of a comparative study between SPET with 123I-alpha-methyl tyrosine and PET with 18F-deoxyglucose. Eur J Nucl Med 24:428–434

Use of ^{11}C-4DST-PET for Imaging of Human Brain Tumors

3

Tadashi Nariai, Motoki Inaji, Muneyuki Sakata, and Jun Toyohara

Contents

Abstract

Brain tumor imaging with positron emission tomography (PET) is now an indispensable modality for intensive treatment of malignant brain tumors. Many tracers have been proposed for this purpose based on the extensive metabolism in malignant tumor cells, such as glucose metabolism, amino acid metabolism, and membrane synthesis. Among them, L-[methyl-^{11}C] methionine (^{11}C-MET) is the most widely used tracer for brain tumor imaging. Theoretically, cell proliferation imaging detects the upstream events of these biochemical changes, and is therefore recognized as a gold standard. Thus, 3′-deoxy-3′-^{18}F-fluorothymidine (^{18}F-FLT) was proposed as a tracer for cell proliferation imaging. However, its uptake into brain tumors is influenced more by blood-to-tumor transport than by cell proliferation. As an alternative, we proposed 4′-[methyl-^{11}C]thiothymidine (^{11}C-4DST) based on its mechanism of incorporation into DNA. In contrast, ^{18}F-FLT is not incorporated into DNA due to lack of a free 3′-hydroxyl group.

In the first clinical trials, we confirmed that dosimetry and pharmacological safety of ^{11}C-4DST were acceptable at the dose required for adequate PET imaging. ^{11}C-4DST uptake into the normal brain and tumor-to-brain contrast are superior to those of ^{11}C-MET. Patlak plot analysis showed a linear increase, indicating irreversible trapping of ^{11}C-4DST in tumor tissues. Interestingly, ^{11}C-4DST accumulates into growing tumors but not

T. Nariai • M. Inaji • M. Sakata • J. Toyohara (✉)
Research Team for Neuroimaging,
Tokyo Metropolitan Institute of Gerontology,
Tokyo 173-0015, Japan
e-mail: toyohara@pet.tmig.or.jp

M.A. Hayat (ed.), *Tumors of the Central Nervous System, Volume 11*,
DOI 10.1007/978-94-007-7037-9_3,

into tumors stabilized by treatment. ^{11}C-4DST uptake into tumor was not influenced by increased transport from blood, such as ^{11}C-MET. Although these are preliminary findings, we consider that ^{11}C-4DST may be the best imaging agent to monitor brain tumor cell proliferation among various PET tracers applied to date. To make use of ^{11}C-4DST, it is necessary to determine the kinetic analysis method to numerically express cell proliferation rate.

Introduction

The biological and clinical manifestations of intracranial malignancy depend largely on the rate of tumor proliferation and increase in tumor size. Knowledge of tumor proliferative activity could be used to estimate tumor growth potential or grade of malignancy, and may be useful for estimating the prognosis of patients with intracranial tumors. A noninvasive method for measurement of tumor cell proliferation would be helpful in the selection of optimal treatments and may provide an earlier measure of response to therapy when compared to tumor volume assessments by X-ray computed tomography (CT) and magnetic resonance imaging (MRI).

The potential for obtaining functional images of tumor cell proliferation using positron emission tomography (PET) has been recognized (Bading and Shields, 2008; van Waarde and Elsinga, 2008). PET provides the opportunity to perform noninvasive measurements of uptake, distribution, and clearance of radiolabeled precursors of DNA in both tumor and normal tissues of patients with cancer. Our proposed use of carbon-11-labeled 4′-thiothymidine (^{11}C-4DST, previously designated as ^{11}C-S-dThd) is substantially different from other investigations using 3′-deoxy-3′-^{18}F-fluorothymidine (^{18}F-FLT) as a radiolabeled precursor of DNA synthesis (Toyohara et al., 2006, 2008). ^{11}C-4DST has been developed based on the mechanisms of incorporation into DNA. In contrast, ^{18}F-FLT is not incorporated into DNA due to the lack of a free 3′-hydroxyl group. As a result, ^{18}F-FLT imaging is regarded as the salvage pathway of DNA synthesis (Been et al., 2004).

This chapter describes the basis of ^{11}C-4DST and its clinical application to brain tumor imaging as well as kinetic analysis. Nucleosides labeled with ^{18}F ($t_{1/2}$ = 109.8 min) have the potential advantage that a single production is sufficient for several patients, or alternatively to be delivered to satellite PET-centers, if the tracers can be prepared with high radiochemical yields. The use of nucleosides labeled with ^{11}C ($t_{1/2}$ = 20.4 min) is restricted to a few subjects in PET-centers with an on-site cyclotron; however, it has potential advantages for patients. Multiple tracers can be administered to individuals on the same day to determine the tumor characteristics with ^{11}C-4DST followed by amino acid metabolism; L-[methyl-^{11}C]methionine (^{11}C-MET). The use of ^{11}C-labeled tracers usually results in decreased absorbed radiation doses compared with the use of ^{18}F-tracers that have longer half-lives. This lower radiation burden allows repeat scans during the course of therapy.

Basis of ^{11}C-4DST

Radiosynthesis

^{11}C-4DST was synthesized by palladium-mediated Stille cross-coupling reaction. Initially, ^{11}C-4DST was prepared with lower radiochemical yields (Toyohara et al., 2008). Later, a modified method with reliable and higher yields was developed for routine clinical use (Toyohara et al., 2011).

Tumor Imaging Potential Evaluated in a Rodent Model

Tumor accumulation of ^{11}C-4DST was first evaluated in tumor-bearing mice (Toyohara et al., 2008). The levels of tumor uptake were high (standardized uptake values (SUVs) between 2 and 7 depending on the tumor type), while non-proliferative tissues, such as the liver, lung, kidneys, etc., had low SUVs (<2). The mean

SUV of ^{11}C-4DST was well correlated with DNA-incorporated SUV of 2-^{14}C-thymidine in various tumor tissues, indicating that the SUV of ^{11}C-4DST reflects DNA synthesis rate under *in vivo* conditions.

Toyohara et al. (2012) evaluated the tissue kinetics and biodistribution of ^{11}C-4DST in a rat tumor and acute sterile inflammation model in comparison with the previously published biodistribution data of ^{18}F-FLT, 2-deoxy-2-^{18}F-fluoro-D-glucose (^{18}F-FDG), ^{11}C-choline, ^{11}C-MET, and 2 σ-receptor ligands in the same animal model. In this study, ^{11}C-4DST showed high tumor uptake (sensitivity) and high tumor selectivity. Rapidly proliferating tissues (tumor and bone marrow) showed steadily increasing uptake. In inflamed muscle, ^{11}C-4DST showed relatively rapid washout, and tracer concentrations in inflamed and noninflamed muscle were not significantly different at intervals greater than 40 min. The different kinetics of ^{11}C-4DST in rapidly proliferating and inflammatory tissue may allow distinction between tumor and acute inflammation in a clinical setting. These promising results for ^{11}C-4DST warrant further investigation of PET studies in patients with various types of tumor.

Safety Evaluation in First Clinical Trial

Radiation dosimetry was used to assess exposure from ^{11}C-4DST in three healthy human subjects who underwent a 2-h whole-body PET scan (Toyohara et al., 2011). The highest absorbed organ dose was that in the urinary bladder wall (17.6 μGy/MBq). The estimated effective dose for ^{11}C-4DST was 4.2 μSv/MBq. Safety data were collected in five patients with brain tumors after administration of ^{11}C-4DST and throughout the 1-week follow-up period (Toyohara et al., 2011). Administration of ^{11}C-4DST was well tolerated by all subjects. No drug-related adverse events were reported among patients. Dosimetry and pharmacological safety were acceptable at the dose required for adequate PET imaging.

Brain Tumor Imaging Using ^{11}C-4DST

Premise of ^{11}C-4DST as PET Brain Tumor Imaging Tracer

Brain tumor imaging with PET is now an indispensable modality for intensive treatment of malignant brain tumors. It has now been widely recognized that morphological imaging with MRI is not sufficient to reveal brain tumor biology, especially when effective radiotherapy or chemotherapy has been applied. Even when the enhanced area in T1 weighted images with gadolinium-diethylenetriamine-pentaacetic acid (Gd-DTPA) and high intensity area in FLAIR image expand, this may sometimes mean that the tumor is undergoing necrosis due to effective treatment, while it may also indicate tumor growth due to ineffective treatment. Therefore, application of functional imaging with PET to precisely monitor tumor cell proliferation is necessary.

The glucose analog ^{18}F-FDG is an established clinical imaging tool for whole-body cancer imaging (Gould et al., 2001; Coleman, 2002). As the sensitivity of PET tumor diagnosis depends on the uptake contrast of tracer into the tumor versus that into the surrounding normal tissue (T/N), ^{18}F-FDG-PET can only be used to good effect in organs in which ^{18}F-FDG does not accumulate at high levels under normal conditions. Thus, this method is not suitable for application to the brain, and therefore PET tracers based on principles other than ^{18}F-FDG have also been used clinically, including amino acid tracers, such as ^{11}C-MET for brain tumors (Nariai et al., 1997, 2005).

Our extensive clinical experience with ^{11}C-MET, as well as many publication on ^{11}C-MET from many institutions, indicated that ^{11}C-MET is the most feasible imaging tool for delineation of brain tumors and for evaluation of their malignancy (Nariai et al., 2005). Uptake of ^{11}C-MET into tissue represents both transport of amino acids from blood to tissue and usage of amino acids as metabolites (Ishiwata et al., 1993).

Therefore, its uptake into tissue is not solely influenced by cell proliferation but may be affected by vessel structure (Nojiri et al., 2009).

We considered that the imaging of DNA synthesis rate in brain tumors may be superior to other PET tracers for evaluating tumor cell proliferation. Use of ^{18}F-FLT was proposed for PET tumor imaging of cell proliferation by assessing DNA synthesis (Chen et al., 2005), but its uptake into brain tumors is influenced more by blood-to-tumor transport rather than cell proliferation (Muzi et al., 2006). Therefore, we considered that use of ^{11}C-4DST in patients with brain tumors may provide more useful information on tumor cell proliferation rate than previous tracers and began a clinical study.

Subjects and Methods

The clinical protocol for use of ^{11}C-4DST in brain tumor patients was approved by the Ethics Committee of Tokyo Metropolitan Institute of Gerontology. Volunteer patients were recruited for the study with informed consent. Fourteen patients with brain tumors (11 malignant glioma, 2 metastatic tumors, 1 craniopharyngioma, and 1 malignant lymphoma) were included in the ^{11}C-4DST PET study. Dynamic scans with serial sampling of arterial blood were performed to calculate the incorporation rates of tracer into tumor and normal tissue. The ^{11}C-MET PET scan was also performed for the patients on the same day. Images of both PET scans were co-registered to patients' own Gd-DTPA enhanced T1 weighted MRI, and the uptakes of ^{11}C-4DST and ^{11}C-MET into Gd-DTPA enhanced lesions were evaluated. PET results, clinical course of patients, and pathological examination were compared.

Results and Discussion

No adverse events occurred in the PET examination of patients using ^{11}C-4DST. ^{11}C-4DST uptake into the normal brain and tumor-to-brain contrast are superior to those of ^{11}C-MET. ^{11}C-4DST PET showed rapid tumor uptake and retention of radioactivity in patients with aggressive tumor masses. Patlak plot graphical analysis (Patlak et al., 1983) showed a linear increase, indicating irreversible trapping of ^{11}C-4DST in tumor tissues. Details of kinetic analysis will be described in the later part of this chapter. Quantitative data for the initial six patients were reported previously (Toyohara et al., 2011). Briefly, when malignant tumors were initially diagnosed or when tumors were growing despite continuous chemotherapy, the uptake index of ^{11}C-4DST and SUV in static phase approximately 30 min after tracer injection were high. Under these conditions, ^{11}C-4DST and ^{11}C-MET images were similar on visual inspection (Fig. 3.1a). In PET examination during effective treatment, such as temozolomide, the distribution pattern of ^{11}C-4DST in tumor regions was not always identical to that of ^{11}C-MET. Large discrepancies were noted in tumors the growth of which was well controlled by temozolomide administration. An example is presented in Fig. 3.1b.

We also observed a marked decrease of ^{11}C-4DST uptake into metastatic lung cancer 5 days after gamma knife radiosurgery (Fig. 3.2). Although ring form enhancement with cystic formation did not disappear completely, tumor growth ceased with this treatment and the patient has maintained favorable activity of daily living 1 year after treatment. These observations indicated that the effectiveness of gamma knife was correctly monitored by ^{11}C-4DST just 5 days after treatment.

Another interesting difference between ^{11}C-4DST and ^{11}C-MET was observed in patients with oligodendroglioma. Newly appearing enhanced lesion of patients showed increased uptake of ^{11}C-MET, but uptake of ^{11}C-4DST was as low as in the control brain (Fig. 3.3). Pathological diagnosis by the second operation was oligoastrocytoma (a mixture of astrocytoma and oligodendroglioma) grade 2, but not with a malignant component. In our previous study, we demonstrated that oligodendrogliomas have high uptake of ^{11}C-MET to the level of malignant astrocytoma, although cell proliferation rate is as

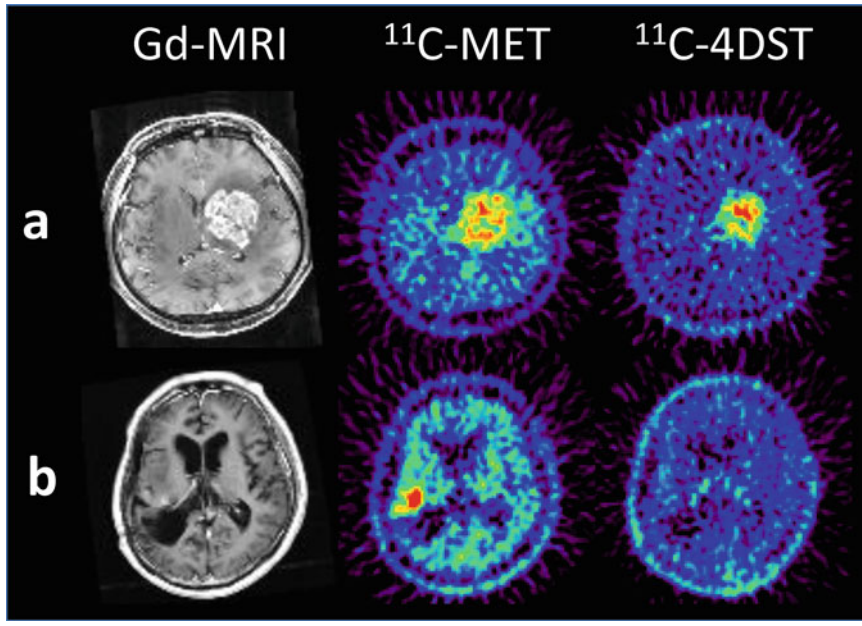

Fig. 3.1 (**a**) Growing malignant glioma despite continuous administration of temozolomide. PET findings of ^{11}C-4DST and ^{11}C-MET were similar. (**b**) Malignant astrocytoma stabilized by continuous administration of temozolomide. Although ^{11}C-MET uptake was continuously high and the enhanced area with Gd-MRI remained, ^{11}C-4DST uptake was as low as in the control brain. These findings supported the stabilized nature of this patient's tumor

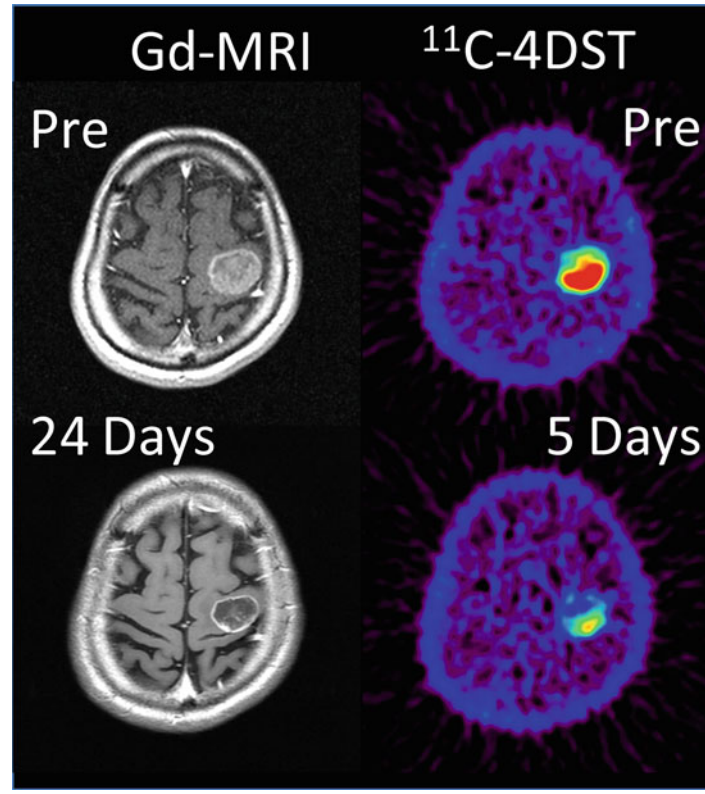

Fig. 3.2 Marked decrease of ^{11}C-4DST uptake into metastatic lung cancer was observed 5 days after gamma knife radiosurgery. Although ring form enhancement with cystic formation did not disappear completely, tumor growth was stopped by this treatment and the patient has maintained favorable activity of daily living 1 year after treatment

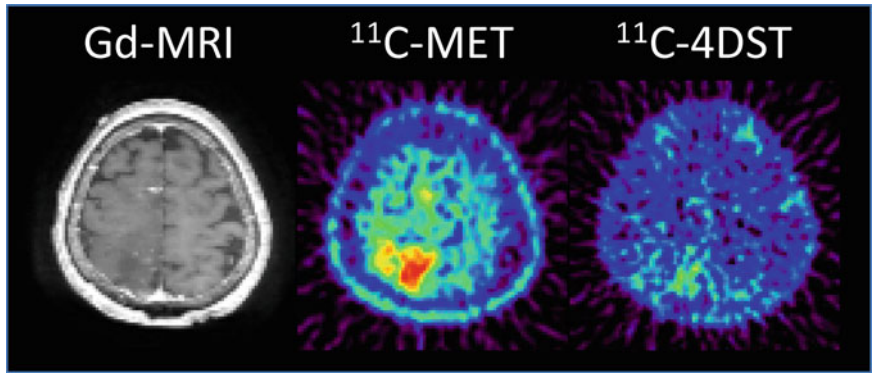

Fig. 3.3 A patient was diagnosed with astrocytoma grade 2 in the initial operation. At 1-year follow-up, an enhanced lesion appeared on MRI and ^{11}C-MET uptake increased around the initially resected lesion. These findings suggested malignant transformation of astrocytoma. ^{11}C-4DST uptake into the tumor, however, was as low as the brain level. Pathological diagnosis by the second operation was oligoastrocytoma grade 2, newly appearing oligodendroglioma component, and not a malignant transformation

low as low-grade astrocytoma. Our pathological analysis demonstrated that such occurs due to the difference of microvessel between astrocytoma and oligodendroglioma; the latter had a larger area than the former. Thus, an increase in microvessel surface area induced increased transport of amino acids into the oligodendroglioma despite low proliferation of tumor cells. Although high uptake of ^{11}C-MET into the oligodendroglial compartment of this patient mimicked malignant transformation, low uptake of ^{11}C-4DST indicated the nonmalignant nature of this tumor. This case presentation indicated that ^{11}C-4DST uptake into the tumor may not be influenced by the transport process through blood to tissue, but may represent tumor cell proliferation.

These case analyses suggested that ^{11}C-4DST accumulates into growing tumors but not into tumors stabilized by treatment. ^{11}C-4DST uptake into tumors was not influenced by increased transport from blood to tissue, as observed for ^{11}C-MET uptake. We consider that ^{11}C-4DST may be the best imaging agent to monitor tumor cell proliferation among various PET tracers reported to date. To make use of these characteristics of ^{11}C-4DST, it is necessary to determine a kinetic analysis method to numerically express cell proliferation rate.

Kinetic Analysis of ^{11}C-4DST

Subjects and Methods

Dynamic ^{11}C-4DST PET scans were performed in five patients with brain tumors (1 oligodendroglioma grade 3, 2 astrocytoma grade 3, 1 metastatic brain tumor from lung cancer, 1 malignant lymphoma) using the SET-2400W scanner (Shimadzu, Kyoto, Japan). After transmission scan with a rotating ^{68}Ge/^{68}Ga line source to correct for attenuation, ^{11}C-4DST (528–817 MBq/1.7–5.9 nmol) was injected intravenously. Then, dynamic PET scan (45–90-min) with 2-dimensional acquisition was performed. During the dynamic PET scan, arterial blood (26 time points maximum) was sampled, and the whole blood and separated plasma were weighed and radioactivity was measured with a NaI well scintillation counter. To analyze the labeled metabolites, additional blood (6 time points maximum) was obtained and unaltered ^{11}C-4DST in the plasma was analyzed by high-performance liquid chromatography (HPLC). PET images were reconstructed using a filtered back-projection method with a cutoff frequency of 1.25 cycles/cm and order 2. Gd-DTPA enhanced MRI

Table 3.1 ^{11}C-4DST model parameters in brain tumor regions

Pathology	vB	K_1 (mL/g/min)	k_2 (1/min)	k_3 (1/min)	k_4 (1/min)	K_i (mL/g/min)	K_i (Patlak) (mL/g/min)
Oligo(Malig)	0.11	0.09	0.09	0.16	0.010	0.058	0.047
AA (stable)	0.04	0.03	0.07	0.14	0.009	0.021	0.017
AA	0.08	0.14	0.18	0.07	0.007	0.038	0.025
Met	0.06	0.07	0.07	0.26	0.011	0.054	0.046
Lym	0.05	0.07	0.01	0.03	<0.001	0.051	0.053

Oligo(Malig) malignant transformation of oligodendroglioma, *AA* anaplastic astrocytoma (grade 3), *Met* metastatic brain tumor from lung cancer, *Lym* malignant lymphoma. $K_1 - k_4$, vB estimates of five fitted parameters

was used for confirmation of breakdown of the blood – brain barrier. Regions of interest (ROI) were placed over tumor and normal brain regions on the ^{11}C-4DST PET images with reference to the co-registered MRI. ROI-averaged time – activity curves (TACs) were analyzed using Patlak plot graphical analysis ($t^* = 15$ min) (Patlak et al., 1983), and the 2-tissue compartmental model (2T model) analysis. Parametric images of the uptake rate (K_i) were also calculated using the Patlak plot.

Results and Discussion

TACs in the tumor region of ^{11}C-4DST were rapidly increased, and they reached a plateau according to the decrease of the input function. Patlak plots showed a linear increase, and the K_i values of untreated clinically aggressive tumor regions (0.03–0.05) were higher than those of normal regions (~0.01) and clinically stable tumor regions treated with radiation therapy (~0.02) (Table 3.1). Although we have not determined the kinetic model because of the limited sample size, the estimated k_4 ($\leq$0.01) in the 2T model was much lower than the k_3 (>0.07) in tumor regions (Table 3.1). Our preliminary analysis showed that K_i values of ^{11}C-4DST were closely correlated to SUV (Toyohara et al., 2011). Furthermore, the correlation coefficient between maximum SUV of ^{11}C-4DST and Ki-67 cell proliferation index was high (r = 0.82) in lung cancer (Minamimoto et al., 2012). These data indicated that a simpler and easier alternative method, such as SUV, may be feasible to generate parametric images of ^{11}C-4DST in routine clinical use.

Acknowledgments This work was supported by Grants-in-Aid for Scientific Research (B) 22390214 and (B) 23390344 from the Japan Society for the Promotion of Science and a grant from the National Center for Global Health and Medicine.

References

Bading JR, Shields AF (2008) Imaging of cell proliferation: status and prospects. J Nucl Med 49:64S–80S

Been LB, Suurmeijer AJ, Cobben DC, Jager PL, Hoekstra HJ, Elsinga PH (2004) [^{18}F]FLT-PET in oncology: current status and opportunities. Eur J Nucl Med Mol Imaging 31:1659–1672

Chen W, Cloughesy T, Kamdar N, Satyamurthy N, Bergsneider M, Liau L, Mischel P, Czernin J, Phelps ME, Silverman DH (2005) Imaging proliferation in brain tumors with ^{18}F-FLT PET: comparison with ^{18}F-FDG. J Nucl Med 46:945–952

Coleman RE (2002) Value of FDG-PET scanning in management of lung cancer. Lancet 359:1361–1362

Gould MK, Maclean CC, Kuschner WG, Rydzak CE, Owens DK (2001) Accuracy of positron emission tomography for diagnosis of pulmonary nodules and mass lesions: a meta-analysis. JAMA 285: 914–924

Ishiwata K, Kubota K, Murakami M, Kubota R, Sasaki T, Ishii S, Senda M (1993) Re-evaluation of amino acid PET studies: can the protein synthesis rates in brain and tumor tissues be measured in vivo? J Nucl Med 34:1936–1943

Minamimoto R, Toyohara J, Seike A, Ito H, Endo H, Morooka M, Nakajima K, Mitsumoto T, Ito K, Okasaki M, Ishiwata K, Kubota K (2012) 4′-[Methyl-^{11}C]-thiothymidine PET/CT for proliferation imaging in non-small cell lung cancer. J Nucl Med 53:199–206

Muzi M, Spense AM, O'Sullivan F, Mankoff DA, Wells JM, Grierson JR, Link JM, Krohn KA (2006) Kinetic

analysis of 3′-deoxy-3′-^{18}F-fluorothymidine in patients with gliomas. J Nucl Med 47:1612–1621

Nariai T, Senda M, Ishii K, Maehara T, Wakabayashi S, Toyama H, Ishiwata K, Hirakawa K (1997) Three-dimensional imaging of cortical structure, function and glioma for tumor resection. J Nucl Med 38:1563–1568

Nariai T, Tanaka Y, Wakimoto H, Aoyagi M, Tamaki M, Ishiwata K, Senda M, Ishii K, Hirakawa K, Ohno K (2005) Usefulness of L-[methyl-^{11}C] methionine-positron emission tomography as a biological monitoring tool in the treatment of glioma. J Neurosurg 103:498–507

Nojiri T, Nariai T, Aoyagi M, Senda M, Ishii K, Ishiwata K, Ohno K (2009) Contributions of biological tumor parameters to the incorporation rate of L-[methyl-^{11}C] methionine into astrocytomas and oligodendrogliomas. J Neurooncol 93:233–241

Patlak CS, Blasberg RG, Fenstermacher JD (1983) Graphical evaluation of blood-to brain transfer constants from multiple-time uptake data. J Cereb Blood Flow Metab 3:1–7

Toyohara J, Kumata K, Fukushi K, Irie T, Suzuki K (2006) Evaluation of 4′-[methyl-^{14}C]thiothymidine for in vivo DNA synthesis imaging. J Nucl Med 47:1717–1722

Toyohara J, Okada M, Toramatsu C, Suzuki K, Irie T (2008) Feasibility studies of 4′-[methyl-^{11}C]thiothymidine as a tumor proliferation imaging agent in mice. Nucl Med Biol 35:67–74

Toyohara J, Nariai T, Sakata M, Oda K, Ishii K, Kawabe T, Irie T, Saga T, Kubota K, Ishiwata K (2011) Whole-body distribution and brain tumor imaging with ^{11}C-4DST: a pilot study. J Nucl Med 52:1322–1328

Toyohara J, Elsinga PH, Ishiwata K, Sijbesma JW, Dierckx RA, van Waarde A (2012) Evaluation of 4′-[methyl-^{11}C]thiothymidine in a rodent tumor and inflammation model. J Nucl Med 53:488–494

van Waarde A, Elsinga PH (2008) Proliferation markers for the differential diagnosis of tumor and inflammation. Curr Pharm Des 14:3326–3339

Part II

Glioma and Glioblastoma

Diffusion Tensor Magnetic Resonance Imaging-Based Tractography for Glioma Surgery

4

Shiro Ohue, Shohei Kohno, Yoshiaki Kumon, and Takanori Ohnishi

Contents

Abstract

Resection of gliomas that are located near or involve eloquent areas or pathways of the brain requires preoperative and intraoperative identification of functional cortical and subcortical sites. Diffusion tensor (DT) magnetic resonance imaging and fiber tractography are based on the concept of anisotropic water diffusion in myelinated fibers, and enable three-dimensional reconstruction and visualization of white matter tracts. Diffusion tensor imaging-based tractography can preoperatively provide information about the exact location of the tracts in relation to the tumor mass. This technique has been used to localize not only motor tracts, but also language and visual tracts, and the information obtained is useful in surgical planning. If the DT imaging data are loaded into a neuronavigation system, DT imaging-based tractography can also be used intraoperatively to aid the safe resection of tumors. Recently, intraoperative magnetic resonance imaging systems have become more widespread, and there have been several reports on the utility of intraoperative DT imaging-based tractography. In this chapter, the authors describe the use of DT imaging-based tractography in glioma surgery and discuss technical aspects and pitfalls of this technique.

S. Ohue (✉) • S. Kohno • Y. Kumon • T. Ohnishi
Department of Neurosurgery, Ehime University Graduate School of Medicine, Shitsukawa, Toon, Ehime 791-0295, Japan
e-mail: sohue@m.ehime-u.ac.jp

M.A. Hayat (ed.), *Tumors of the Central Nervous System, Volume 11*,
DOI 10.1007/978-94-007-7037-9_4,

Introduction

Gliomas are the most common primary neoplasms of the central nervous system. With exception of World Health Organization grade I tumors, gliomas are difficult to cure with surgery alone. The majority of patients with gliomas will experience some form of tumor recurrence, and have poor prognosis (Sanai and Berger, 2008). Among the many tumor- and treatment-related prognostic factors for gliomas, only patient age and tumor histology have been identified as reliable predictors of prognosis, although functional status can also be a statistically significant predictor (Sanai and Berger, 2008). Although the importance of glioma resection in obtaining tissue diagnosis and alleviating symptoms is clear, a lack of class I evidence prevents similar certainly in assessing the influence of extent of resection. However, there is growing evidence that extensive surgical resection of both low- and high-grade gliomas is associated with prolonged survival (Sanai and Berger, 2008). Thus, we believe that the primary goal in glioma surgery is to remove as much tumor as possible while preserving neurological function. Radical resection of gliomas carries the risk of injuring the adjacent vital structures in the brain due to the infiltrating nature of the tumors, especially when they are located near eloquent areas or pathways. Therefore, in order to achieve this surgical goal, it is necessary to identify the functionally important cortices and tracts, and evaluate the location of these structures in relation to the tumors before or during surgery. Several techniques have been used to identify the motor, language and visual cortices. These include positron emission tomography, magnetic source imaging and functional magnetic resonance (MR) imaging (Tharin and Golby, 2007). However, these imaging modalities cannot show the location of white matter tracts. Diffusion tensor (DT) MR imaging-based tractography is the only non-invasive imaging modality to visualize white matter tracts *in vivo*. Diffusion tensor imaging-based tractography has been used prior to surgery to demonstrate the three-dimensional course of the white matter tracts and the location of the tumors relative to these tracts. Preoperative DT imaging-based tractography data can be also integrated into frameless neuronavigation systems and subsequently used with anatomical and functional neuronavigation during surgery (Bello et al., 2008; Berman et al., 2007; Berntsen et al., 2010; Kamada et al., 2009; Mikuni et al., 2007; Ohue et al., 2012). Recently, some neurosurgeons have reported that intraoperative DT imaging-base tractography enables intraoperative visualization of the course of subcortical fibers (D'Andrea et al., 2012; Maesawa et al., 2010; Nimsky et al., 2005). These authors demonstrated that DT imaging-based tractography performed before or during surgery is useful for tumor resection in patients with gliomas. In this chapter, we describe the principles of DT imaging-based tractography, and how to use this technique for glioma surgery.

Principles of DT MR Imaging-Based Tractography

Diffusion tensor imaging-based tractography can delineate the subcortical courses of white matter tracts. The principle of DT imaging is to measure changes in the MR signal with diffusion sensitization pulses along non-collinear directions and to calculate apparent anisotropic components (Basser et al., 1994). The technique is based on the restriction of water diffusion by axonal membranes and myelin (Tharin and Golby, 2007). In DT imaging, magnet field gradients are applied in multiple orientations, and a matrix (mathematical model) is used to estimate the direction of maximum diffusivity of water molecules based upon the MR imaging data for every voxel. The direction of maximum diffusivity corresponds to the axis of white matter tracts in that voxel (Jellison et al., 2004). A fiber-tracking process identifies pixels on DT MR images that contain singular anisotropic values and visualizes the possible white matter profiles. This process produces DT imaging-based tractography (Kamada et al., 2009).

Acquisition of DT MR Imaging Data

Diffusion tensor imaging acquisition sequences are readily available on most commercial high-magnetic-field MR scanner platforms, and DT images for tractography are usually acquired as echo planner images (Bermann, 2009; Nimsky et al., 2006). Magnet field gradients are applied in multiple orientations. A minimum of six diffusion gradient directions is required to calculate the DT image, but a significant improvement in image quality can be obtained by increasing the number of directions (Jones, 2004). The image slices must be contiguous and not thicker than 3 mm (Berman, 2009). In a recent report from our institute, DT imaging with a 3.0 T MR scanner was performed with a single-shot spin-echo echo-planar image sequence (repetition time, 5,500 ms; echo time, 55 ms; flip angle, 90°) with a motion-probing gradient in 15 orientations (Ohue et al., 2012). A b value of 1,000 s/mm^2 was used, and 112×59 data points were recorded using a parallel imaging technique. Resolution of the acquired images was equivalent to 112×112 pixels with a 224 mm field of view. A total of 60 axial sections were obtained with a thickness of 2 mm and without intersection gaps, so the voxel size was 2×2×2 mm. In another report (Berman, 2009), DT imaging with a 1.5 T MR system was performed with a repetition time of 1,100 ms, an echo time of 78 ms, 3 mm thick slices, a 128×128 matrix with a 260×260 mm field of view, and 15 diffusion directions with two averaged acquisitions, with a b value of 1,000 s/mm^2. In addition to DT MR images, high-resolution three-dimensional T1- or/and T2-weighted anatomical MR images are also acquired to evaluate the relative location tracts and tumors and for use with surgical navigation systems.

Visualization of Tractography

Tractography is performed with single or multiple regions of interest (ROIs), using an algorithm that is predominantly based on deterministic fiber assignment by continuous tracking methods (Mori et al., 1999). Various fiber tracking software such as Extended MR WorkSpace (Philips Medical Systems), Stealth DTI (Medtronic Navigation), iPLAN (BrainLAB), VOLUME-ONE and dTV (http//volume-one.org), DTI task card (Magnetic resonance Center, Massachusetts General Hospital) and DTI studio (Laboratory of Brain Anatomic MRI, John Hopkins Medical Institute) are available to perform tractography (Berntsen et al., 2010; Kamada et al., 2009; Maesawa et al., 2010; Ohue et al., 2012; Romano et al., 2009). In general, fiber tracks are first generated from a selected region (the starting region) on the b=0 s/mm^2 echo planner images or the colored fractional anisotropy (FA) maps from the DT MR imaging sequence. If necessary, one or more regions (the target regions) are added, because extraneous fiber tracks are removed through the use of multiple ROIs. Tractography algorithms require a minimum anisotropy threshold to be specified. If the fiber track encounters a voxel with anisotropy below the threshold, the streamline is terminated at that location. Although Berman (2009) used a relatively low FA threshold of 0.1 for presurgical tractography, Stadlbauer et al. (2007) reported that an FA threshold in the range of 0.15–0.2 represented the best compromise to gain fiber tract reconstructions that reflect the structural situation in and around an infiltrating intrinsic brain tumor.

For visualizing the motor tract, two ROIs are usually selected; the cerebral peduncle and primary motor cortex (Kamada et al., 2009; Maesawa et al., 2010; Ohue et al., 2012). Figure 4.1a–e show a motor tract that was visualized using the two ROI-method in a glioma patient. Bermans' group (2009) used three ROI, the cerebral peduncle, posterior limb of the internal capsule, and precentral gyrus, to delineate the motor tract. We think that either two- or three-ROI methods are acceptable to demonstrate the motor tract. Although it is relatively easy to track the motor tract, it is more difficult to track other tracts.

The language tracts, including the arcuate or uncinate fasciculus, have been delineated with tractography. Authors have employed different ROI approaches for tractography of the language tracts, including, manual ROIs in the white

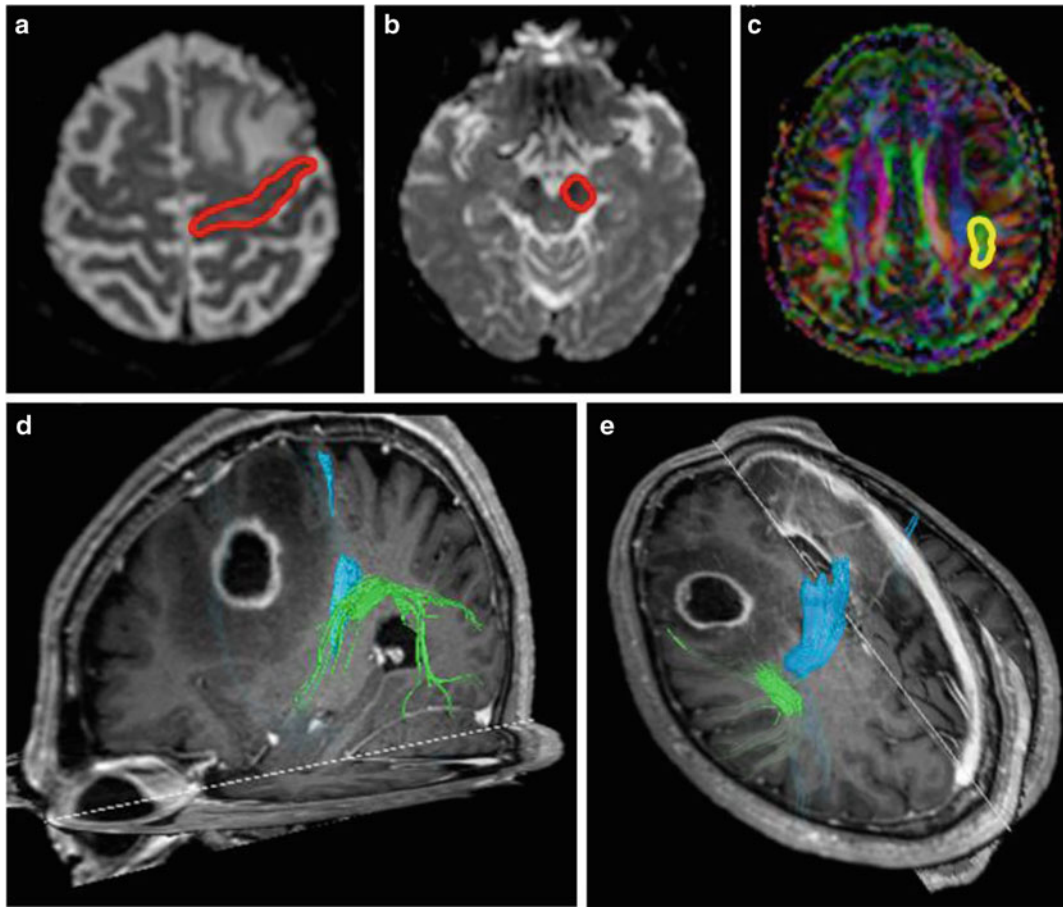

Fig. 4.1 Diffusion tensor imaging-based tractography in a patient with left frontal glioblastoma. (**a**, **b**) Echo planar images (b = 0 s/mm^2) with the regions of interest for visualization of the motor tract (the precentral gyrus and cerebral peduncle) indicated in *red*. Note this with (**a**) and (**b**) next to these areas in text. (**c**) Colored fiber orientation map with the region of interest for visualization of the language tract indicated in *yellow*. (**d**, **e**) Images from diffusion tensor fiber tractography. *Blue* and *green lines* show the motor and language tracts, respectively

matter bundle (Catani et al., 2005), ROIs in the anatomically defined anterior and posterior language areas (Parker et al., 2005), and ROIs in the functionally defined language areas (Powell et al., 2006). All studies consistently showed the classical C-shaped segment of the arcuate fasciculus. Catani et al. (2005) performed visualization of the arcuate fasciculus using one and two ROIs. Guided by color fiber orientation maps, an ROI was defined on the FA map to encompass the horizontal fibers lateral to the corona radiate and medial to the cortex extending from Talairach z = 22 to z = 28. A one-ROI approach was described, in which all fibers passing through this ROI were reconstructed in three dimensions. A two-ROI approach was also described, in which two spatially separated regions were defined in the FA volume, and all fibers passing though both ROIs were visualized. The delineation of regions used in the two-ROI approach was guided by the results of the one-ROI approach. Figure 4.1c–e show the arcuate fasciculus that was visualized using the one-ROI approach in a glioma patient.

The visual tract is challenging to delineate with tractography because it is a thin ribbon of white matter that turns at a sharp angle through Mayer's loop (Berman, 2009). Several investigators have reported tractography for optic radiation, and the selected ROIs were either the

lateral geniculate ganglion only (Romano et al., 2009), the lateral geniculate body and paraventricular area of the trigone of the lateral ventricle (Shinoura et al., 2010), or the lateral geniculate body and the adjacent temporal lobe, and the lingual and cuneus gyri in the occipital lobe (Wang et al., 2010). All studies showed good visualization of the optic pathway.

Validation of Tractography

Several investigators have validated DT imaging-based tractography using subcortical electric stimulation, because the gold standard for the identification of white matter tracts is thought to be the subcortical stimulation. Some neurosurgeons (Bello et al., 2008; Berman et al., 2007; Mikuni et al., 2007) have analyzed the distance between the stimulus point and the motor tracts of identified by tractography using neuronavigation systems with preoperative MR imaging. Mikuni et al. (2007) reported that the distance between the stimulus point and the tractography-identified tract in patients with positive subcortical motor evoked potentials (MEPs) after bipolar stimulation was less than 20 mm. Berman et al. (2007) used direct bipolar subcortical stimulation and reported that the mean distance between the stimulation site and the DT imaging-based fiber tract was 8.7 mm. Bello et al. (2008) described that there was a high correlation between the motor tract identified by DT imaging and intraoperative subcortical mapping. These studies indicated for validity of tractography using navigation system. However, these studies may be inaccurate, because neuronavigation systems must deal with shifts of the brain that occur during surgery. Some authors (Kamada et al., 2009; Ohue et al., 2012) have examined the relation between subcortical stimulation and the motor tract using postoperative tractography. We measured the minimum distance between the resection cavity and the motor tract identified by DT imaging-based tractography within 3 days after operation in 32 patients with gliomas near the motor tracts (Ohue et al., 2012). There was a significant linear correlation between the minimum stimulus intensity required to elicit positive subcortical MEPs and the minimum distance between the motor tract and the resection cavity. In four patients in whom the distance between the resection cavity and PT was over 20 mm, subcortical stimulation at 20 mA did not obtained any MEPs. These results suggested that tractography is a valid method to demonstrate the motor tract. Kamada et al. (2009) reported similar findings in clinical research, with their results indicating strong nonlinear correlations between intensity of subcortical stimulation and the distance between the motor tract and stimulus points, and a failure to elicit subcortical MEPs when stimulation was more than 25 mm from the motor tract. Furthermore, Maesawa et al. (2010) reported DT MR imaging and subcortical stimulation that were performed during surgery for gliomas around the motor tract, and found that the distance between MEP responsive sites and intraoperative tractography was significantly correlated with the intensity of subcortical stimulation. Some investigators (Bello et al., 2008; Kamada et al., 2007) have also reported good correlation between tractography and subcortical stimulation in patients with gliomas near the language tracts. These studies indicate that DT imaging-based fiber tractography offers a reliable way to map motor and language tracts throughout the brain during clinical use.

Preoperative Use of Tractography

As mentioned above, DT imaging-based tractography can show the three-dimensional course of functionally important white matter tracts and inform the surgeon of the detailed relation between these tracts and the tumors. Knowledge of the structural integrity and location of eloquent white matter tracts relative to cerebral tumors is crucial in the planning of tumor resection, because damage to these clinically eloquent pathways can result in postoperative neurological deficits (Bagadia et al., 2011; Romano et al., 2009). Romano et al. (2009) evaluated the impact of the information provided by preoperative tractography on surgical planning and procedure in

28 patients with tumors, including 21 with gliomas. They separately reconstructed the motor tract, arcuate fasciculus and optic radiation. Assessment of the 37 visualized trajectories close to the tumor resulted in a modification of the surgical approach to corticotomy in six patients (21 %), and had an impact on the definition of the resection margins during surgery in 18 patients (64 %). Overall, the information had an impact on the surgical procedure in 82 % of patients, and they concluded that DT image-based tractography provides the neurosurgeon with a new anatomical view that has an impact on the surgical resection planning for brain neoplasms. Bagadia et al. (2011) also assessed the role of DT image-based tractography in surgical planning in 50 patients, including 39 with gliomas. The tractography significantly altered planning by changing the surgical approach in 19 patients (38 %), and had a defined impact on surgical procedure by limiting the retraction and resection margins in another 12 patients (24 %), and they concluded that tractography improves surgical safety and aids prognostication in surgery of patients with eloquent cortex lesions.

In addition to informing the surgeon of the relative location of tracts and tumors, DT-imaging based tractography can provide information about the normal course, the displacement, or the interruption of white matter tracts around a tumor, and can be used to detect a widening of fiber bundles because of edema or tumor infiltration (Bello et al., 2008). Yu et al. (2005) evaluated the relation between tracts and tumors using DT imaging-based tractography in 16 patients, including 12 with gliomas. The relation was classified as type I (simple displacement), type II (displacement with disruption), or type III (simple disruption). In 12 cases in which the tumor involved in the motor tract, one was type I and showed reduction of displacement after surgery, nine were type II and showed reduction of displacement after surgery, and two were type III and did not show any improvement after surgery. Bagadia et al. (2011) also used preoperative DT imaged-based tractography to analyze the pattern of fiber tract involvement, and reported that the tracts were displaced in 72 % of patients, completely infiltrated in 14 % of patients and had a combined pattern in the remaining 14 %. Patients with pure displacement had the best chance of improvement and good postoperative outcome. In our experience of DT imaged-based tractography in 32 patients (Ohue et al., 2012), the relationship of the motor tracts and the high-intensity areas on fluid attenuation inversion recovery (FLAIR) images was evaluated. The high-intensity areas on FLAIR images indicate the areas with tumor infiltration or peritumoral edema. The motor tracts ran inside the high-intensity areas on fluid attenuation inversion recovery images in nine patients. In the other 22 patients, the tracts were outside the high-intensity areas. Bello et al. (2008) evaluated tumor-induced modifications in fiber trajectory in 64 glioma patients. In patients with high-grade gliomas, the majority of tracts depicted by DT image-based tractography were dislocated (50 %), and fewer were infiltrated and interrupted (37.5 %) by the tumor. On the other hand, in patients with low-grade gliomas, the majority of tracts were infiltrated and interrupted (62.5 %), and fewer were dislocated (25 %) by the tumor. They concluded that the fibers were frequently located inside the tumor mass in low-grade tumors. This information can be useful to the surgeon, as in cases where the eloquent white matter tracts run inside the tumor, it is necessary to take care to avoid the fiber during tumor resection.

Intraoperative Use of Tractography

For intraoperative use of DT imaging-based tractography, it is necessary to load the data provided by the DT imaging into a neuronavigation system. Many neurosurgeons have developed and used tractography-integrated navigation systems for glioma surgery (Bello et al., 2008; Berman et al., 2007; Berntsen et al., 2010; Kamada et al., 2009; Mikuni et al., 2007; Ohue et al., 2012), and most of these reports indicate that integration of the navigation system with tractography was useful for tumor resection in patients with gliomas that were located near or involved the eloquent fibers. Intraoperative neurophysiological monitoring,

such as the monitoring of MEPs, has also used with tractography-integrated navigation systems, and is useful for avoiding tract injury during surgery and preserving postoperative neurological function (Bello et al., 2008; Kamada et al., 2007; Maesawa et al., 2010; Mikuni et al., 2007). We have used a tractography-integrated navigation system with cortical or subcortical MEPs, and achieved satisfactory tumor resection and preservation of motor function in patients with gliomas near the motor tracts (Ohue et al., 2012). Figure 4.2 shows a navigation display from a representative case in which the DT imaging data was loaded into the neuronavigation system. The tumor was totally resected using the tractography-integrated navigation system without deterioration of neurological function. Bello et al. (Bello et al., 2008) also reported their experiences of using a tractography-integrated navigation system during surgery in 64 patients with gliomas near the motor or language tracts. They concluded that combined use of the tractography and intraoperative subcortical mapping allowed accurate identification eloquent fiber tracts and enhanced surgical performance and safety, while maintaining a high rate of functional preservation.

However, the reliability of any type functional neuronavigation can be reduced by brain shift that occurs during surgery as a consequence of tumor resection, loss of cerebrospinal fluid, surgical retraction, or gravity. We used intraoperative ultrasonography to evaluate the brain shift that occurred during tumor resection (Ohue et al., 2010). The magnitude of the brain shift increased progressively from pre- to post-resection and depended on the type of structure, being greater in patients with gliomas than in patients with meningiomas or other tumors. Other investigators (Maesawa et al., 2010; Nimsky et al., 2005) have also reported that intraoperative tractography of the motor tract demonstrates inward or outward shift during surgery.

One method to solve the problem of brain shift is to use intraoperative imaging modalities such as ultrasonography and MR imaging. The ultrasonography is easy to use intraoperatively and can evaluate the degree of brain shift (Berntsen et al., 2010; Ohue et al., 2010), but cannot be used to obtain information about fiber tractography. On the other hand, intraoperative MR imaging, which has recently become widespread, enables intraoperative visualization of the white matter tracts even after brain shift has occurred (D'Andrea et al., 2012; Nimsky et al., 2005; Maesawa et al., 2010). In addition, intraoperative MR imaging enables the surgeon to estimate the degree of tumor resection during surgery. Nimsky et al. (2005) compared pre- and intra-operative DT imaged-based tractography in 37 patients undergoing glioma surgery and reported a marked shift of major white matter tracts during glioma removal. Maximum shift ranged from −8 to +15 mm, with an inward shift detected in 29.7 % of patients, and an outward shift detected in 62.2 % of patients. They concluded that these results emphasized the need for intraoperative updates from navigation systems during resection of deep-seated tumor portions near eloquent brain areas. Maesawa et al. (2010) also reported pre- and intra-operative DT imaging-based tractography of the motor tract in 28 patients with gliomas in and around the motor tract, and found that intraoperative tractography demonstrated the location of the motor tract more accurately than preoperative tractography did. Their surgical results using intraoperative tractography and MEPs indicated that more than subtotal resection was achieved in 24 patients (85.7 %) and a permanent deficit was seen in only one patient (3.5 %). Although a significant loss or decrease in amplitudes of MEPs was seen in three patients, MEPs were stable during tumor resection in the remaining 25 patients. They concluded that intraoperative tractography combined with monitoring of MEPs could enhance the quality of surgery for gliomas in motor eloquent areas. D'Andrea et al. (2012) used intraoperative updating of MR imaging with DT imaging for reconstruction of motor tract after dural opening and subcortical neuronavigated stimulation. They studied 18 patients with tumors, including 14 patients with gliomas, that involved the motor cortex and/or the subcortical pathway, and attempted to remove the tumor between 0 and 5 mm from the motor tract identified after intraoperative updating of MR images. They stressed

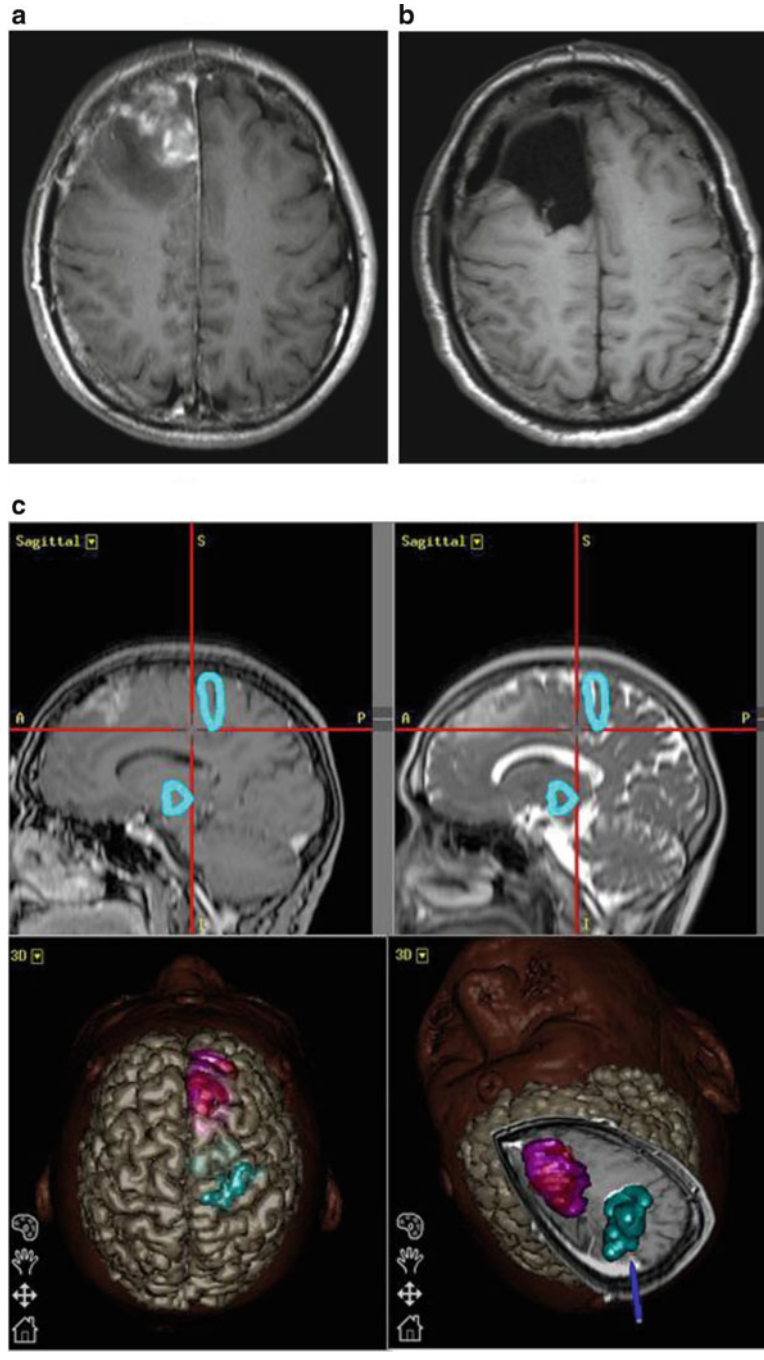

Fig. 4.2 Illustration of a tractography-integrated navigation system in a patient with right frontal anaplastic astrocytoma. (**a**, **b**) Pre- (**a**) and post- (**b**) operative gadolinium-enhanced T1-weighted magnetic resonance images. The tumor in this patient was totally resected using the tractography-integrated navigation system without deterioration of motor function. (**c**) The display of the tractography-integrated navigation system. *Blue* and *pink* areas indicate the motor tracts and tumors, respectively

that intraoperative update of MR imaging with DT imaging allowed treatment of complex tumors that, without its auxilium, they would not be able to deal with.

Another method to avoid the problem of brain shift is to perform fence post techniques before tumor resection using tractography-integrated navigation (Ohue et al., 2012; Yoshikawa et al., 2006). In this technique (Yoshikawa et al., 2006), a cuboidal area containing the tumor mass is completely assumed. Before beginning tumor resection, silicon catheters are inserted at the borders of the cuboid as fence posts under the guidance of the navigation system, and the cuboid containing the tumor mass is resected under the guidance of these fence posts. Yoshikawa et al. (2006) demonstrated that this navigation-guided fence post procedure improved the rate of resection and functional outcome after surgery of glioblastoma in 13 patients. We performed this fence post technique using tractography-integrated navigation systems for tumor resection in 28 of 32 patients with gliomas near the motor tracts (Ohue et al., 2012). In 19 of these patients, we performed fence post techniques around the motor tract before tumor resection, and placed the catheters more than 10 mm away from the motor tract. The degree of resection was total in 14 patients, subtotal in nine patients, and partial in nine patients (mean rate of resection, 93.1 %). All patients showed preservation of motor function at 1 month post-surgery compared with pre-surgery. Figure 4.3 shows one patient whose tumor was totally resected using the fence post technique under the tractography-integrated navigation. Performing fence post techniques before tumor resection using tractography-integrated navigation is useful for minimizing the influence of the brain shift.

Discussion

As described above, DT imaging-based tractography has become an important clinical tool that can delineate functionally important white matter tracts for surgical planning and intraoperative use in glioma surgery. However, there are some pitfalls to interpreting tractography data. Firstly, tractography does not identify all fibers of the white matter tract. Technical aspects including the magnetic strength of the MR imaging system, MR imaging sequences, and the placement of the ROIs for the tracking, and fiber crossing can influence the position or amount of fibers of the white matter tract that are identified (Nimsky et al., 2005). A higher strength MR imaging system provides better visualization of various tracts (Okada et al., 2006). Diffusion tensor images are usually acquired using echo planar imaging sequences. Anatomic distortions of the echo planar images are caused by the air/brain interface. These distortions primarily occur at the brain surface, and therefore do not substantially affect registration at the deeper structures. Nonetheless, the problem of image distortion can be solved by the use of other imaging sequences such as sensitivity coding, measuring field maps that describe the image distortion, or applying nonlinear registration and transformation algorithms (Nimsky et al., 2006). A significant improvement in data quality was also obtained by increasing the number of diffusion gradient directions or b values in DT imaging sequences (Jones, 2004). Tractography is dependent on the size and location of the selected ROIs, and the experience of the individual processing the data. The crossing fiber effect is a crucial problem in tractography. The crossing effects indicate that correct identification of fiber tracts in areas of fiber crossings is not possible using DT imaging. For example, the motor tracts spread out subcortically beneath the primary motor cortex of the hand or face. This area was affected by superior longitudinal fibers and callosal fibers, and the visualization was technically difficult. The crossing effects are attributed to the inability to resolve more than a single axon direction within each imaging voxel. Techniques that can resolve multiple axon directions within a single voxel, such as q-ball imaging, may solve the crossing fiber effect, as well as white matter insertions into the cortex (Nimsky et al., 2006). Tractography based on these advanced MR methods has been shown to traverse white matter regions with crossing

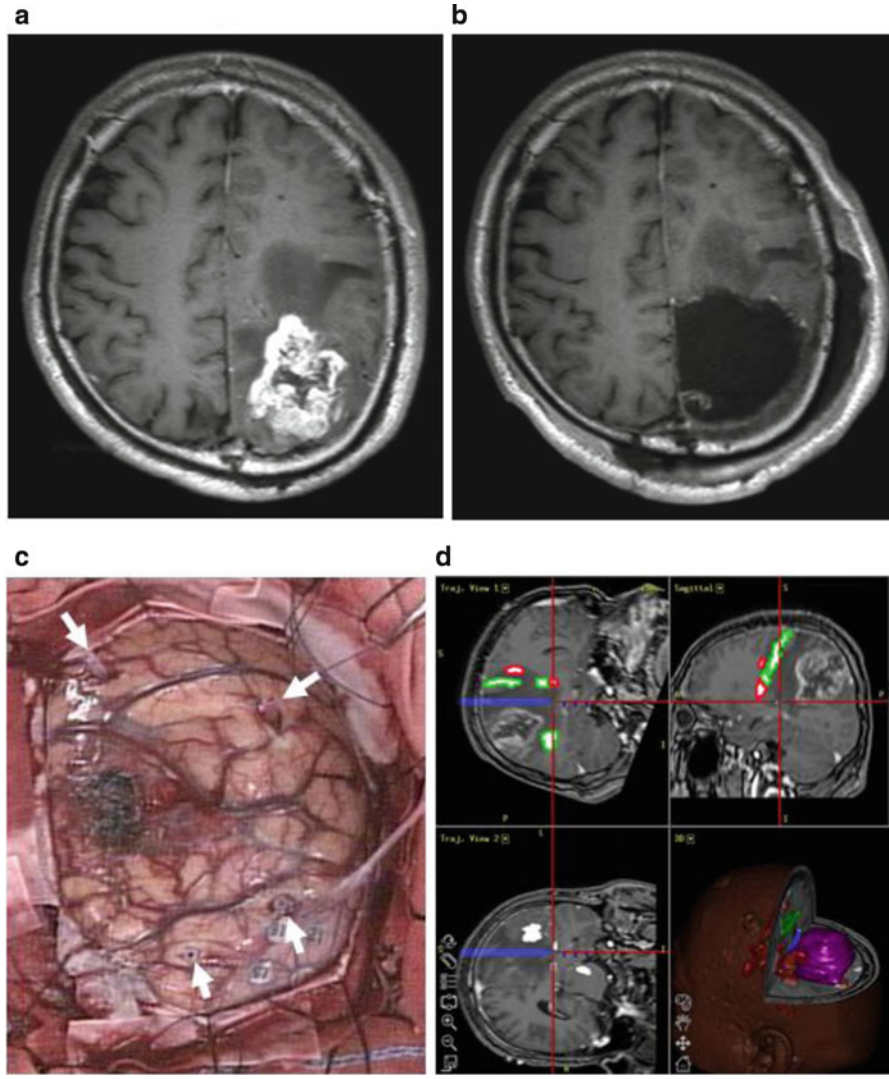

Fig. 4.3 Illustration of a tractography-integrated navigation system in a patient with left parietal glioblastoma. (**a**, **b**) pre- (**a**) and post- (**b**) operative gadolinium-enhanced T1-weighted magnetic resonance images. The tumor was completely resected using fence post techniques. (**c**) An intraoperative photograph taken before tumor resection. Three catheters (*arrows*) were inserted around tumor margin. (**d**) The display of the navigation system at point at which the catheter was inserted into the posterior margin of the tumor. *Green, red* and *pink* areas indicate motor and language tracts, and tumor, respectively. *Blue line* and *red cross* hairs indicate the direction and position of the catheter, respectively

fibers and reveal a greater portion of tracts (Nimsky et al., 2006).

Another pitfall to interpreting tractography is the fact that fiber tracking does not accurately estimate the size of fiber bundle in pathologic conditions (Bello et al., 2008). Tumor infiltration and peritumoral edema both influence the anisotropy of water molecules, regardless of the intra- or extra-cellular location of the edema. In the presence of tumor infiltration, the distribution of fiber orientations is nearly random, therefore the FA value can be significantly

reduced even if the functionality of fibers can be maintained (Bello et al., 2008). Low FA values reduce the reliability of the tracking.

Fiber tracking algorithms differ in their expression of three-dimensional tracts. Multiple algorithms are used and there is currently no accepted gold standard. Fiber tracts can be also exaggerated or underestimated by using various threshold values of FA for tracking.

In conclusion diffusion tensor imaging-based tractography has become a useful tool for tumor resection in patients with gliomas in or around eloquent white matter tracts. Although tractography still has some problems, fiber tracking provides an exciting avenue for further investigation.

References

Bagadia A, Purandare H, Misra BK, Gupta S (2011) Application of magnetic resonance tractography in the perioperative planning of patients with eloquent region intra-axial brain lesions. J Clin Neurosci 18:633–639

Basser PJ, Mattiello J, Le Bihan D (1994) MR diffusion tensor spectroscopy and imaging. Biophys J 66:259–267

Bello L, Gambini A, Castellano A, Carrabba G, Acerbi F, Fava E, Giussani C, Cadioli M, Blasi V, Casarotti A, Papagno C, Gupta AK, Gaini S, Scotti G, Falini A (2008) Motor and language DTI fiber tracking combined with intraoperative subcortical mapping for surgical removal of gliomas. Neuroimage 39:369–382

Berman J (2009) Diffusion MR tractography as a tool for surgical planning. Magn Reson Imaging Clin N Am 17:205–214

Berman J, Berger M, Chung S, Nagarajan S, Henry R (2007) Accuracy of diffusion tensor magnetic resonance imaging tractography assessed using intraoperative subcortical stimulation mapping and magnetic source imaging. J Neurosurg 107:488–494

Berntsen EM, Gulati S, Solheim O, Kvistad KA, Torp SH, Selbekk T, Unsgård G, Håberg AK (2010) Functional magnetic resonance imaging and diffusion tensor tractography incorporated into an intraoperative 3-dimensional ultrasound-based neuronavigation system: impact on therapeutic strategies, extent of resection, and clinical outcome. Neurosurgery 67:251–264

Catani M, Jones DK, Fjytche DH (2005) Perisylvian language networds of the human brain. Ann Neurol 57:8–16

D'Andrea G, Angelini A, Romano A, Di Lauro A, Sessa G, Bozzao A, Ferrante L (2012) Intraoperative DTI and brain mapping for surgery of neoplasm of the motor cortex and the corticospinal tract: our protocol and series in BrainSUITE. Neurosurg Rev 35:401–412

Jellison BJ, Field AS, Medow J, Lazar M, Salamat MS, Alexander AL (2004) Diffusion tensor imaging of cerebral white matter: a pictorial review of physics, fiber tract anatomy, and tumor imaging patterns. AJNR Am J Neuroradiol 25:356–369

Jones DK (2004) The effect of gradient sampling schemes on measures derived from diffusion tensor MRI: a Monte Carro study. Magn Reson Med 51:807–815

Kamada K, Todo T, Masutani Y, Aoki S, Ino K, Morita A, Saito N (2007) Visualization of the frontotemporal language fibers by tractography combined with functional magnetic resonance imaging and magnetoencephalography. J Neurosurg 106:90–98

Kamada K, Todo T, Ota T, Ino K, Matsutani Y, Aoki S, Takeuchi F, Kawai K, Saito N (2009) The motor-evoked potential threshold evaluated by tractography and electrical stimulation. J Neurosurg 111:785–795

Maesawa S, Fujii M, Nakahara N, Watanabe T, Wakabayashi T, Yoshida J (2010) Intraoperative tractography and motor evoked potential (MEP) monitoring in surgery for gliomas around the corticospinal tract. World Neurosurg 74:153–161

Mikuni N, Okada T, Enatsu R, Miki Y, Hanakawa T, Urayama S, Kikuta K, Takahashi JA, Nozaki K, Fukuyama H, Hashimoto N (2007) Clinical impact of integrated functional neuronavigation and subcortical electrical stimulation to preserve motor function during resection of brain tumors. J Neurosurg 106:593–598

Mori S, Crain BJ, Chacko VP, van Ziji PC (1999) Three-dimensional tracking of axonal projections in the brain by magnetic resonance imaging. Ann Neurol 45:265–269

Nimsky C, Ganslandt O, Hastreiter P, Wang R, Benner T, Sorensen AG, Fahlbusch R (2005) Preoperative and intraoperative diffusion tensor imaging-based fiber tracking in glioma surgery. Neurosurgery 61(Suppl):178–185

Nimsky C, Ganslandt O, Fahlbusch R (2006) Implementation of fiber tract navigation. Neurosurgery 58(Suppl 2):ONS292–ONS303

Ohue S, Kumon Y, Nagato S, Kohno S, Harada H, Nakagawa K, Kikuchi K, Miki H, Ohnishi T (2010) Significance of an ultrasound-linked navigation system for brain tumor surgery: evaluation of intraoperative shift. Neurol Med Chir (Tokyo) 50:201–300

Ohue S, Kohno S, Inoue A, Yamashita D, Harada H, Kumon Y, Kikuchi K, Miki H, Ohnishi T (2012) Accuracy of diffusion tensor magnetic resonance imaging-based tractography for surgery of gliomas near the pyramidal tract: a significant correlation between subcortical electrical stimulation and postoperative tractography. Neurosurgery 70:283–294

Okada T, Miki Y, Fushimi Y, Hanakawa T, Kanagaki M, Yamamoto A, Urayama S, Fukuyama H, Hiraoka M, Togashi K (2006) Diffusion-tensor fiber tractography: intraindividual comparison of 3.0-T and 1.5-T MR imaging. Radiology 238:668–678

Parker GJM, Luzzi S, Alexander DC, Wheeler-Kingshott CAM, Ciccarelli O, Ralph MAL (2005) Lateralization

of ventral and dorsal auditory-language pathways in the human brain. Neuroimage 24:656–666

Powell HWR, Parker GJM, Alexander DC, Symms MR, Boulby RA, Wheeler-Kingshott CAM, Barker GJ, Noppeney U, Koepp M, Duncan JS (2006) Hemispheric asymmetries in language-related pathways: a combined functional MRI and tractography study. Neuroimage 32:388–399

Romano A, D'Andrea G, Minniti G, Mastronardi L, Ferrante L, Fantozzi LM, Bozzao A (2009) Presurgical planning and MR-tractography utility in brain tumour resection. Eur Radiol 19:2798–2808

Sanai N, Berger MS (2008) Glioma extent of resection and its impact on patient outcome. Neurosurgery 62:753–766

Shinoura N, Suzuki Y, Yamada R, Tabei Y, Saito K, Yagi K (2010) Relationships between brain tumor and optic tract or calcarine fissure are involved in visual field deficits after surgery for brain tumor. Acta Neurochir (Wien) 152:637–642

Stadlbauer A, Nimsky C, Buslei R, Salomonowitz E, Hammen T, Buchfelder M, Moser E, Ernst-Stecken A, Ganslandt O (2007) Diffusion tensor imaging and optimized fiber tracking in glioma patients: histopathologic evaluation of tumor-invaded white matter structures. Neuroimage 34:949–956

Tharin S, Golby A (2007) Functional brain mapping and its applications to neurosurgery. Neurosurgery 60:185–201

Wang YX, Zhu XL, Deng M, Siu DY, Leung JC, Chan Q, Chan DT, Mak CH, Poon WS (2010) The use of diffusion tensor tractography to measure the distance between the anterior tip of the Meyer loop and the temporal pole in a cohort from Southern China. J Neurosurg 113:1144–1151

Yoshikawa K, Kajiwara K, Morioka J, Fujii M, Tanaka N, Fujisawa H, Kato S, Nomura S, Suzuki M (2006) Improvement of functional outcome after radical surgery in glioblastoma patients: the efficacy of a navigation-guided fence-post procedure and neurophysiological monitoring. J Neurooncol 78:91–97

Yu CS, Li KC, Xuan Y, Ji XM, Wen Q (2005) Diffusion tensor tractography in patients with cerebral tumors: a helpful technique for neurosurgical planning and postoperative assessment. Eur J Radiat 56:197–204

5 Angiocentric Glioma, Pilomyxoid Astrocytoma, and Pituicytoma: New Entities in the World Health Organization Classification

Jamie L. Odem and Douglas C. Miller

Contents

Abstract

The 2007 World Health Organization (WHO) Classification of CNS Tumors added three new entities to its compendium of primary CNS neoplasms which are similar in that they consist of relatively monomorphous spindle cells: angiocentric glioma (AG), pilomyxoid astrocytoma (PMA), and pituicytoma. This chapter describes the clinical features, histopathology, diagnosis, treatment, and prognosis of these three newly codified entities. Angiocentric glioma, a cortically-based neoplasm that causes intractable epilepsy in young people, shares many similarities with ependymoma. However, these similarities were not enough to classify it as an ependymoma subtype, and AG is under "Other Neuroepithelial Tumors" in the new classification. A WHO Grade I tumor, it is an indolent, slow-growing neoplasm characterized by bipolar cells with spindled nuclei that tend to cluster around intratumoral vessels (giving this tumor its name). The primary differential diagnosis is cortical ependymoma but also includes pilomyxoid astrocytoma. Angiocentric glioma is usually cured with surgical excision, even in subtotally resected tumors. Pilomyxoid astrocytoma is categorized as an aggressive variant of pilocytic astrocytoma encountered mainly in very young children but may present in older children or adults. PMA is usually located in the optic chiasm/hypothalamic region. Histologically, PMA is a strikingly monomorphous tumor composed of bipolar

J.L. Odem • D.C. Miller, MD, PhD (✉)
Department of Pathology and Anatomical Sciences,
University of Missouri School of Medicine,
One Hospital Drive, 65212 Columbia, MO, USA
e-mail: millerdc@health.missouri.edu

M.A. Hayat (ed.), *Tumors of the Central Nervous System, Volume 11*,
DOI 10.1007/978-94-007-7037-9_5,

cells in a richly myxoid background which lacks the biphasic pattern of pilocytic astrocytoma and in which the tumor cells form ependymoma-like perivascular pseudorosettes. Considerations in the differential of PMA include pilocytic astrocytoma with a myxoid component, angiocentric glioma, and infiltrating glioma. Because PMA behaves more aggressively, following a biopsy diagnosis, it is treated with chemotherapy for low-grade gliomas with or without gross total resection, depending on tumor burden. Last, pituicytoma is listed as a separate entity under "Tumors of the Sellar Region" and is a solid tumor of the posterior pituitary and stalk. Thought to be derived from pituicytes, the glial cells of the pituitary stalk and neurohypophysis, this tumor presents in adults as an intrasellar or suprasellar mass causing visual or hormonal disturbances. Histopathologically, pituicytomas are composed of spindled, bipolar cells which arrange themselves in a characteristic storiform pattern. The differential diagnosis of pituicytoma includes pituitary adenoma, spindle cell oncocytoma, and granular cell tumor. Pituicytoma is cured by surgical excision and is WHO Grade I.

Introduction

The most recent World Health Organization (4th Edition, 2007) "Blue Book" for central nervous system (CNS) tumors adds three new entities to the list of tumor types, all of which are similar in that they are composed mostly of monomorphous spindle cells: angiocentric glioma, pilomyxoid astrocytoma, and pituicytoma. All three of these entities are relatively newly described (within the last 15 years). As case reports and small case series have accumulated, it has become clearer how these entities should be formally classified, thus leading to their adoption into the WHO classification scheme. This chapter will review the historical context, clinical presentation including radiographic findings, histopathology, genetic abnormalities, differential diagnosis, and treatment of these three entities.

Angiocentric Glioma

Introduction and Historical Context

Angiocentric glioma first came to the forefront of the literature in 2005, with two nearly-simultaneous case series (Lellouch-Tubiana et al., 2005; Preusser et al., 2006), although Wang et al., had previously described this entity in 2002 as angiocentric bipolar astrocytoma (Wang et al., 2002). These case series described cortically-based tumors with superficial subcortical extension in young patients with intractable epilepsy, usually partial seizures. At the time of this writing, there have been only 44 cases of angiocentric glioma described (Pokharel et al., 2011). Histologically, these tumors are composed of spindled, monomorphous cells which cluster around vessels, somewhat like cells of most ependymomas, and lack atypia. They typically express Epithelial Membrane Antigen (EMA) in a cytoplasmic dot-like positive pattern similar to ependymomas, and the perivascular pattern and this immunohistochemical feature have engendered speculation that these are a variant of ependymoma, although the WHO classification places them outside of the ependymoma group. Angiocentric glioma is characterized as WHO Grade I as it is usually cured by surgical resection, even in some cases by subtotal resections. Synonyms for this entity include monophasic angiocentric glioma and angiocentric neuroepithelial tumor (ANET).

Clinical Presentation and Imaging

Angiocentric gliomas affect mainly young adults (mean age 17 years), but have been described in younger children and older adults (up to 70 years of age) (Brat et al., 2007). To date, all described examples have been located peripherally in the cerebral hemispheres, most often the temporal lobe, with parietal and frontal locations also being common (Lellouch-Tubiana et al., 2005; Preusser et al., 2006; Koral et al., 2012). (We have seen one example which histologically resembled

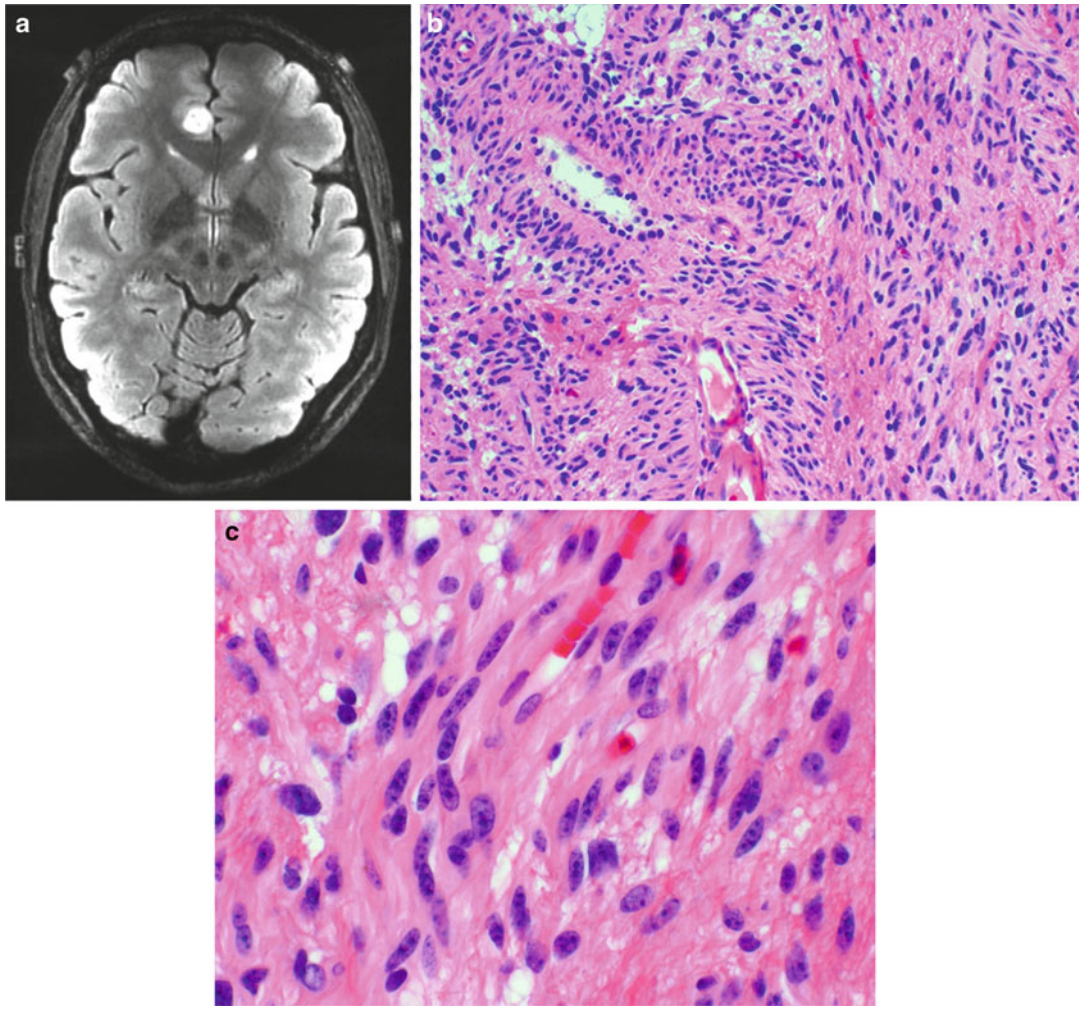

Fig. 5.1 Angiocentric glioma: (**a**) Axial, CUBE (3d TSE) image. Cortical-based well-demarcated lesion in the right cingulate gyrus with bright signal. (**b**) Bipolar spindle cells orient around the vasculature, recapitulating perivascular pseudorosettes seen in ependymoma, H&E, 100×. (**c**) The nuclei are angular to spindled, showing very little pleiomorphism. H&E, 400× (*MRI Image Courtesy Dr. Tarik Tihan, H&E Images Courtesy Dr. Tony Yachnis)*

angiocentric glioma but which was located in the dorsal midbrain's tectal region. The diagnosis for this tumor has been debated among several neuropathologists to whom it has been shown.) The typical cortical location results in chronic, intractable partial seizures, and almost all angiocentric gliomas are resected from patients with a history of chronic epilepsy. Imaging shows a diffuse nonenhancing cortical lesion with extension into the subcortical white matter which expands the parenchyma rather than forming a discrete mass (Brat et al., 2007) (Fig. 5.1a). Magnetic Resonance Imaging (MRI) shows a cortical tumor which often has rim-like hyperintensity on T1-weighted imaging. T2-weighted imaging shows subcortical hyperintensity which may have a stalk-like extension up to the border of the closest lateral ventricle. The rim-like T1 hyperintensity is present in 62 % of cases and can be a helpful imaging feature to distinguish this tumor from other epileptogenic cortical neoplasms such as dysembryoplastic neuroepithelial tumors (DNTs) (Koral et al., 2012).

Histopathology

Angiocentric gliomas are diffuse, monomorphous tumors composed of bipolar spindle cells which have a striking orientation around the vasculature, giving the tumor its name. Mitotic figures are rarely seen and MIB-1 immunostains demonstrate low proliferative activity (1–5 %). Anaplasia is absent. The neoplastic cells are composed of a small, angular to spindled nucleus with indistinct lightly eosinophilic cytoplasm (Fig. 5.1b, c). The elongated cells may arrange themselves in a loose, streaming pattern around the vessels or in a more palisaded configuration similar to the perivascular pseudorosettes seen in ependymomas (Fig. 5.1b). A subset of tumors may also show subpial palisading. Angiocentric glioma is a diffuse tumor that may infiltrate the surrounding white or gray matter. One of the original descriptions of this entity indicated that neurons with synaptophysin immunoreactivity may be part of the neoplasm, hence the early name angiocentric neuroepithelial tumor (ANET) (Lellouch-Tubiana et al., 2005), but this is controversial and others have suggested such neurons are native cells entrapped by the infiltrating glial cells (Wang et al., 2005; Brat et al., 2007).

Immunohistochemically, these tumors are positive for antibodies to glial markers such as glial fibrillary acidic protein (GFAP), Vimentin, and S-100 protein, and also have the mentioned dot-like cytoplasmic positivity for epithelial membrane antigen (EMA). The EMA staining pattern is similar to that seen in ependymoma, and the ultrastructural evidence of ciliated microlumens with projecting microvilli also supports an ependymal origin for this tumor (Pokharel et al., 2011; Preusser et al., 2007). The interpretation of synapthophysin immunopositivity is controversial, as mentioned above. Other negative immunohistochemical markers include chromogranin, neurofilament protein, and p53.

Genetic Abnormalities

There is very little literature on the cytogenetic and molecular abnormalities in angiocentric glioma, and so far with the small number of cases described there has been no consistent pattern of such abnormalities. Preusser et al. (2007) showed one tumor to have a copy number gain of 11p11.2 and another tumor to have a 6q24-6q25 deletion. Tatevossian et al. (2010) described an angiocentric glioma with a 6q23 deletion involving the *MYB* gene. The significance of these genetic abnormalities is uncertain and further studies are needed.

Differential Diagnosis

The clinical and neuroimaging differential diagnosis for angiocentric glioma can be complex, with the main contenders for diagnosis being other cortical epileptogenic neoplasms. Indeed, much of the literature to date has emphasized the importance of considering angiocentric glioma in the differential diagnosis of a resection specimen from a patient with intractable epilepsy, along with cortical dysplasia, ganglioglioma, dysembroplastic neuroepithelial tumor (DNT), diffuse astrocytoma, cortical ependymoma, pleiomorphic xanthoastrocytoma (PXA), pilocytic astrocytoma and pilomyxoid astrocytoma (Pokharel et al., 2011; Lum et al., 2008; Shakur et al., 2009). Diagnosis rests on histopathological features, which quickly eliminate much of the above differential but clearly one must exclude true ependymomas and perhaps pilocytic astrocytomas with careful histological analysis and immunostains.

On ordinary (H&E) morphologic grounds, DNT and ganglioglioma can be ruled out, as can focal cortical dysplasia (unless coexistent with the neoplasm). But the differential diagnosis with these other entities may become difficult. Angiocentric glioma may have solid, infiltrative areas that resemble diffuse astrocytoma. However, the perivascular nature of the tumor should be striking enough to eliminate the possibility of diffuse astrocytoma. As previously stated, angiocentric glioma shares several features with ependymoma, including the striking angiocentricity, perivascular pseudorosettes, and the dot-like cytoplasmic EMA positivity. In fact, the distinction between cortically-based ependymoma and

angiocentric glioma may be impossible, as pointed out by Lum et al. (2008). As for pilocytic and pilomyxoid astrocytoma, these tumors share the elongate piloid cell shape with angiocentric glioma, and pilomyxoid astrocytoma may have perivascular pseudorosettes. However, angiocentric glioma lacks the biphasic pattern of pilocytic astrocytoma or the extensive myxoid background seen in pilomyxoid astrocytoma (Pokharel et al., 2011; Lum et al., 2008). Furthermore, these tumors have different typical locations: pilomyxoid astrocytoma almost always occurs in the hypothalamic/third ventricle region rather than the cortex.

Treatment and Prognosis

Treatment is generally recommended to be surgical excision without adjuvant therapy. Studies have shown that this usually resolves the patient's seizures, unless the tumor is subtotally resected (Shakur et al., 2009). Even subtotally resected tumors are thought not to recur in the sense of progressive growth, although experience remains limited and so this conclusion should be stated with caution. Of note, in this regard, is that despite the so-called low-grade nature of this tumor, there have been reports of angiocentric gliomas with higher MIB1-labeling indices (Pokharel et al., 2011; Wang et al., 2005), and one such case did recur as an anaplastic astrocytoma, illustrating that this tumor may evolve into a more aggressive lesion. However, the majority of these neoplasms are slow-growing and indolent. Gross total resection is considered the treatment of choice, but failure to achieve gross total excision may justify radiation therapy (Shakur et al., 2009).

Pilomyxoid Astrocytoma

Introduction and Historical Context

The term pilomyxoid astrocytoma (PMA) was first coined by Tihan et al. in 1999 as a distinct subset of hypothalamic/optic pathway pilocytic astrocytomas mainly occurring in infants. Since then, such tumors have also been described in adults. PMA is recognized by the WHO as a subcategory of pilocytic astrocytoma (PA) with a worse prognosis, *ie* it has more frequent local recurrence and CSF metastases than its ordinary pilocytic counterpart. For that reason, it has been assigned to WHO Grade II. It typically occurs in infants who present with failure to thrive, and has mainly been described along the optic chiasm, in the third ventricle and in the hypothalamus. Histologically, pilomyxoid astrocytomas are monomorphous tumors which lack the biphasic pattern and Rosenthal fibers of typical pilocytic astrocytomas and only rarely contain eosinophilic granular bodies.

PMA is often treated with partial resection, followed by chemotherapy and/or radiation therapy, although precise treatment modalities are still debated. Cottingham et al. (1996) was the original descriptor of PMA (called at that time pilocytic astrocytoma in infants) and indicated that PMA may "mature" into PA, which has since been demonstrated. Furthermore, recent literature has also been exploring the concept of the "intermediate" PMA, or intermediate pilomyxoid tumor (IPT) which has overlapping features of PMA and PA.

Clinical Presentation/Imaging

PMA mainly affects infants and young children with a median age at presentation of 10 months (Louis et al., 2007) as compared with a median age of 14 months for patients with PA. Rarely, adults, usually in the third decade, are diagnosed with PMA, and there has been one report of a 77-year old with this entity (Toyoda et al., 2009). Infants with PMA typically present with failure to thrive, developmental delay, and altered consciousness (Tihan et al., 1999). In older children, clinical presentation may include headaches, nausea, and disorientation (Brat et al., 2007). One report describes PMA presenting with spontaneous hemorrhage, although the exact cause of the hemorrhage remains unclear (Gottfried et al., 2002). Since then, intratumoral hemorrhage has been described not infrequently in PMA (Linscott et al., 2008).

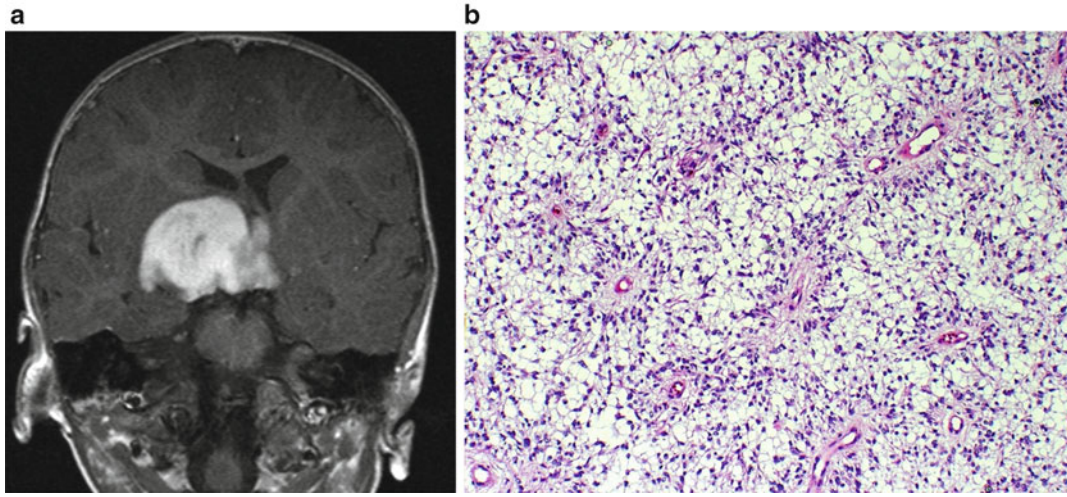

Fig. 5.2 Pilomyxoid astrocytoma: (**a**) T1-weighted MRI, post-contrast, coronal view. A mainly solid, enhancing mass near the optic chiasm compresses the right lateral ventricle. (**b**) Bipolar cells in a markedly myxoid background arrange themselves in loose, fibrillar perivascular arrangements. H&E, 100× (*Images courtesy of Dr. Tony Yachnis*)

PMA is classically a tumor of the chiasmatic/hypothalamic area, but PMA has been described in other locations, including the cerebellum, the thoracic and cervical spinal cord, basal ganglia, thalamus, lateral ventricle, and 4th ventricle (Forbes et al., 2011; Matsuzaki et al., 2010; Omura et al., 2008). In general, these tumors show a predilection for central, supratentorial brain parenchyma, in contrast to the usual cerebellar location of PA (Lee et al., 2011). However, one series found that nearly half of PMAs occurred in other locations, highlighting the need for increased awareness for PMA in non-classic locations (Linscott et al., 2008).

MRI findings in PMA show a solid enhancing lesion with homogeneous T2 signal intensity (Fig. 5.2a). Aside from the classic chiasmatic/hypothalamic location, other features that are often present include hydrocephalus, tumor extension into deep white and gray matter, a small cystic component, and leptomeningeal dissemination. In contrast, PA typically does not enhance, more often has a predominant cystic component, and is more frequently in a cerebellar location (Arslanoglu et al., 2003; Lee et al., 2011).

Histopathology

Pilomyxoid astrocytomas are mainly solid tumors composed of bland bipolar (piloid) cells that often show an angiocentric arrangement, although these arrangements are looser and more fibrillar than a typical ependymal pseudorosette. The cells are embedded in a lightly fibrillar and rich myxoid background (Fig. 5.2b). PMAs lack the biphasic pattern seen in PA, nor do they exhibit Rosenthal fibers. Eosinophilic granular bodies are rarely seen. The piloid cells are elongate, with a regular, hyperchromatic nucleus and lightly eosinophilic cytoplasm. In solid areas, nuclear pleiomorphism may be more striking. Necrosis may be present, as may focal peripheral infiltration of the parenchyma, but neither characteristic is so prominent as to meet the criteria for infiltrating astrocytoma (Tihan et al., 1999; Brat et al., 2007). Both PA and PMA may show vascular hyperplasia.

Immunohistochemically, the MIB-1 labeling indices are regionally variable within a PMA and range from 2 to 5 %, which is not significantly different from the MIB-1 labeling of PA (0–4 %), although PA does not usually demonstrate the

regional variability. Otherwise, PMA has strong and diffuse staining for GFAP, which highlights the myxoid and fibrillar background as well as the tumor cells. The tumor cells are vimentin positive, but antibodies to synaptophysin, chromogranin, and neurofilament protein are usually negative (Tihan et al., 1999; Brat et al., 2007). However, Miller (2009) described several cases of PMA with positive neuronal markers, indicating that PMA may be a type of glio-neuronal tumor. Mixed glio-neuronal staining and ultrastructural features have also been reported by others (De Chadarevian et al., 2006; Fuller et al., 2001). The tumor cells are variably immunoreactive for nestin, and Nagaishi et al. (2011) indicate that strong nestin staining correlates with a higher MIB-1 labeling index and a higher rate of recurrence.

Genetic Abnormalities

As with angiocentric glioma, there is little literature on the genetic abnormalities in PMA, and there is no consistent genetic abnormality at the time of his writing. Two patients with neurofibromatosis type 1 (NF1) have been described with PMA, although the exact association is unclear (Jimenez et al., 2010). (Of course there is a well-known association of PA with NF1, particularly in the optic chiasm/hypothalamic region.) There has been one report of a derivative chromosome 17 (the same chromosome that is affected in NF1) which carried and disrupted the BCR gene (Melendez et al., 2006). These authors postulate that the BCR gene may be constitutively active (similar to the BCR-ABL fusion protein and its constitutive activation) and result in tumorigenesis. Two array-comparative genomic hybridization studies have been performed. The first, a preliminary study by Komotar et al. (2004), found no genetic abnormalities in PMA. The second, by Jeon et al. (2008) found no significant difference in the number of copy gains or losses in PMA as compared with PA, although a clustering analysis was able to separate the tumors into distinct subgroups.

Differential Diagnosis

The main differential diagnosis for pilomyxoid astrocytoma includes pilocytic astrocytoma with a myxoid component, angiocentric glioma, and infiltrating astrocytoma. Purely on clinical grounds, angiocentric glioma may be ruled out because of its cortical location and presentation with epilepsy. PMA may be differentiated morphologically from PA with a myxoid component because PMA is much more homogeneous and lacks the biphasic pattern of PA, as well as Rosenthal fibers. Eosinophilic granular bodies, often present in PA, are only rarely present in PMA. As for infiltrating astrocytoma, this is also a morphologic distinction: PMA may infiltrate the brain parenchyma at the periphery of the lesion, but does not have the extensive infiltrative nature of an infiltrating astrocytoma.

Prognosis and Treatment

As previously mentioned, PMA has a worse prognosis compared to PA, with more frequent local recurrence and leptomeningeal spread as well as lower overall survival. Therefore, PMA is usually treated more aggressively than PA. Tihan et al. (1999) in their original (retrospective) description of PMA indicated that 76 % of patients with PMA had local recurrence after a variety of treatment modalities (13 of 17; two of these cases also had CSF tumor spread) with 2-year overall survival of 39 %. The PA group, by comparison, had a 2-year overall survival of 100 %. A subsequent study by Komotar et al. (2004, 2005) compared 21 hypothalamic/chiasmatic PMAs with 42 PA's in the same location. PMA had a 76 % local recurrence rate, a progression-free survival time of only 26 months, and an overall survival time of 63 months. In comparison, the PA group had a 50 % local recurrence rate, a progression-free survival time of 147 months, and an overall survival time of 213 months. Furthermore, 14 % of PMAs had CSF dissemination, which did not occur in any PAs, and one third of PMA patients died of disease, compared with 17 % of PA patients.

There is no current standard of care in the treatment of PMA. Ideally, PMA is treated with gross total resection (GTR). However, most chiasmatic/hypothalamic tumors are not amenable to GTR and are treated with partial resection followed by chemotherapy and/or radiation (Komotar et al., 2005). Because of the effects on the CNS of radiotherapy in very early life, chemotherapy is the adjuvant treatment of choice in infants, and radiotherapy is used after the age of 3–5 years. Chemotherapy may be used to delay radiotherapy in infants who have recurrent or persistent disease. Tsugu et al. (2009) indicate that cisplatin/carboplatin-based chemotherapy regimens may be useful for initial treatment of PMA and intermediate pilomyxoid tumors (see next paragraph). However, in patients with leptomeningeal dissemination, frontline chemotherapy is often ineffective. Terasaki et al. (2012) describe a case of a 5-year old child with leptomeningeal disease who responded to craniospinal irradiation and temazolimide after failed frontline chemotherapy.

Of interest is the concept of a "maturing" PMA or one that, upon recurrence, shows more features of pilocytic astrocytoma, its less aggressive counterpart. This concept is closely related to the idea of the "intermediate pilomyxoid tumor," (IPT) which shows histologic features of both PA and PMA. Recent reviews have indicated that, indeed, IPTs are not rare, and that it is unclear if these intermediate tumors carry the worse prognosis of pure PMA (Johnson et al., 2010), although Forbes et al. (2011) demonstrated that pilomyxoid tumors of the cerebellum do have a higher rate of recurrence and leptomeningeal disease than cerebellar PAs. Because of the uncertain significance of pilomyxoid features, the pathologist should note such features when they are present. Of note, PMAs do not always mature towards a less aggressive neoplasm. Paraskevopoulos et al. (2011) reported a case of a 12 year old girl with PMA with leptomeningeal dissemination that recurred in 3 months as glioblastoma.

Pituicytoma

Intro/Historical Context

Pituicytoma is a term that previously was once used synonymously with granular cell tumor or pilocytic astrocytoma of the posterior pituitary, infundibulum, or suprasellar region. However, Brat et al. (2000) defined criteria for pituicytoma, and this tumor is now restricted to a distinct clinicopathologic entity that the WHO has recognized as a "Tumor of the Sellar Region," separate from its previous synonyms. At the time of this writing, there are 54 described cases of pituicytoma, including one incidental finding at autopsy. Alternate, but less preferred names, for pituicytoma include infundibuloma and posterior pituitary astrocytoma.

Clinical Presentation/Imaging

Pituicytomas are located in the neurohypophysis (posterior pituitary) or infundibulum and may be intra- or suprasellar. Because of their location, they may result in compression of the optic chiasm, causing visual disturbances, or hypopituitarism. Hyperprolactinemia (resulting in decreased libido and amenorrhea) may occur when the cytoplasm of the neoplastic pituicytes engulfs normal infundibulum, causing interruption of the normal dopamine release pathway (Brat et al., 2000; Islamian et al., 2012). Although pituicytoma is mainly a tumor of adults, there has been one described case in an 11-year old girl (Yilmaz et al., 2012).

Imaging demonstrates pituicytomas as predominantly solid masses of the sellar, suprasellar, or (less commonly) parasellar region. Pituicytoma has a similar appearance with MRI to pituitary adenoma: a demarcated lesion with marked homogeneous enhancement with contrast administration (Fig. 5.3a). Pituicytomas are usually isointense on T1-weighted imaging, and iso- to hyperintense on T2-weighted imaging. Bony remodeling and cystic change are

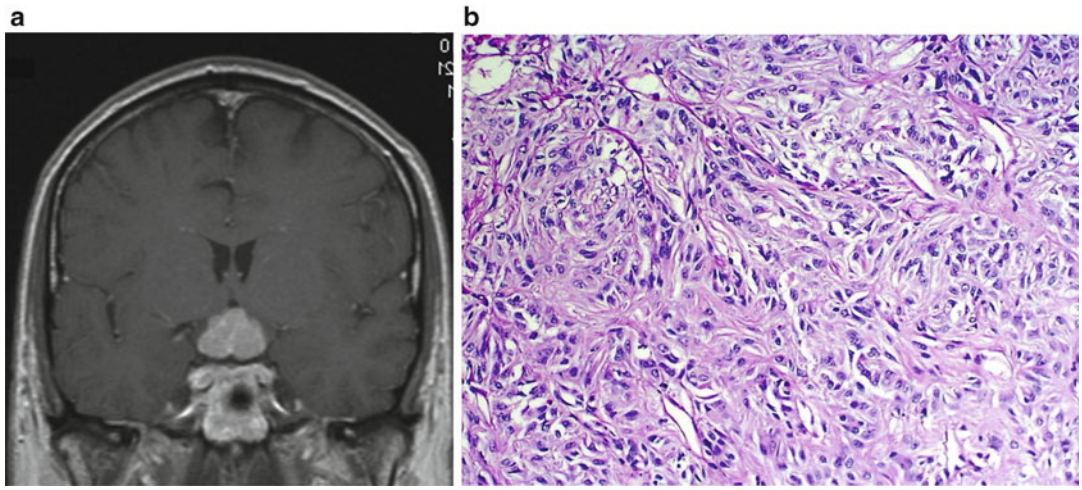

Fig. 5.3 Pituicytoma: (**a**) MRI, coronal view. Pituicytoma, indistinguishable on imaging from pituitary adenoma, presents as a demarcated, solid sellar and suprasellar mass. (**b**) Histologically, pituicytoma forms intersecting fascicles of bland, moderately-sized pituicytes. H&E, 400× (*Images courtesy of Dr. Tony Yachnis)*

rarely described, and these tumors are rarely if ever calcified, unlike craniopharyngiomas which also occur here, half of which have significant calcification. Radiologically, the differential diagnosis of this lesion will almost always include pituitary macroadenoma and meningioma, and distinction with pituicytoma is not possible based on imaging (Hammoud et al., 2010; Chu et al., 2011).

Histopathology

Pituicytomas are circumscribed, solid tumors composed of bipolar (piloid) cells thought to be derived from pituicytes, a type of specialized glial cell (Fig. 5.3b). These tumors may locally infiltrate surrounding pituitary, but are otherwise non-infiltrative. The bipolar cells form intersecting fascicles, often in a storiform pattern. Pituicytes have abundant eosinophilic cytoplasm and moderately-sized, oval nuclei which lack pleiomorphism (Fig. 5.3b). The cells lie in a glioma-like delicate fibrillary background which may be very vascular. Pituicytomas are more cellular than the normal neurohypophysis. Mitotic figures are rare or absent.

Immunohistochemically, pituicytes are immunopositive for glial fibrillary acidic protein (GFAP), vimentin, and S-100 protein, although their immunoreactivity may be variable, especially for GFAP. Neuronal markers such as synaptophysin, chromogranin, and neurofilament protein are immunonegative (Miller, 2009). Antibody stains for pituitary hormones are also negative. Importantly, the eosinophilic cytoplasm of pituicytoma is not granular and has only minimal positivity with Periodic-Acid-Schiff (PAS) stains, unlike granular cell tumor and oncocytoma, in which the PAS-positivity is striking (Brat et al., 2000), and which can also be found as an infundibular mass. Interestingly, Phillips et al. (2010) demonstrated strong, diffuse Bcl-2 immunopositivity and suggested that mutations in Bcl-2 may provide clues to tumorigenesis.

Genetic Abnormalities

There is no known consistent genetic abnormality in pituicytoma. An array-comparative genomic hybridization study of one pituicytoma showed a gain on 5p, and losses on 1p, 14q, and 22p. Although these copy gains and losses are different

from the majority of genetic abnormalities in pituitary adenomas, case reports have reported individual pituitary adenomas with the same abnormalities, suggesting that pituicytoma is a distinct, but related, entity (Phillips et al., 2010).

Differential Diagnosis

The main considerations for the clinical differential diagnosis of pituicytoma include pituitary adenoma, spindle cell oncocytoma, and granular cell tumor. Histologically the tumors have no resemblance to pituitary adenomas, their cells do not have the finely granular oncocytic cytoplasm seen in the oncocytomas or granular cell tumors, and ultrastructurally they lack the abundant lysosomes or mitochondria that are found in these two entities respectively (Brat et al., 2007). In small biopsies, one must be careful not to overdiagnose a distorted fragment of non-neoplastic neurohypophysis as a pituicytoma. As the cells in the neurohypophysis are also glia, and will be immunopositive for GFAP, vimentin, and S100, the distinction may rest in part on proliferative activity (MIB1) as well as on the recognition in the normal neurohypophysis of the dilated nerve endings (Herring Bodies) from which the neurohypophysial hormones are released (Miller, 2009).

Prognosis and Treatment

Pituicytoma is treated with surgical resection. Because of its location, its vascularity, and its propensity to adhere to (but not invade) surrounding structures, gross total resection may not be possible. Studies indicate that even with only partial resection, pituicytomas regrow only slowly. Secci et al. (2012) describe a recurrence rate of 21 % in subtotally resected tumors, with a mean time to recurrence of 24 months (range 5–60 months). Islamian et al. (2012), on the other hand, describe a recurrence rate of 39 % in subtotally resected tumors, with time to recurrence ranging from 3 to 84 months. Several patients have undergone post-operative adjuvant radiation therapy, but the follow-up data are insufficient to indicate the role of radiotherapy in pituictyoma (Islamian et al., 2012). Malignant transformation or leptomeningeal spread has not been reported.

References

Arslanoglu A, Cirak B, Horska A, Okoh J, Tihan T, Aronson L, Avellino AM, Burger PC, Yousem DM (2003) MR imaging characteristics of pilomyxoid astrocytomas. Am J Neuroradiol 24:1906–1908

Brat DJ, Scheithauer BW, Staugaitis SM, Holtzmann RNN, Morgello S, Burger PC (2000) Pituicytoma: a distinctive low-grade tumor of the neurohypophysis. Am J Surg Pathol 24:362–368

Brat DJ, Scheithauer BW, Fuller GN, Tihan T (2007) Newly codified glial neoplasms of the 2007 WHO classification of tumours of the central nervous system: angiocentric glioma, pilomyxoid astrocytoma, and pituicytoma. Brain Pathol 17:319–324

Chu J, Yang Z, Meng Q, Yang J (2011) Pituicytoma: case report and literature review. Br J Radiol 84:e55–e57

Cottingham SL, Boesel CP, Yates AJ (1996) Pilocytic astrocytoma in infants: a distinctive histological pattern. (Abstract). J Neuropathol Exp Neurol 55:654

De Chadarevian JP, Halligan GE, Reddy G, Bertrand L, Pascasio JM, Faerber EN, Katsetos CD (2006) Glioneuronal phenotype in a diencephalic pilomyxoid astrocytoma. Pediatr Dev Pathol 9:480–487

Forbes JA, Mobley BC, O'Lynnger TM, Cooper CM, Ghiassi M, Hanif R, Pearson MM (2011) Pediatric cerebellar pilomyxoid astrocytomas: report of 2 cases. J Neurosurg Pediatr 8:90–96

Fuller CE, Frankel B, Smith M, Rodziewitz G, Landas SK, Caruso R, Schelper R (2001) Suprasellar monomorphous pilomyxoid neoplasm: an ultrastructural analysis. Clin Neuropathol 20:256–262

Gottfried ON, Fults DW, Townsend JJ, Couldwell WT (2002) Spontaneous hemorrhage associated with a pilomyxoid astrocytoma. J Neurosurg 99:416–420

Hammoud DA, Munter FM, Brat DJ, Pomper MG (2010) Magnetic resonance imaging features of pituicytoma: analysis of 10 cases. J Comput Assist Tomogr 35:757–761

Islamian AP, Buslei R, Saeger W, Fahlbusch R (2012) Pituicytoma: overview of treatment strategies and outcome. Pituitary 15:227–236

Jeon Y-K, Cheon J-E, Kim S-K, Wang K-C, Byung-Kyu C, Park S-H (2008) Clinicopathologic features and global copy number alterations of pilomyxoid astrocytoma in the hypothalamus/optic pathway: comparative analysis with pilocytic astrocytoma using array-based comparative genomic hybridization. Mod Pathol 21:1345–1356

Jimenez L, Correa-Rivas M, Colon-Castillo L, Rivera-Zengotita M, Colon G, Vigo J, McBurney E (2010) Pilomyxoid astrocytoma in unusual location in a child with neurofibromatosis type 1: case report and review of the literature. P R Health Sci J 29:123–126

Johnson MW, Eberhart CG, Perry A, Tihan T, Cohen KJ, Rosenblum MK, Rais-Bahrami S, Goldthwaite P, Burger PC (2010) Spectrum of pilomyxoid astrocytomas: intermediate pilomyxoid tumors. Am J Surg Pathol 34:1783–1791

Komotar RJ, Burger PC, Carson BS, Brem H, Olivi A, Goldthwaite PT, Tihan T (2004) Pilocytic and pilomyxoid hypothalamic/chiasmatic astrocytomas. Neurosurgery 54:72–80

Komotar RJ, Mocco J, Jones JE, Zacharia BE, Tihan T, Feldstein NA, Anderson RCE (2005) Pilomyxoid astrocytoma: diagnosis, prognosis, and management. Neurosurg Focus 18(E7):1–4

Koral K, Koral KM, Sklar F (2012) Angiocentric glioma in a 4-year old boy: imaging characteristics and review of the literature. Clin Imaging 36:61–64

Lee IH, Kim JH, Suh Y-L, Eo H, Shin HJ, Yoo S-Y, Lee KS (2011) Imaging characteristics of pilomyxoid astrocytomas in comparison with pilocytic astrocytomas. Eur J Radiol 79:311–316

Lellouch-Tubiana A, Boddaert N, Bourgeois M, Fohlen M, Jouvet A, Delalande O, Seidenwurm D, Brunelle F, Sainte-Rose C (2005) Angiocentric Neuroepithelial Tumor (ANET): a new epilepsy-related clinicopathological entity with distinctive MRI. Brain Pathol 15:281–286

Linscott LL, Osborn AG, Blaser S, Castillo M, Hewlett RH, Wieselthaler N, Chin SS, Krakenes J, Hedlund GL, Sutton CL (2008) Pilomyxoid astrocytoma: expanding the imaging spectrum. Am J Neuroradiol 29:1861–1866

Louis DN, Ohgaki H, Wiestler OD, Cavenee WK, Burger PC, Jouvet A, Sheithauer BW, Kleihues P (2007) The 2007 WHO classification of tumours of the central nervous system. Acta Neuropathol 114:97–109

Lum DL, Halliday W, Watson M, Smith A, Law A (2008) Cortical ependymoma or monomorphous angiocentric glioma? Neuropathology 28:81–86

Matsuzaki K, Kageji T, Watanbe H, Hirose T, Nagahiro S (2010) Pilomyxoid astrocytoma of the cervical spinal cord successfully treated with chemotherapy. Neurol Med Chir (Tokyo) 50:939–942

Melendez B, Fiano C, Ruano Y, Hernandez-Moneo JL, Mollejo M, Martinez P (2006) BCR gene disruption in a pilomyxoid astrocytoma. Neuropathology 26:442–446

Miller DC (2009) Special types of astrocytomas, and pituitary tumors. Modern Surgical Neuropathology. Cambridge University Press, New York, pp 52–54, 285–288

Nagaishi M, Yokoo H, Hirato J, Yoshimoto Y, Nakazato Y (2011) Clinico-pathologic features of pilomyxoid astrocytomas: three case reports. Neuropathology 31:152–157

Omura T, Nawashiro H, Osada H, Shima K, Tsuda H, Shinsuke A (2008) Piloymyxoid astrocytoma of the fourth ventricle in an adult. Acta Neurochir 150:1203–1206

Paraskevopoulos D, Patsalas I, Karkavelas G, Foroglou N, Magras I, Selviaridis P (2011) Pilomyxoid astrocytoma of the cervical spinal cord in a child with rapid progression into glioblastoma: case report and literature review. Childs Nerv Syst 27:313–321

Phillips JJ, Misra A, Feuerstein BG, Kunwar S, Tihan T (2010) Pituicytoma characterization of a unique neoplasm by histology, immunohistochemistry, and array-based comparative genomic hybridization. Arch Pathol Lab Med 134:1063–1069

Pokharel S, Parker JR, Parker JC Jr, Coventry S, Stevenson CB, Moeller KK (2011) Angiocentric glioma with high proliferative index: case report and review of the literature. Ann Clin Lab Sci 41:257–261

Preusser M, Novak K, Czech T, Panneck HW, Tuxhorn LEB, Hans VH (2006) Angiocentric glioma: report of eight cases. Acta Neuropathol 112:382–383

Preusser M, Hoischen A, Novak K, Czech T, Prayer D, Hainfellner JA, Baumgartner C, Woermann FG, Tuxhorn IE, Pannek HW, Bergmann M, Radlwimmer B, Villagran R, Weber RG, Hans VH (2007) Angiocentric glioma: report of clinico-pathologic and genetic findings in 8 cases. Am J Surg Pathol 31:1709–1718

Secci F, Merciadri P, Rossi DC, D'Andrea A, Zona G (2012) Pituicytomas: radiologic findings, clinical behavior, and surgical management. Acta Neurochir 154:649–657

Shakur SF, McGirt MJ, Johnson MW, Burger PC, Ahn E, Carson BS, Jallo GI (2009) Angiocentric glioma: a case series. J Neurosurg Pediatr 3:197–202

Tatevossian RG, Tang B, Dalton J, Forshew T, Lawson AR, Ma J, Neale G, Shurtleff SA, Bailey S, Gajjar A, Baker SJ, Sheer D, Ellison DW (2010) *MYB* upregulation and genetic aberrations in a subset of pediatric low-grade gliomas. Acta Neuropathol 120:731–743

Terasaki M, Bouffet E, Maeda M, Sugita Y, Sawamura Y, Morioka M (2012) Successful treatment of leptomeningeal gliomatosis of pilomyxoid astrocytoma after failed frontline chemotherapy. Neurologist 18:32–35

Tihan T, Fisher PG, Kepner JL, Godfraind C, McComb RD, Goldthwaite PT, Burger PC (1999) Pediatric astrocytomas with monomorphous pilomyxoid features and a less favorable outcome. J Neuropathol Exp Neurol 58:1061–1068

Toyoda K, Tsutsumi K, Ono T, Takahata H, Toda K, Ito M, Sugita Y, Masuda T, Ichinose K, Baba H, Yonekura M (2009) Pilomyxoid astrocytoma presenting in an elderly patient: a case report. No Shinkei Geka 37:1123–1128

Tsugu H, Oshira S, Yanai F, Komatsu F, Abe H, Fukushima T, Nomura Y, Matsumoto S, Nabeshima K, Takano K, Utsunomiya H (2009) Management of pilomyxoid astrocytomas: our experience. Anticancer Res 29:919–926

Wang M, Tihan T, Rojiani A, Bodhireddy S, Burger PC (2002) Angiocentric bipolar astrocytoma: a distinctive infiltrating astrocytoma (Abstract). J Neuropathol Exp Neurol 61:475

Wang M, Tihan T, Rojiani AM, Bodhireddy SR, Prayson RA, Iacuone JJ, Alles AJ, Donahue DJ, Hessler RB, Kim JH, Haas M, Rosenblum MK, Burger PC (2005) Monomorphous angiocentric glioma: a distinctive epileptogenic neoplasm with features of infiltrating astrocytoma and ependymoma. J Neuropathol Exp Neurol 64:875–881

Yilmaz O, Turan A, Yigit H, Duymus M, Kosar U (2012) Case of pituicytoma in childhood. Childs Nerv Syst 28:11–12

Diffuse Intrinsic Pontine Gliomas in Children: Treatment (An Update)

6

Amy Lee Bredlau and David N. Korones

Contents

Abstract

Diffuse intrinsic pontine glioma (DIPG) is a devastating childhood malignancy. The tumors are diagnosed radiographically and symptomatically. Biopsy is not recommended. The pathology is almost always a WHO grade II, III, or IV astrocytoma. Patients present with less than 6 months of cranial nerve defects, ataxia, and/or long tract signs. Radiographically, tumors are hypointense on T1, hyperintense on T2 and have an infiltrating mass that occupies at least 2/3 of the pons. The standard of care for treatment of a DIPG is radiation therapy. Neither surgery nor chemotherapy has been found to improve survival for these children. The average survival from diagnosis is 8–12 months.

Introduction

Diffuse intrinsic pontine glioma (DIPG) is one of the most devastating of all childhood malignancies. In spite of decades of clinical trials, no therapy has been found that offers a chance of cure in these children. Radiation is the only therapy that has been shown to prolong survival (Korones, 2007), although only by a few months. DIPGs have been termed brainstem gliomas, brainstem tumors, diffuse brainstem tumors, diffuse intrinsic brainstem gliomas, pontine gliomas, and diffuse pontine gliomas. In this chapter, we shall use the term DIPG, as it best describes the infiltrative nature of the tumor and the fact that it arises in the pons.

A.L. Bredlau (✉)
Division of Pediatric Neuro-Oncology, University of Medical University of South Carolina, 135 Rutledge Avenue, MSC 558, 29425 Charleston, SC, USA
e-mail: bredlau@musc.edu

D.N. Korones
Division of Pediatric Hematology/Oncology and Division of Palliative Care, University of Rochester Medical Center, 601 Elmwood Avenue, Box 777, 14642 Rochester, NY

M.A. Hayat (ed.), *Tumors of the Central Nervous System, Volume 11*,
DOI 10.1007/978-94-007-7037-9_6,

Epidemiology

Brain stem gliomas can be focal or diffuse and they may or may not be exophytic. They may arise in the medulla or in the midbrain. Brain stem gliomas make up 10–20 % of childhood brain tumors and the majority of these (58–75 %) are DIPGs. Therefore DIPG accounts for somewhere between 6 and 15 % childhood brain tumors or 150–300 case per year in the U.S. (Jallo, 2006). The age at diagnosis of a DIPG is generally 7–9 years (Jallo, 2006) though it can be diagnosed from birth into adulthood. The tumors affect males and females equally (Broniscer et al., 2010).

Biology

Because biopsy is not the standard of care for patients who present with the classic clinical and radiographic findings of DIPG, little is known about the biology of this disease. However, in the past, biopsies and attempts at resection were undertaken, and therefore we have some data on the histology of DIPG. In addition, more recent tissue analyses (based on archived specimens and autopsies) have given us new insights into the biology of this disease.

Histologically, DIPGs are usually high-grade gliomas (anaplastic astrocytomas, WHO grade III, or glioblastoma multiforme, WHO grade IV) though they can occasionally be lower grade diffuse astrocytomas (WHO grade II) (Korones, 2007).

More recently, investigators have focused on the molecular biology of DIPGs. Zarghooni showed that PDGFRA (platelet-derived growth factor receptor alpha) expression is common in DIPGs both at diagnosis and at autopsy. Gains in PDGFRA are found in about one third of DIPG tumors. PARP-1 (poly ADP-ribose polymerase) was increased in some DIPG tumors, as well, including one de novo tumor (Zarghooni et al., 2010). Paugh noted that 47 % of DIPGs at autopsy have tyrosine kinase-Ras-phosphoinositide 3-kinase signaling pathway gene amplification (the most common of which are *PDGFRA* and *MET*-hepatocyte growth factor receptor gene) (Paugh et al., 2011). This is similar to what has been found in glioblastoma multiforme (Szerlip et al., 2012).

Gilbertson examined DIPG tissue at both diagnosis and autopsy and found that ERBB1 expression was increased in higher grade DIPGs. Few of the tumors his group examined had increased or mutated TP53 (Korones, 2007). Grill examined tumor tissue of 20 DIPG patients at diagnosis and found mutations in TP53 (40 %), PI3KCA (15 %) and ATM/MPL (5 %) (Grill et al., 2012). Prerna found that p53 mutation was related to grade of the brainstem tumor, with p53 mutations present in 50 % of glioblastoma multiformes, 28.6 % of anaplastic astrocytomas, 12.5 % of WHO grade II astrocytomas, and none in WHO grade I astrocytomas (Badhe et al., 2004). Additionally, there are many studies indicating increased VEGF in astrocytomas of various stages (Hendriksen et al., 2009), though none of these studies were done specifically in DIPG tumors. There are clinical studies that link increased amount of VEGF in mononuclear cells to prolonged survival when treated with VEGF inhibitors (Broniscer et al., 2010), which indicate that VEGF may be increased in DIPGs. These studies offer important insights into the biology of this tumor; it is likely that future clinical trials will be based on therapeutic agents that target these abnormalities.

Diagnosis

The time from onset of symptoms to diagnosis for children with DIPG is generally short. The median duration of symptoms is approximately 1 month. Symptoms fall into three neurologic categories: long track signs, ataxia, and/or cranial nerve deficits (Korones, 2007). The most common cranial nerve deficits include the sixth nerve (diplopia) and the seventh nerve (facial palsy) (Guillamo et al., 2001).

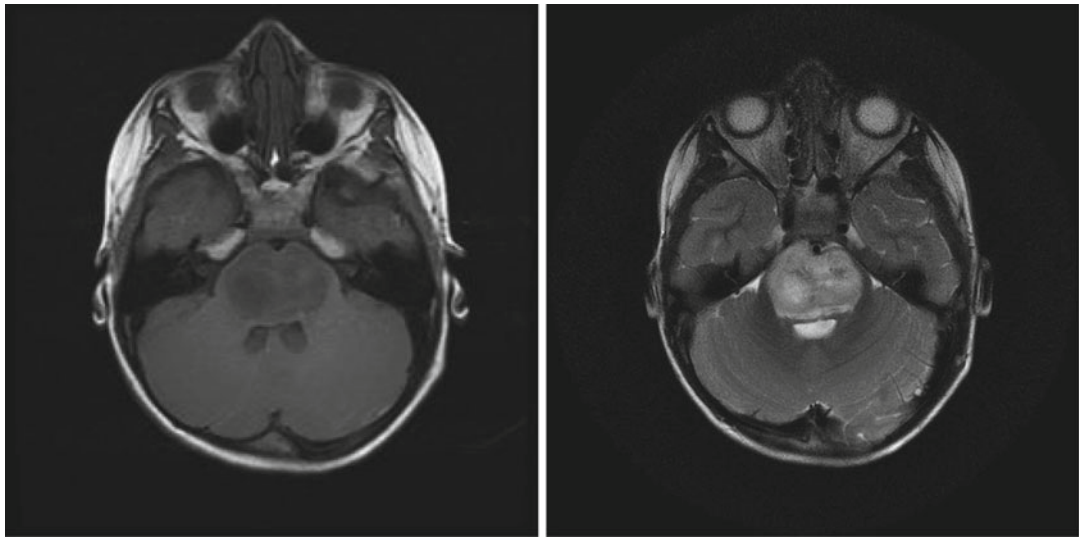

Fig. 6.1 3 yo female, presented with left sided weakness, and left facial droop with ptosis, with diffuse intrinsic pontine glioma on MRI. *Left*, T1 with diffuse tumor and hypointensity. *Right*, noncontrast T2 with hyperintensity

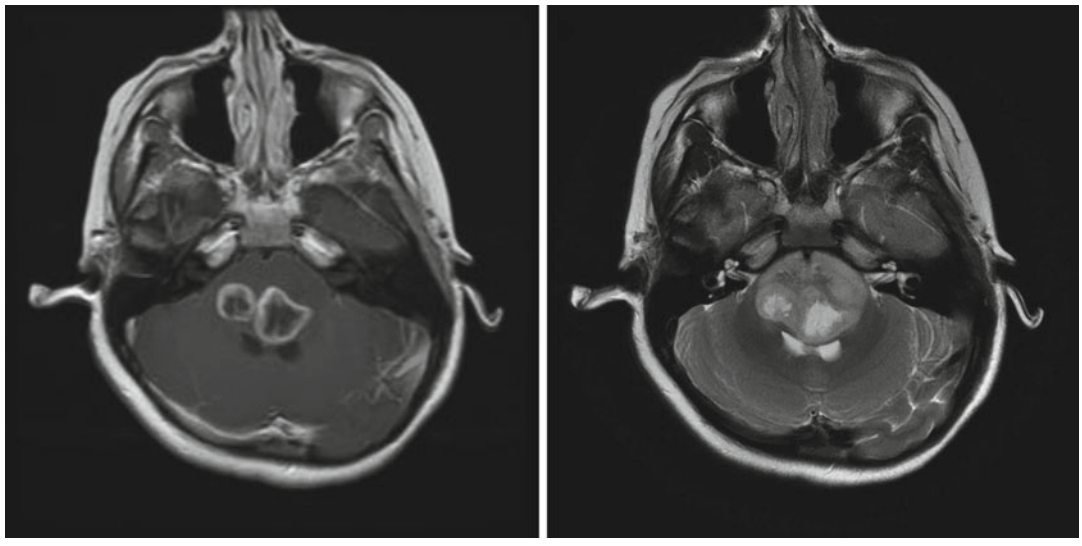

Fig. 6.2 MRI of 9 yo female with contrast enhancing portions of the diffuse pontine lesion on T1 image (*left*). T2 MRI demonstrates a diffuse hyperintense glioma (*right*)

Diagnosis of DIPG in children is generally confirmed radiographically. On MRI, these tumors typically have an epicenter in the pons with diffuse infiltration of the lesion occupying at least 2/3 of that structure. They are generally >2 cm in size with indistinct margins (Jallo, 2006). The tumors generally are not exophytic though there is occasionally a ventral exophytic component (Guillamo et al., 2001). They are hypointense on T1 with hyperintensity on T2 (Fig. 6.1) (Jallo, 2006). Some tumors are contrast enhancing, though most are not (Fig. 6.2), and this has no prognostic significance (Jallo, 2006). Biopsy is not required for diagnosis. The generally accepted standard for diagnosis of DIPG is outlined in Children's Oncology

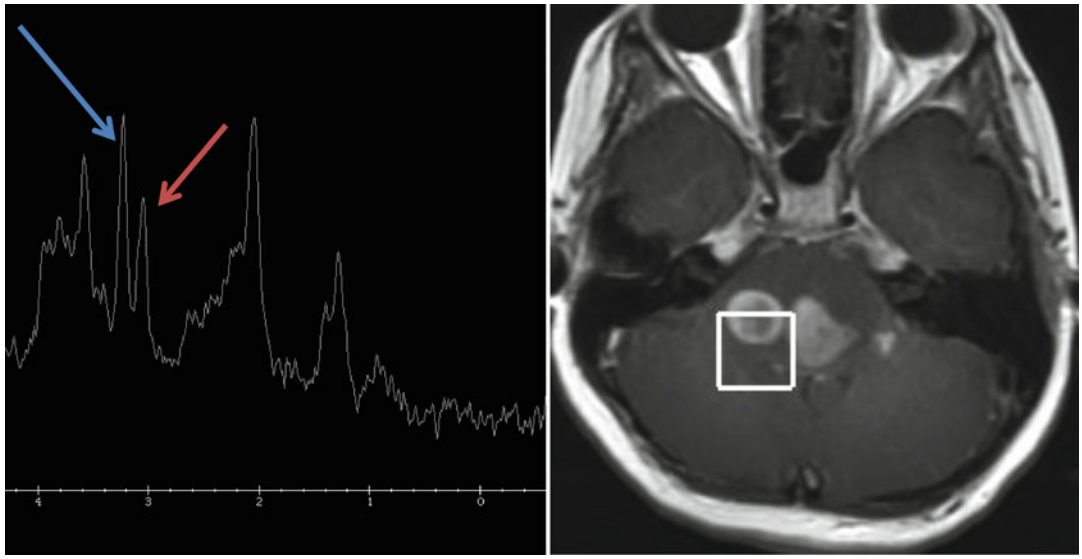

Fig. 6.3 MRS of the same patient as Fig. 6.2. Note the increased choline/creatine ratio in the area of tumor and contrast enhancement. The choline peak is indicated by the *blue arrow*; the creatine peak is indicated by the *red arrow*

Group (COG) studies: "tumors with a pontine epicenter and diffuse involvement of at least 2/3 of the pons" on MRI. Central nervous system (CNS) dissemination of DIPGs is uncommon at the time of initial diagnosis (Benesch et al., 2005); however, CNS dissemination at the time of recurrence occurs frequently. Wagner et al. (2006) reported CNS dissemination in 17 % of 270 children with DIPG while Benesch et al. (2005) found only one patient with dissemination at presentation out of 198 children with DIPG. Although dissemination is not common at presentation, most neuro-oncologists recommend a full spine MRI at diagnosis (and relapse) to assess for the possibility of spinal cord lesions.

Magnetic resonance spectroscopy (MRS) can also be used to determine the malignancy of a brainstem tumor. The choline/creatine values can be used to differentiate between indolent and aggressive brainstem lesions (Fig. 6.3) (Curless et al., 2002). These changes in MRS may precede clinical changes (Laprie et al., 2005) and can be useful for early prognostication (Thakur et al., 2006).

Since the diagnosis of DIPG is radiographic and not tissue-based, caution must be exercised in making this diagnosis. There are other entities that can mimic DIPG and might be treated differently. The differential diagnosis of a pontine lesion includes tuberculoma (Knauer-Fischer et al., 1999), atypical teratoid rhabdoid tumor, primitive neuroectodermal tumor (Donaldson et al., 2006), lymphoma, ganglioglioma, oligodendroglioma, hemangioblastoma, cavernous malformation, and epidermoid tumors (Jallo et al., 2004). If the appearance of the lesion on MRI is not typical for DIPG (or the clinical presentation differs), a biopsy should be considered.

Outcomes

In spite of decades of research and clinical trials, the survival of children with DIPG has remained essentially unchanged and dismal. Multiple modalities (radiation, hyperfractionated radiation, adjuvant chemotherapy, neoadjuvant chemotherapy) have been attempted with no consistently meaningful responses to any therapy other than radiation. Radiation therapy prolongs life by a few months and generally improves quality of life for a brief time for these children, but it is not curative.

The median survival for children with DIPG is approximately 8–12 months with a 30–50 % 1 year survival and a 10–20 % 2 year survival (Massimino et al., 2008). Most children with DIPG succumb to their disease within the first 2 years of diagnosis, although a small proportion of children with DIPGs do achieve greater than 2-year survival (Broniscer and Gajjar, 2004; Massimino et al., 2008). It is unclear if these children have a similar biology of their tumor.

There are, however, some useful prognostic factors for DIPGs in children. Children with a long history (>3 month) prior to diagnosis (Shuper et al., 1998) and lack of neurologic deficits from brainstem involvement (Broniscer and Gajjar, 2004) tend to have a better prognosis. Interestingly, the prognosis is strikingly better for children less than 3 years of age (Broniscer et al., 2008) and for adults (Kesari et al., 2008). Not surprisingly, higher grade of DIPG, when known, is associated with a shorter survival (Korones, 2007).

Surgery

In 1993, Albright et al. published the results of a COG study in which he proposed that biopsy was not necessary as part of the diagnostic workup for DIPG. He argued that MRI was diagnostic and that biopsy of the pons carried risks and seldom changed therapy (Korones, 2007). Since that time, diagnosis without biopsy has been the standard of care for children with DIPGs. It should be noted that although biopsy in this location does carry some risk of morbidity, a number of studies have demonstrated that biopsies of the pons or brainstem are safe to perform with stereotactic techniques in the hands of an experienced neurosurgeon (Cartmill and Punt, 1999; Korones, 2007). Cartmill and Punt reported two patients with transient hemiparesis and three patients with a transient increase in eye movement deficits out of 18 stereotactic biopsies, with all of these deficits resolving within 1 week. They also noted that no patient had any biopsy-related mortality or ventilation requirement (Cartmill and Punt, 1999). Chico-Ponce de Leon reported six hemorrhages and three pneumocrania after stereotactic brainstem biopsies in 50 children (18 % morbidity) with no mortalities (Korones, 2007). Such studies show that the risk of permanent neurologic deficits is quite low.

Surgical resection of DIPG is not recommended, as the brainstem and pons are exquisitely sensitive parts of the brain and the tumor is so infiltrative. Attempts at resection in the past have not been successful: Pierre-Kahn et al. demonstrated that survival of children with DIPGs was not prolonged after surgery (Pierre-Kahn et al., 1993).

Radiation Therapy

Radiation is the only modality that has been shown to prolong survival in children with DIPGs. This was first demonstrated in 1975 by Sheline at UCLA, when he showed that the median survival for children with brainstem lesions treated with radiation was 6 months from diagnosis. At that time, no MRI or biopsy diagnosis was available for the reported children, and so no differentiation between DIPG and other brainstem lesions was done (Sheline, 1975). Since that time, a number of studies have been conducted, consistently showing that children with DIPG respond to radiation, have improvement of their symptoms, and have improved overall survival. Langmoen demonstrated that radiation therapy, compared to supportive care without chemotherapy or radiation, doubled the median survival time from 140 to 280 days (Korones, 2007). In 1992, Hibi demonstrated that there was a dose response to radiation therapy in DIPG patients, with patients receiving less than 45 Gy responding least well to radiation treatment (Hibi et al., 1992). In 1997, Lewis demonstrated that 46 % of children with DIPG treated with radiation had a sustained neurologic improvement allowing cessation of steroid therapy and that 50 % of children showed radiographic evidence of partial response to radiation therapy of 48.6–50.4 Gy. These children had a median survival time of 8.5 months (Lewis et al., 1997). Many studies have been done to optimize radiation therapy as offered to children with

DIPGs. With radiation, the median survival of children with DIPG is generally around 8 months (Lewis et al., 1997).

The standard of care for radiotherapy for children with DIPG is conventional fractionated radiation in 30 doses of 1.8 Gy to a total of 54 Gy (Korones, 2007). Because radiation is so effective, radiation oncologists have looked at other ways to deliver radiotherapy to further boost responses and overall survival. One such approach is hyperfractionated radiation therapy (therapy given twice a day, 5 days a week, to allow for even higher doses of radiation to be given while minimizing toxicity). This was first demonstrated to be a viable strategy in 1988 by Freeman when patients were given hyperfractionated radiation to a total dose of 70.2 Gy (Korones, 2007). In similar studies, doses as high as 78 Gy were given. However, these higher doses did not result in significantly improved survival. Finally, Mandell in 1999 conducted a randomized trial of conventional versus hyperfractionated radiation for children with DIPG and found that the outcome was uniformly poor in both groups (Korones, 2007).

Radiosensitizers are agents (usually chemotherapies, though oxygen is a potent radiosensitizer) that increase the sensitivity of a tumor to radiation therapy. Many chemotherapeutic agents have been tested as radiosensitizers for DIPGs. These include carboplatin, cisplatinum, tamoxifen, and topotecan. These therapies were not effective and occasionally were associated with worse outcomes for patients with DIPG than radiation therapy alone (Korones, 2007).

Chemotherapy and Stem Cell Transplantation

To date, no chemotherapy has been demonstrated to prolong the lives of children with DIPGs.

Adjuvant Chemotherapy

Traditional chemotherapeutic agents, such as idarubicin (Dreyer et al., 2003), carboplatin and etoposide, and vincristine and etoposide, have been investigated for treatment of DIPG, with no effect. Novel agents such as thalidomide have also been evaluated, without improvement in the management of DIPGs. Most of these therapies also caused toxicity and therefore are not used for treatment of DIPG (Korones, 2007).

Temozolomide has been used in the treatment of DIPGs since 2002. Lashford administered temozolomide to 21 patients with DIPG in an open label trial. In this study, there was no significant difference between children treated with temozolomide and historical controls, though there were two toxic deaths (Lashford et al., 2002). In 2011, Cohen published the report of a Children's Oncology Group phase II open-labeled trial of adjuvant temozolomide for children with newly diagnosed DIPG. This study confirmed prior studies that there is no improvement in survival for children treated with temozolomide for DIPG compared to historical controls (Cohen et al., 2011).

Neoadjuvant Therapy

Neoadjuvant therapy (chemotherapy given before radiation therapy) has also been attempted for treatment of children with DIPG. In 1993, Kretschmar evaluated neoadjuvant chemotherapy with cisplatin and cyclophosphamide followed by hyperfractionated radiation therapy. This study demonstrated a mean survival of 9 months, which was associated with moderate toxicity (including bone marrow suppression, brainstem swelling from intravenous fluids, electrolyte abnormalities, and ototoxicity) (Korones, 2007). Carboplatin, etoposide and vincristine were compared to cisplatin, cyclophosphamide, etoposide, and vincristine by Jennings in 2002 (Korones, 2007). These studies did not demonstrate prolonged survival compared to historical controls. Neoadjuvant therapy is therefore no longer attempted in control of DIPGs.

High Dose Chemotherapy with Stem Cell Rescue

High dose chemotherapy followed by autologous bone marrow transplantation has been evaluated

for children with DIPG by multiple investigators and has not been shown to prolong survival, although it does cause significant toxicities. Conditioning regimens have included busulfan/thiotepa, cyclophosphamide/thiopa, BCNU, and high dose probarbazine/CCNU/vincristine, but none have proven effective (Korones, 2007; Wolff et al., 2010).

Biologic and Targeted Therapies

Biologic (and other targeted) therapies are promising medications that have the potential to treat the tumor specifically without the side effects of broad based chemotherapies. Examples of such targeted therapies include monoclonal antibodies to tumor specific antigens, growth factor receptor blockers, and immune-mediated therapies. Theoretically, these targeted therapies would demonstrate improved control of DIPGs and reduced systemic toxicities when compared to traditional therapies.

The first such treatment for DIPG was investigated in 1996 by Packer. He and the Children's Cancer Group administered β-interferon to 32 children with diffuse intrinsic brainstem gliomas in a dose escalating study. This study demonstrated a safe dosage range but failed to prolong the median time to death beyond 9 months (Packer et al., 1996).

In 2010, Gururangan and the Pediatric Brain Tumor Consortium presented the results of a phase II study of bevacizumab (a VEGF inhibitor which inhibits angiogenesis) and irinotecan (a topoisomerase 1 inhibitor) in 34 patients with recurrent malignant glioma or DIPG. This intervention was well tolerated but did not increase survival of either group of patients (Gururangan et al., 2010). One promising study of bevacizumab in children with DIPGs was published in 2009 by Lui. This article is a case report of four patients with improvement in their radiation necrosis in response to bevacizumab therapy (Liu et al., 2009).

In 2011, Pollack and the Pediatric Brain Tumor Consortium presented the results of a phase II study of gefitinib (an oral EGFR tyrosine kinase inhibitor) along with radiation for treatment of children with newly diagnosed DIPG. This study, once again, showed poor long-term survival, with overall survival of 20.9 % and 9.3 % at 1 and 2 years, respectively. However, these results are marginally better than the historical control for DIPGs. Of the 43 patients treated on this protocol, three patients remain alive without progression at more than 36 months after diagnosis (Pollack et al., 2011).

Tipifarnib, a farnesyl transferase inhibitor, was evaluated along with radiation in a phase II study for children with newly diagnosed DIPG and showed no improvement over historical controls (Haas-Kogan et al., 2011). Similarly, pegylated interferon failed to improve the 2-year survival of children with DIPG, though it did delay the time to progression when compared to historical controls (Warren et al., 2012).

Controversies in Management

Biopsy at presentation of a patient with radiographically diagnosed DIPG is a controversial topic. The dilemma is that on the one hand, biopsy does not change therapy, but on the other, we are unable to learn the biology of this tumor without obtaining tumor specimens. There is much hope that molecular targeting might be the next step toward curative therapy for children with DIPGs. However, without biopsy of these tumors at presentation, we are unable to learn just what pathways molecular therapies should target. Biopsies done at autopsy may be helpful, but are less reliable for targeting as the biology of the tumor may be different in the late stages of disease than at diagnosis.

It is difficult to ask a parent or child to undergo biopsy at such a distressing time in their lives, especially when one cannot say that that biopsy will help that child. Perhaps if the results of such a biopsy are linked to proposed interventions in the context of a clinical trial (e.g., bevacizumab for children whose tumors express VEGF), this approach might be more acceptable to families and treating physicians. In addition, these biopsies will add to the data to determine future therapies, which might have more curative potential than current therapies (Grill et al., 2012; MacDonald, 2012).

Future Directions

As the field of oncology advances and improves upon the strategies of molecularly guided therapies and personalized medicine, it is likely that these advances will be applied to the treatment of DIPGs. Developing either of these strategies for DIPG will require a better understanding of the biology of these tumors. That is a particular challenge since biopsy of these lesions is not typically done. In the meantime, many molecular targets (such as imatinib, tipifarnib, and gefitinib) are being tested.

Gefitinib, as noted above, has been tested by Pollack in 2011 and has shown some promise in the treatment of DIPGs in children. This study produced an overall survival of 56 % at 1 year and 20 % at 2 years, with 3/43 patients surviving >3 years, an improvement over previous therapies (Pollack et al., 2011). However, this will need to be confirmed before changing the standard of care for DIPGs, as many promising agents in early phase trials have not proven effective in larger, confirmatory trials.

Imatinib, which is a platelet-derived growth factor inhibitor (as well as having a better known activity as a bcr-abl inhibitor), is being investigated for treatment of DIPGs. A phase I study identifying the maximum tolerated dose of imatinib has been done both with and without enzyme-inducing anticonvulsant drugs (Pollack et al., 2007). Results of the phase II trial for imatinib in children with DIPGs should be forthcoming in the near future.

References

Badhe PB, Chauhan PP, Mehta NK (2004) Brainstem gliomas–a clinicopathological study of 45 cases with p53 immunohistochemistry. Indian J Cancer 41(4):170–174

Benesch M, Wagner S, Berthold F, Wolff JE (2005) Primary dissemination of high-grade gliomas in children: experiences from four studies of the Pediatric Oncology and Hematology Society of the German Language Group (GPOH). J Neurooncol 72(2):179–183

Broniscer A, Gajjar A (2004) Supratentorial high-grade astrocytoma and diffuse brainstem glioma: two challenges for the pediatric oncologist. Oncologist 9(2):197–206

Broniscer A, Laningham FH, Sanders RP, Kun LE, Ellison DW et al (2008) Young age may predict a better outcome for children with diffuse pontine glioma. Cancer 113(3):566–572

Broniscer A, Baker JN, Tagen M, Onar-Thomas A, Gilbertson RJ et al (2010) Phase I study of vandetanib during and after radiotherapy in children with diffuse intrinsic pontine glioma. J Clin Oncol 28(31):4762–4768

Cartmill M, Punt J (1999) Diffuse brain stem glioma. A review of stereotactic biopsies. Childs Nerv Syst 15(5):235–237; discussion 238

Cohen KJ, Heideman RL, Zhou T, Holmes EJ, Lavey RS et al (2011) Temozolomide in the treatment of children with newly diagnosed diffuse intrinsic pontine gliomas: a report from the Children's Oncology Group. Neuro Oncol 13(4):410–416

Curless RG, Bowen BC, Pattany PM, Gonik R, Kramer DL (2002) Magnetic resonance spectroscopy in childhood brainstem tumors. Pediatr Neurol 26(5):374–378

Donaldson SS, Laningham F, Fisher PG (2006) Advances toward an understanding of brainstem gliomas. J Clin Oncol 24(8):1266–1272

Dreyer ZE, Kadota RP, Stewart CF, Friedman HS, Mahoney DH et al (2003) Phase 2 study of idarubicin in pediatric brain tumors: Pediatric Oncology Group study POG 9237. Neuro Oncol 5(4):261–267

Grill J, Puget S, Andreiuolo F, Philippe C, MacConaill L et al (2012) Critical oncogenic mutations in newly diagnosed pediatric diffuse intrinsic pontine glioma. Pediatr Blood Cancer 58(4):489–491

Guillamo JS, Monjour A, Taillandier L, Devaux B, Varlet P et al (2001) Brainstem gliomas in adults: prognostic factors and classification. Brain 124(Pt 12):2528–2539

Gururangan S, Chi SN, Young Poussaint T, Onar-Thomas A, Gilbertson RJ et al (2010) Lack of efficacy of bevacizumab plus irinotecan in children with recurrent malignant glioma and diffuse brainstem glioma: a Pediatric Brain Tumor Consortium study. J Clin Oncol 28(18):3069–3075

Haas-Kogan DA, Banerjee A, Poussaint TY, Kocak M, Prados MD et al (2011) Phase II trial of tipifarnib and radiation in children with newly diagnosed diffuse intrinsic pontine gliomas. Neuro Oncol 13(3):298–306

Hendriksen EM, Span PN, Schuuring J, Peters JP, Sweep FC et al (2009) Angiogenesis, hypoxia and VEGF expression during tumour growth in a human xenograft tumour model. Microvasc Res 77(2):96–103

Hibi T, Shitara N, Genka S, Fuchinoue T, Hayakawa I et al (1992) Radiotherapy for pediatric brain stem glioma: radiation dose, response, and survival. Neurosurgery 31(4):643–650; discussion 650–641

Jallo G (2006) Brainstem gliomas. Childs Nerv Syst 22(1):1–2

Jallo GI, Biser-Rohrbaugh A, Freed D (2004) Brainstem gliomas. Childs Nerv Syst 20(3):143–153

Kesari S, Kim RS, Markos V, Drappatz J, Wen PY et al (2008) Prognostic factors in adult brainstem gliomas: a multicenter, retrospective analysis of 101 cases. J Neurooncol 88(2):175–183

Knauer-Fischer S, Schaper J, Janssen HT, Ratjen F (1999) Tuberculoma of the pons. Pediatr Neurol 20(1):57–59

Korones DN (2007) Treatment of newly diagnosed diffuse brain stem gliomas in children: in search of the holy grail. Expert Rev Anticancer Ther 7(5):663–674

Laprie A, Pirzkall A, Haas-Kogan DA, Cha S, Banerjee A et al (2005) Longitudinal multivoxel MR spectroscopy study of pediatric diffuse brainstem gliomas treated with radiotherapy. Int J Radiat Oncol Biol Phys 62(1):20–31

Lashford LS, Thiesse P, Jouvet A, Jaspan T, Couanet D et al (2002) Temozolomide in malignant gliomas of childhood: a United Kingdom Children's Cancer Study Group and French Society for Pediatric Oncology Intergroup Study. J Clin Oncol 20(24):4684–4691

Lewis J, Lucraft H, Gholkar A (1997) UKCCSG study of accelerated radiotherapy for pediatric brain stem gliomas. United Kingdom Childhood Cancer Study Group. Int J Radiat Oncol Biol Phys 38(5):925–929

Liu AK, Macy ME, Foreman NK (2009) Bevacizumab as therapy for radiation necrosis in four children with pontine gliomas. Int J Radiat Oncol Biol Phys 75(4):1148–1154

MacDonald TJ (2012) Diffuse intrinsic pontine glioma (DIPG): time to biopsy again? Pediatr Blood Cancer 58(4):487–488

Massimino M, Spreafico F, Biassoni V, Simonetti F, Riva D et al (2008) Diffuse pontine gliomas in children: changing strategies, changing results? A mono-institutional 20-year experience. J Neurooncol 87(3):355–361

Packer RJ, Prados M, Phillips P, Nicholson HS, Boyett JM et al (1996) Treatment of children with newly diagnosed brain stem gliomas with intravenous recombinant beta-interferon and hyperfractionated radiation therapy: a childrens cancer group phase I/II study. Cancer 77(10):2150–2156

Paugh BS, Broniscer A, Qu C, Miller CP, Zhang J et al (2011) Genome-wide analyses identify recurrent amplifications of receptor tyrosine kinases and cell-cycle regulatory genes in diffuse intrinsic pontine glioma. J Clin Oncol 29(30):3999–4006

Pierre-Kahn A, Hirsch JF, Vinchon M, Payan C, Sainte-Rose C et al (1993) Surgical management of brain-stem tumors in children: results and statistical analysis of 75 cases. J Neurosurg 79(6):845–852

Pollack IF, Jakacki RI, Blaney SM, Hancock ML, Kieran MW et al (2007) Phase I trial of imatinib in children with newly diagnosed brainstem and recurrent malignant gliomas: a Pediatric Brain Tumor Consortium report. Neuro Oncol 9(2):145–160

Pollack IF, Stewart CF, Kocak M, Poussaint TY, Broniscer A et al (2011) A phase II study of gefitinib and irradiation in children with newly diagnosed brainstem gliomas: a report from the Pediatric Brain Tumor Consortium. Neuro Oncol 13(3):290–297

Sheline GE (1975) Radiation therapy of tumors of the central nervous system in childhood. Cancer 35(3 suppl): 957–964

Shuper A, Kornreich L, Loven D, Michowitz S, Schwartz M et al (1998) Diffuse brain stem gliomas. Are we improving outcome? Childs Nerv Syst 14(10): 578–581

Szerlip NJ, Pedraza A, Chakravarty D, Azim M, McGuire J et al (2012) Intratumoral heterogeneity of receptor tyrosine kinases EGFR and PDGFRA amplification in glioblastoma defines subpopulations with distinct growth factor response. Proc Natl Acad Sci U S A 109(8):3041–3046

Thakur SB, Karimi S, Dunkel IJ, Koutcher JA, Huang W (2006) Longitudinal MR spectroscopic imaging of pediatric diffuse pontine tumors to assess tumor aggression and progression. AJNR Am J Neuroradiol 27(4):806–809

Wagner S, Benesch M, Berthold F, Gnekow AK, Rutkowski S et al (2006) Secondary dissemination in children with high-grade malignant gliomas and diffuse intrinsic pontine gliomas. Br J Cancer 95(8):991–997

Warren K, Bent R, Wolters PL, Prager A, Hanson R et al (2012) A phase 2 study of pegylated interferon alpha-2b (PEG-Intron((R))) in children with diffuse intrinsic pontine glioma. Cancer 118(14):3607–3613

Wolff JE, Driever PH, Erdlenbruch B, Kortmann RD, Rutkowski S et al (2010) Intensive chemotherapy improves survival in pediatric high-grade glioma after gross total resection: results of the HIT-GBM-C protocol. Cancer 116(3):705–712

Zarghooni M, Bartels U, Lee E, Buczkowicz P, Morrison A et al (2010) Whole-genome profiling of pediatric diffuse intrinsic pontine gliomas highlights platelet-derived growth factor receptor alpha and poly (ADP-ribose) polymerase as potential therapeutic targets. J Clin Oncol 28(8):1337–1344

Gliomatosis Cerebri: Implications of Genetic Findings

7

Marcel Seiz and Christian Hartmann

Contents

Abstract

Gliomatosis cerebri (GC) is defined as a glioma that intensely infiltrates the brain with expansion in at least three cerebral lobes. In the current version of the WHO classification of brain tumors GC is listed among astrocytic tumors due to morphological similarities. Because of the malignant course of the disease the WHO assigned an anaplastic grade (WHO grade III) to this tumor entity. Due to the various settings in which the definition criteria of GC are fulfilled it was suggested to divide GC in primary and secondary GC. Furthermore, the definition of primary GC (pGC) contains subgroups classified by diffuse growth without (type I, the 'classical' variant) or with a solid tumor portion (type II). A diffuse infiltration initiating from a solid tumor is classified as secondary GC (sGC). Various studies analysed genetic alterations in GC that typically occur in diffusely infiltrating gliomas. Some findings suggested genetically a relation between GC and low-grade astrocytomas. However, the frequency of identified genetic glioma-like alterations in GC was rather low. Recently, mutations in the *IDH1* gene were identified in a high frequency nearly only in diffusely infiltrating gliomas of the WHO grades II and III and in secondary glioblastomas. The marker was successfully used to separate these tumors from other entities that may show morphologically similarities. Therefore, *IDH1* mutations seem to be a promising

M. Seiz • C. Hartmann (✉)
Clinical Cooperation Unit Neuropathology, German Cancer Center and Department of Neuropathology, Institute of Pathology, Ruprecht-Karls University Heidelberg, Heidelberg, Germany
e-mail: Christian.hartmann@med.uni-heidelberg.de

M.A. Hayat (ed.), *Tumors of the Central Nervous System, Volume 11*,
DOI 10.1007/978-94-007-7037-9_7,

marker to determine the relationship of GC to diffusely infiltrating gliomas. Interestingly, *IDH1* mutations were identified only in pGC type II, but not in 'classical' pGC type I. These findings support the notion that the current definition of GC allows inclusion of different tumor entities and indicates that 'classical' pGC type I is rather not that related to diffusely infiltrating gliomas as formerly assumed.

Definition

The term 'gliomatosis cerebri' (GC) was introduced by Nevin (1938) characterizing a glioma with extensively infiltrative growth pattern preserving the local parenchymal architecture. GC occurs often bilaterally and shows frequent extension to the infratentorial space. Due to its malignant biological behaviour in the majority of cases GC is assigned according to the WHO classification of brain tumors as grade III (anaplasia) (Louis and International Agency for Research on Cancer, 2007).

The current WHO definition criteria of GC allow the inclusion of tumors exhibiting heterogeneous radiological, clinical and histopathological features, thereby raising the question whether these subtypes form a single entity (Louis and International Agency for Research on Cancer, 2007). Jennings suggested already in 1995 three GC subgroups based on growth pattern and absence or presence of a solid tumor mass. Primary gliomatosis cerebri (pGC) type I, the 'classical' variant, includes a diffuse glioma affecting at least three cerebral lobes without forming a solid tumor mass. pGC type II shows additionally such a solid tumor area. Instead, secondary gliomatosis cerebri (sGC) is a solid tumor that involves at least three cerebral lobes during the course of disease (Jennings et al., 1995). However, in the current WHO classification this subgrouping scheme is discussed, but not incorporated (Louis and International Agency for Research on Cancer, 2007) (Fig. 7.1).

The Origin of GC

The origin of GC remains uncertain. In the first WHO classification of brain tumors by Zülch in the year 1979 GC was listed in the group of undifferentiated and embryonic tumors (Zülch and World Health Organization, 1979). In the following two revised editions of the WHO classifications from the years 1993 to 2000 GC was grouped to neuroepithelial tumors of uncertain origin (Kleihues et al., 1993; Kleihues and Cavenee, 2000). In the current WHO classification from the year 2007 GC is assigned to astrocytic tumors including such different entities as pilocytic astrocytoma WHO grade I, pleomorphic xanthoastrocytoma WHO grade II, diffuse astrocytoma of WHO grades II and II and glioblastoma (Louis and International Agency for Research on Cancer, 2007). The basis for the current grouping within astrocytic tumors was justified by frequent expression of glial fibrillary acid protein (GFAP) (Schober et al., 1991) and detection of astrocytic features by electron microscope (Cervos-Navarro et al., 1987). However, in a previously published larger GC series included up to 40 % of tumors exhibiting oligodendroglial features challenging the concept to group GC within astrocytic tumors (Taillibert et al., 2006). In summary, 'classical' morphology did not allow drawing final conclusions regarding the origin of GC.

Grading and Prognosis of GC

Furthermore, the grading of GC is not finally resolved. Different reports described survival periods ranging from 1 month up to 17 years, thereby challenging the effort to assign a particular WHO grade to GC (Artigas et al., 1985; Cervos-Navarro et al., 1987). Two studies demonstrated that histological features that allow grading of diffuse gliomas are also applicable for GC (Perkins et al., 2003; Vates et al., 2003). In a retrospective meta-analysis of 124 patients 52 % of the patients died within the first, 63 % within the

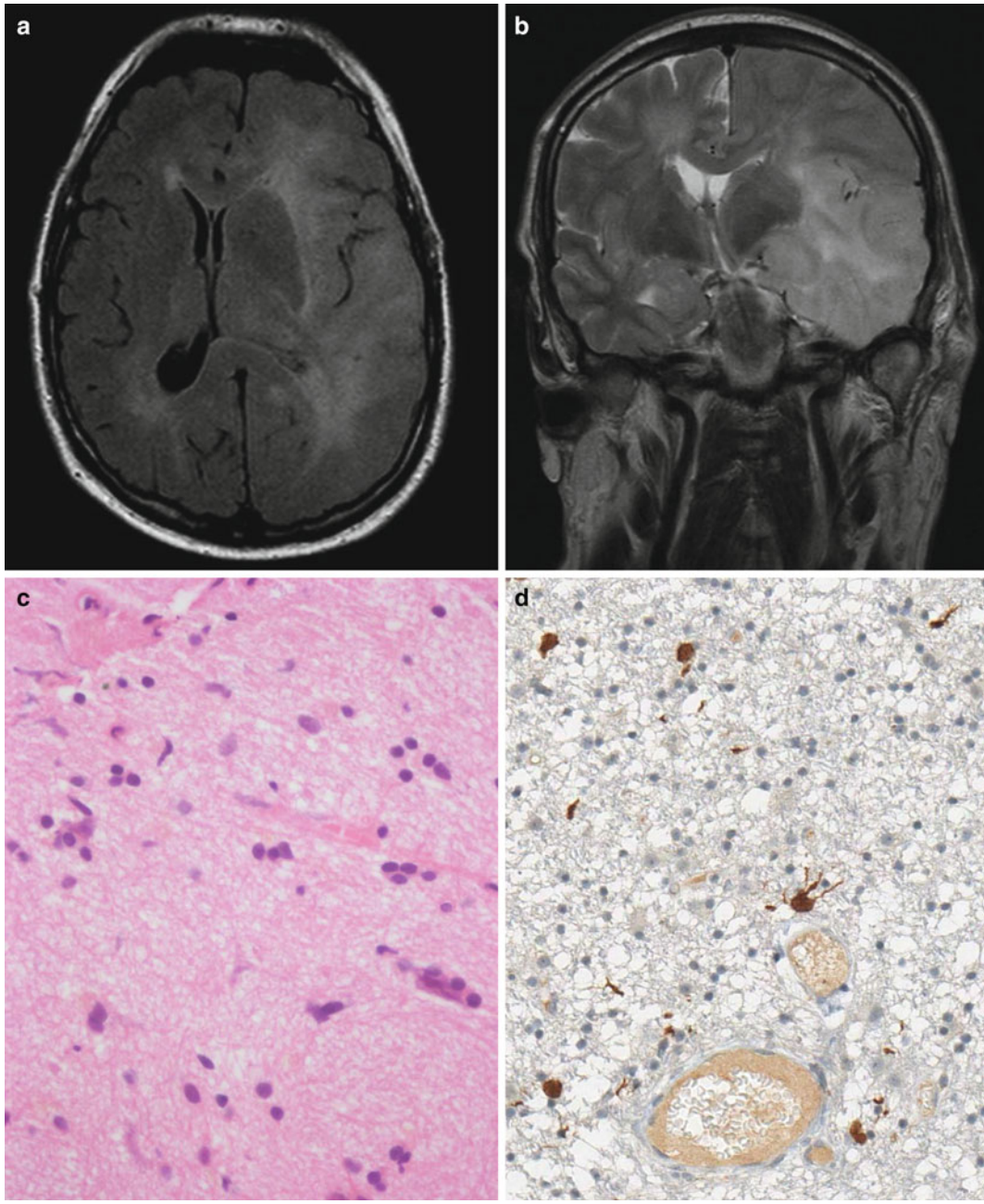

Fig. 7.1 MRI and histology pictures of gliomatosis cerebri. (**a**): transversal FLAIR MRI-sequence with diffuse infiltration of the left hemisphere with expansion to the right side and resulting mass effect without solid tumor, corresponding to primary gliomatosis cerebri type 1 (pGC type 1); (**b**): diffuse infiltration of the temporal lobe on the left side with expansion to the insula and parietal lobe in coronal T2-weighted MRI-sequence; (**c**): H&E staining showing a pGC type I tumor with diffuse infiltration of the brain parenchyma without forming a solid tumor mass; (**d**): immunohistochemistry using the monoclonal antibody H09 that selectively binds mutant IDH1 R132 protein (Capper et al., 2009) – single diffusely infiltrating tumor cells in a pGC type II sample became visible

second and 74 % within the third year after onset of symptoms (Jennings et al., 1995). Therefore, the authors of the WHO classification suggest assigning an anaplastic WHO grade III in a majority of cases to patients suffering from GC with a biopsy even showing histologically features of grade II gliomas. They argue that this assignment is justified either due to the wide-ranging expansion of the tumor or due to non-representative tissue obtained by stereotactic biopsy (Louis and International Agency for Research on Cancer, 2007). If necrosis and/or vascular proliferation are present the prognosis corresponds to WHO grade IV and the diagnosis of a glioblastoma (GBM) is mandatory. It has to be noted that the diagnosis of GC can be established by neuropathologists solely if whole brain autopsy material is available. In a biopsy setting the neuropathologists essentially requires radiological information (Jennings et al., 1995).

Established prognostic factors for patients with GC are younger age, higher Karnofsky performance score at first presentation, histologically features corresponding to a WHO grade II in diffuse gliomas, oligodendroglial morphology and losses on 1p (Perkins et al., 2003; Sanson et al., 2004; Taillibert et al., 2006). These factors are the same that are established for diffusely infiltrating gliomas.

General Considerations on Genetic Findings in GC

The unclear origin and relation of GC to other brain tumor entities raised the idea to use genetically markers to obtain further insights. However, all genetic studies are hampered by the infiltrative nature of this tumor entity: the admixture of tumor cells with infiltrative CNS tissue reduces the sensitivity to detect genetic alteration. Furthermore, the majority of tissue probes are rather small because they are obtained by stereotactic biopsies. Therefore, the considerable risk for performing analysis on suboptimal tissue raises the question whether negative readings of genetic studies reflects the lack of alterations in general or whether they are not detected due to a high background noise of constitutional tissue. Presumably due to the assumed relation between GC and astrocytic tumors predominately genetic markers that are frequently altered in low- and high-grade astrocytomas were analysed. The number of studies focusing on genetic alterations in GC is rather low. As well, the number of analyzed samples is those studies is fairly limited.

Alterations of Low Grade Glioma Markers in GC

The *TP53* gene on 17p13.1 encodes the p53 protein that plays a role in different cellular processes including the cell cycle control, DNA damage response, apoptosis, differentiation and neovascularization.p53 becomes expressed and activated after DNA damage and activates as a transcription factor multiple other genes. Mutations in the tumor suppressor gene*TP53*on 17p13.1are common in astrocytomas of the WHO grades II (>60 %) and III (50–60 %) and in secondary glioblastomas (sGBM) (>65 %) and represent an early event in the development of these tumors (Louis and International Agency for Research on Cancer, 2007). One study reported *TP53* mutations in 3 of 7 analyzed GC samples (43 %) (Herrlinger et al., 2002). However, in two different studies that analyzed a larger number of samples *TP53* mutations were only found in 2 of 18 samples (11 %) (Mawrin et al., 2003) and in 3 if 30 samples (10 %) (Seiz et al., 2010). In a single case report by Kros et al. (2002) the same *TP53* mutations was detected in 20 of the 24 analysed tissue samples. In summary, *TP53* mutations were identified by different studies in GC but the frequency of occurrence is lower than in diffusely infiltrating astrocytomas.

Combined losses of 1p and 19q are typically found in oligodendroglial tumors and are associated with a better prognosis (Hartmann et al., 2009). By focusing only on 1p allelic losses were identified in 4 of 10 analyzed samples (40 %). Interestingly, 1p losses were found in 3 of 4 patients who responded to PCV or TMZ chemotherapy but only in 1 of 6 patients who did not. In this study many GC samples with an

oligodendroglial morphology were included. Unfortunately, the authors do not give further information regarding an association between 1p status and oligodendroglial morphology (Sanson et al., 2004). In a series of 24 samples with an astrocytic morphology no combined 1p/19q losses by fluorescence in situ hybridization (FISH) were identified. However, one sample showed an isolated 19q loss, two samples three copies of 19q and three samples demonstrated three or more copies of all analyzed FISH probes (Seiz et al., 2010). Isolated losses or gains on 19q are typically found in malignant astrocytomas (Hartmann et al., 2009).

Mutations of High Grade Glioma Markers in GC

The $p16^{INK4}$ protein encoded by the *CDKN2A* gene on 9p21 is an important player in the control of progression through G1into the S phase of the cell cycle. Homozygous *CDKN2A* deletions are frequently identified in anaplastic astrocytomas WHO grade III. Alterations in genes that encode proteins that control the cell cycle are assumed to be a hallmark alteration for the transition of astrocytomas WHO grade II to anaplasia (Louis and International Agency for Research on Cancer, 2007). This marker for high-grade gliomas was investigated in GC samples as well. However, no significant molecular genetic alteration in *CDKN2A* has been reported so far. In the first so far published study no alteration of *CDKN2A* in the analyzed GC samples was reported (Herrlinger et al., 2002). The second study that focused on the gene identified no homozygous *CDKN2A* deletion but found in 5 of 8 GC samples a heterozygous *CDKN2A* deletion. However, all tumors expressed p16 protein, thereby indicating that these alterations presumably have a moderate importance (Mawrin et al., 2005). The lack of homozygous *CDKN2A* deletion may imply that genetically GC is closer to low grade than high grade diffusely infiltrating gliomas.

The *EGFR* gene on 7p11 encodes the epithelial growth factor receptor that binds ligands like EGF and TGF-α and, thereby, transduces extracellular proliferation signals in the cell. *EGFR* amplification is an event found in approximately 40 % of primary glioblastomas (pGBM) in a lower frequency in anaplastic gliomas (Louis and International Agency for Research on Cancer, 2007). One study failed to detect *EGFR* amplification in 9 analyzed GC samples (Mawrin et al., 2005). In a different study in 1 of 7 GC samples a twofold increase in gene copy number of *EGFR* was reported that was not interpreted to be already gene amplification (Herrlinger et al., 2002).

The *PTEN* gene on 10q23 encodes a protein that dephosphorylates phosphatidylinositol-(3,4,5)-trisphosphate (PIP3) to phosphatidylinositol-(4,5)-bisphosphate (PIP2). Thereby, it antagonizes the activity of the oncogenic phosphatidylinositol-3′-kinases (PI3K) that convert PIP2 to PIP3.PIP3 activates the oncoprotein Akt that regulates multiple other proteins involved in cell cycle progression, cell growth and survival, cell migration, invasion and angiogenesis. Allelic loss of one *PTEN* and a mutation in the remaining copy are found in up to 40 % of pGBM (Louis and International Agency for Research on Cancer, 2007). In 1 of 7 GC samples a *PTEN* mutation was identified (Herrlinger et al., 2002). However, a different study failed to detect any *PTEN* mutation in 18 GC samples (Mawrin et al., 2005). MDM2 promotes the degradation of p53 protein. Amplification of the *MDM2*gene on 12q15 allows the escape from p53-regulated cell growth control and was found in approximately 10 % of pGBM. However, no*MDM2* amplification was reported in 9 GC samples (Mawrin et al., 2005).

In summary, the genetic findings may indicate a relation between GC and low-grade gliomas due to the detection of *TP53* mutations or 1p losses but do not imply that GC is linked to anaplastic astrocytomas WHO grade III or GBM (Sanson et al., 2004; Mawrin, 2005). However, these findings are not that evident that they would allow a conclusion that GC is an exceedingly infiltrative subvariant of an astrocytoma WHO grade II.

IDH1 Mutations in GC

Recently, *IDH1* mutations were identified in 60–90 % of diffusely infiltrating gliomas of the WHO grade II and III (astrocytomas, oligoastrocytomas, oligodendrogliomas) and in sGBM. *IDH1* mutations occur only in around 5 % of pGBM and in nearly no other brain tumor entity (Balss et al., 2008; Parsons et al., 2008; Hartmann et al., 2009; Weller et al., 2009; Wick et al., 2009; Yan et al., 2009; Hartmann et al., 2010). IDH1 protein, localized in the cytosol, and IDH2 protein, localized in mitochondria, catalyses the oxidative decarboxylation of isocitrate to α -ketoglutarate. Instead, mutated IDH1 leads to a simultaneous loss and gain of activities in the production of α-ketoglutarate (α-KG) and 2-hydroxyglutarate (2-HG), respectively (Dang et al., 2009). 2-HG acts in excessive elevated concentrations as a competitive inhibitor of α-KG -dependent dioxygenases like histone demethylases and TET family of 5-methlycytosine (5mC) hydroxylases, thereby leading to various epigenetic alterations (Xu et al., 2011). In the field of diagnosis and glioma classification the detection of *IDH1* mutations allows separation of diffusely infiltrating gliomas from other brain tumors that may share histopathological similarities as demonstrated for example for astrocytomas WHO grade II and pilocytic astrocytomas WHO grade I (Korshunov et al., 2009). Furthermore, patients with diffusely infiltrative gliomas of the WHO grades II to IV carrying an *IDH1* mutation have a significantly longer overall survival compared to patients without *IDH1* mutation (Parsons et al., 2008; Dubbink et al., 2009; Sanson et al., 2009; Weller et al., 2009; Wick et al., 2009; Yan et al., 2009; Hartmann et al., 2010; Houillier et al., 2010).

The detection of *IDH1* mutations in GC may facilitate to draw further conclusions regarding the relation of this tumor entity to diffusely infiltrating gliomas. However, the detection of *IDH1* mutations in 10 of 35 GC samples (29 %) did not allow deductions that extend the knowledge beyond the *TP53*-based findings: some GC samples seem to be related to diffusely infiltrating gliomas while others are not (Seiz et al., 2010). But the same study brought up a different issue: all *IDH1* mutations were found in pGC type II samples, none of the 11 ‘classical’ pGC type I samples without a solid tumor mass carried a mutation. Furthermore, no *TP53* mutation was found in the group of pGC type I samples. These findings indicate that pGC type I tumors are not related to diffusely infiltrating gliomas and that they may indeed constitute a distinct tumor entity. Instead, pGC type II tumors carried in 38 % *IDH1* mutations (Seiz et al., 2010). This mutations frequency indicates a relation to diffusely infiltrating gliomas even though not reaching the frequency of up to 90 % mutations reported for those tumors. These findings in pGC type II can be best explained by a concept that assumes that this subgroup consists of two entities, (i) pGC type I that have progressed towards a solid tumor portion and, (ii) diffuse astrocytomas with a more pronounced infiltration pattern.

Conclusion

Recent molecular findings demonstrated an absence of *IDH1*or *TP53*mutation in pGC type I (Seiz et al., 2010). These findings support the notion that that GC is a heterogeneous group of tumors that may be further subgrouped according to the concept introduced by Jennings (Jennings et al., 1995). Independent support derives from a recent clinical study that demonstrates different outcomes in pGC type I and pGC type II with pGC type I patients being older and having a more favorable outcome (Park et al., 2009). Therefore, it appears necessary to incorporate the GC subgrouping concept from Jennings in the upcoming WHO classification of brain tumors.

In summary these results strengthen the concept that ‘classic’ pGC type I is a tumor entity not related to diffuse astrocytomas WHO grades II and III. With regard to pGC type II it seems important to evaluate in a next step whether these tumors exhibit different clinical courses depending on their *IDH1* status. These analyses can be expected to be of relevance for inclusion criteria of future clinical trials.

References

Artigas J, Cervos-Navarro J, Iglesias JR, Ebhardt G (1985) Gliomatosis cerebri: clinical and histological findings. Clin Neuropathol 4:135–148

Balss J, Meyer J, Mueller W, Korshunov A, Hartmann C, von Deimling A (2008) Analysis of the IDH1 codon 132 mutation in brain tumors. Acta Neuropathol 6:597–602

Capper D, Zentgraf H, Balss J, Hartmann C, von Deimling A (2009) Monoclonal antibody specific for IDH1 R132H mutation. Acta Neuropathol 5:599–601

Cervos-Navarro J, Artigas J, Aruffo C, Iglesias J (1987) The fine structure of gliomatosis cerebri. Virchows Arch A Pathol Anat Histopathol 1:93–98

Dang L, White DW, Gross S, Bennett BD, Bittinger MA, Driggers EM, Fantin VR, Jang HG, Jin S, Keenan MC, Marks KM, Prins RM, Ward PS, Yen KE, Liau LM, Rabinowitz JD, Cantley LC, Thompson CB, Vander Heiden MG, Su SM (2009) Cancer-associated IDH1 mutations produce 2-hydroxyglutarate. Nature 7274:739–744

Dubbink HJ, Taal W, van Marion R, Kros JM, van Heuvel I, Bromberg JE, Zonnenberg BA, Zonnenberg CB, Postma TJ, Gijtenbeek JM, Boogerd W, Groenendijk FH, Smitt PA, Dinjens WN, van den Bent MJ (2009) IDH1 mutations in low-grade astrocytomas predict survival but not response to temozolomide. Neurology 21:1792–1795

Hartmann C, Meyer J, Balss J, Capper D, Mueller W, Christians A, Felsberg J, Wolter M, Mawrin C, Wick W, Weller M, Herold-Mende C, Unterberg A, Jeuken JW, Wesseling P, Reifenberger G, von Deimling A (2009) Type and frequency of IDH1 and IDH2 mutations are related to astrocytic and oligodendroglial differentiation and age: a study of 1,010 diffuse gliomas. Acta Neuropathol 4:469–474

Hartmann C, Hentschel B, Wick W, Capper D, Felsberg J, Simon M, Westphal M, Schackert G, Meyermann R, Pietsch T, Reifenberger G, Weller M, Loeffler M, von Deimling A (2010) Patients with IDH1 wild type anaplastic astrocytomas exhibit worse prognosis than IDH1-mutated glioblastomas, and IDH1 mutation status accounts for the unfavorable prognostic effect of higher age: implications for classification of gliomas. Acta Neuropathol 6:707–718

Herrlinger U, Felsberg J, Kuker W, Bornemann A, Plasswilm L, Knobbe CB, Strik H, Wick W, Meyermann R, Dichgans J, Bamberg M, Reifenberger G, Weller M (2002) Gliomatosis cerebri: molecular pathology and clinical course. Ann Neurol 4:390–399

Houillier C, Wang X, Kaloshi G, Mokhtari K, Guillevin R, Laffaire J, Paris S, Boisselier B, Idbaih A, Laigle-Donadey F, Hoang-Xuan K, Sanson M, Delattre JY (2010) IDH1 or IDH2 mutations predict longer survival and response to temozolomide in low-grade gliomas. Neurology 75(17):1560–1566

Jennings MT, Frenchman M, Shehab T, Johnson MD, Creasy J, LaPorte K, Dettbarn WD (1995) Gliomatosis cerebri presenting as intractable epilepsy during early childhood. J Child Neurol 1:37–45

Kleihues P, Cavenee WK (2000) Pathology and genetics of tumours of the nervous system. IARC Press, Lyon

Kleihues P, Burger PC, Scheithauer BW, Zülch KJ (1993) Histological typing of tumours of the central nervous system. Springer, Berlin/Heidelberg/New York

Korshunov A, Meyer J, Capper D, Christians A, Remke M, Witt H, Pfister S, von Deimling A, Hartmann C (2009) Combined molecular analysis of BRAF and IDH1 distinguishes pilocytic astrocytoma from diffuse astrocytoma. Acta Neuropathol 3:401–405

Kros JM, Zheng P, Dinjens WN, Alers JC (2002) Genetic aberrations in gliomatosis cerebri support monoclonal tumorigenesis. J Neuropathol Exp Neurol 9:806–814

Louis DN, International Agency for Research on Cancer (2007) WHO classification of tumours of the central nervous system. International Agency for Research on Cancer, Lyon

Mawrin C (2005) Molecular genetic alterations in gliomatosis cerebri: what can we learn about the origin and course of the disease? Acta Neuropathol 6:527–536

Mawrin C, Kirches E, Schneider-Stock R, Scherlach C, Vorwerk C, Von Deimling A, Van Landeghem F, Meyermann R, Bornemann A, Muller A, Romeike B, Stoltenburg-Didinger G, Wickboldt J, Pilz P, Dietzmann K (2003) Analysis of TP53 and PTEN in gliomatosis cerebri. Acta Neuropathol 6:529–536

Mawrin C, Kirches E, Schneider-Stock R, Boltze C, Vorwerk CK, von Mawrin A, von Deimling A, Stoltenburg-Didinge G, Bornemann A, Romeike B, Sellhaus B, Dietzmann K (2005) Alterations of cell cycle regulators in gliomatosis cerebri. J Neurooncol 2:115–122

Nevin S (1938) Gliomatosis cerebri. Brain 61:170–191

Park S, Suh YL, Nam DH, Kim ST (2009) Gliomatosis cerebri: clinicopathologic study of 33 cases and comparison of mass forming and diffuse types. Clin Neuropathol 2:73–82

Parsons DW, Jones S, Zhang X, Lin JC, Leary RJ, Angenendt P, Mankoo P, Carter H, Siu IM, Gallia GL, Olivi A, McLendon R, Rasheed BA, Keir S, Nikolskaya T, Nikolsky Y, Busam DA, Tekleab H, Diaz LA Jr, Hartigan J, Smith DR, Strausberg RL, Marie SK, Shinjo SM, Yan H, Riggins GJ, Bigner DD, Karchin R, Papadopoulos N, Parmigiani G, Vogelstein B, Velculescu VE, Kinzler KW (2008) An integrated genomic analysis of human glioblastoma multiforme. Science 5897:1807–1812

Perkins GH, Schomer DF, Fuller GN, Allen PK, Maor MH (2003) Gliomatosis cerebri: improved outcome with radiotherapy. Int J Radiat Oncol Biol Phys 4:1137–1146

Sanson M, Cartalat-Carel S, Taillibert S, Napolitano M, Djafari L, Cougnard J, Gervais H, Laigle F, Carpentier A, Mokhtari K, Taillandier L, Chinot O, Duffau H,

Honnorat J, Hoang-Xuan K, Delattre JY (2004) Initial chemotherapy in gliomatosis cerebri. Neurology 2:270–275

Sanson M, Marie Y, Paris S, Idbaih A, Laffaire J, Ducray F, El Hallani S, Boisselier B, Mokhtari K, Hoang-Xuan K, Delattre JY (2009) Isocitrate dehydrogenase 1 codon 132 mutation is an important prognostic biomarker in gliomas. J Clin Oncol 25:4150–4154

Schober R, Mai JK, Volk B, Wechsler W (1991) Gliomatosis cerebri: bioptical approach and neuropathological verification. Acta Neurochir (Wien) 3–4:131–137

Seiz M, Tuettenberg J, Meyer J, Essig M, Schmieder K, Mawrin C, von Deimling A, Hartmann C (2010) Detection of IDH1 mutations in gliomatosis cerebri, but only in tumors with additional solid component: evidence for molecular subtypes. Acta Neuropathol 2:261–267

Taillibert S, Chodkiewicz C, Laigle-Donadey F, Napolitano M, Cartalat-Carel S, Sanson M (2006) Gliomatosis cerebri: a review of 296 cases from the ANOCEF database and the literature. J Neurooncol 2:201–205

Vates GE, Chang S, Lamborn KR, Prados M, Berger MS (2003) Gliomatosis cerebri: a review of 22 cases. Neurosurgery 2:261–271, discussion 271

Weller M, Felsberg J, Hartmann C, Berger H, Steinbach JP, Schramm J, Westphal M, Schackert G, Simon M, Tonn JC, Heese O, Krex D, Nikkhah G, Pietsch T, Wiestler O, Reifenberger G, von Deimling A, Loeffler M (2009) Molecular predictors of progression-free and overall survival in patients with newly diagnosed glioblastoma: a prospective translational study of the German glioma network. J Clin Oncol 34:5743–5750

Wick W, Hartmann C, Engel C, Stoffels M, Felsberg J, Stockhammer F, Sabel MC, Koeppen S, Ketter R, Meyermann R, Rapp M, Meisner C, Kortmann RD, Pietsch T, Wiestler OD, Ernemann U, Bamberg M, Reifenberger G, von Deimling A, Weller M (2009) NOA-04 randomized phase III trial of sequential radiochemotherapy of anaplastic glioma with procarbazine, lomustine, and vincristine or temozolomide. J Clin Oncol 35:5874–5880

Xu W, Yang H, Liu Y, Yang Y, Wang P, Kim SH, Ito S, Yang C, Xiao MT, Liu LX, Jiang WQ, Liu J, Zhang JY, Wang B, Frye S, Zhang Y, Xu YH, Lei QY, Guan KL, Zhao SM, Xiong Y (2011) Oncometabolite 2-hydroxyglutarate is a competitive inhibitor of alpha-ketoglutarate-dependent dioxygenases. Cancer Cell 1:17–30

Yan H, Parsons DW, Jin G, McLendon R, Rasheed BA, Yuan W, Kos I, Batinic-Haberle I, Jones S, Riggins GJ, Friedman H, Friedman A, Reardon D, Herndon J, Kinzler KW, Velculescu VE, Vogelstein B, Bigner DD (2009) IDH1 and IDH2 mutations in gliomas. N Engl J Med 8:765–773

Zülch KJ, World Health Organization (1979) Histological typing of tumours of the central nervous system. World Health Organization, Geneva

Impact of Bevacizumab Chemotherapy on Glioblastomas

8

Brandyn A. Castro and Manish K. Aghi

Contents

Abstract

Glioblastomas are the most common primary tumor of the brain. These tumors are differentiated from other tumors because of their highly vascularized nature, making them a prime target for anti-angiogenic therapies. Multiple phase II trials have investigated the efficacy of bevacizumab (Avastin), an antibody targeting vascular endothelial growth factor (VEGF), on recurrent glioblastomas. The beneficial results of bevacizumab in these studies have led to randomized Phase III trials looking at the impact of using bevacizumab at the time of diagnosis by adding it to the standard Stupp protocol of radiation therapy plus 6 months of temozolomide. Due to the fact that there continues to be a fraction of patients who do not respond or have disease progression while on bevacizumab therapy as well as patients who experience side effects of bevacizumab requiring stoppage of treatment, future studies will be needed to determine, potentially by gene expression studies, the best candidates for this targeted therapy.

Introduction

Glioblastomas carry a poor prognosis with a median survival of 12 months and a 3-year survival of 3–5 % (Krex et al., 2007). Treatment for these aggressive tumors requires a multifaceted approach including surgery, radiation, and chemotherapy. Surgery is done with the primary

B.A. Castro
Department of Neurological Surgery and Hellen Diller Family Comprehensive Cancer Center, University of California, San Francisco, CA 94143-0112, USA

M.K. Aghi (✉)
UCSF Neurosurgery, 505 Parnassus Avenue Room M779, San Francisco, CA 94143-0112, USA
e-mail: AghiM@neurosurg.ucsf.edu

M.A. Hayat (ed.), *Tumors of the Central Nervous System, Volume 11*,
DOI 10.1007/978-94-007-7037-9_8,

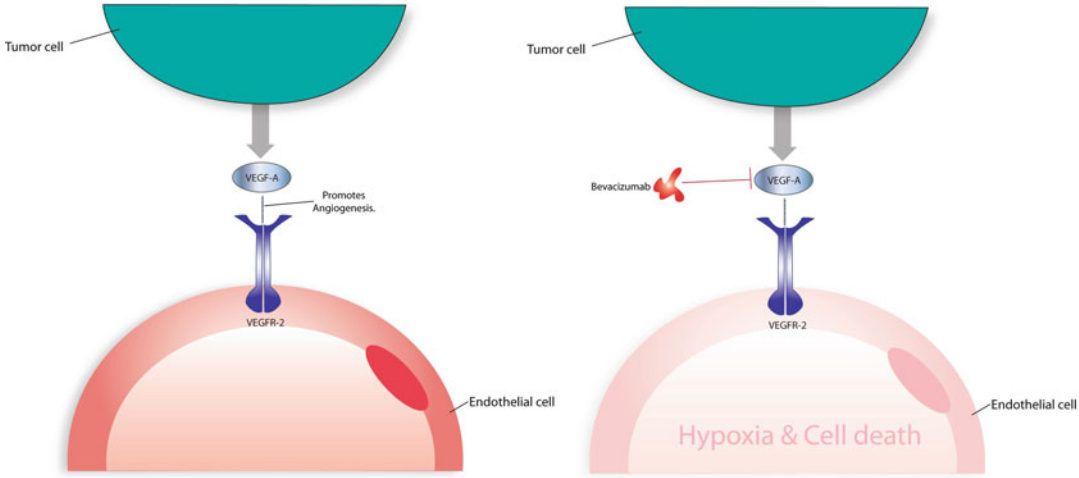

Fig. 8.1 Mechanism of action of bevacizumab. Bevacizumab is a neutralizing antibody that binds vascular endothelial growth factor-A (VEGF-A), which is produced mostly by tumor cells and promotes the health and viability of endothelial cells by binding VEGF receptors (VEGFRs), mostly VEGFR-2

purpose of debulking the mass. Inevitably neoplastic cells are left behind, even at a microscopic level after radiographic gross total resection, which is why these additional therapies are necessary. The process of oncogenesis is one that includes initiation which involves cell cycle mutations, promotion where these mutations are copied, and progression where invasion and migration of these cells takes place (Michor et al., 2004). Progression may also encompass the concept of further mutations for drug resistance, a process which causes much difficulty when treating glioblastomas (Michor et al., 2004). Signal transduction agents, in particular, are drugs that target various signals in the tumor progression sequence including tumor cell proliferation, survival/apoptosis, and invasion/migration as well as angiogenesis. The highly vascular nature of glioblastomas makes them a prime target for the monoclonal mouse anti-human VEGF antibody bevacizumab (Avastin), which inhibits angiogenesis (Fig. 8.1). With tumoral VEGF-A levels approximately 30-fold higher in patients with glioblastoma when compared to lower-grade astrocytomas, VEGF is recognized as a particularly important factor in the vascularity of glioblastomas (Narayana et al., 2012). Bevacizumab is most effective against solid tumors such as renal cell cancer and metastatic colorectal cancer. In May of 2009, based on the results of phase II clinical trials showing efficacy of bevacizumab as monotherapy for recurrent glioblastomas, bevacizumab was granted accelerated FDA approval for recurrent glioblastomas (Cohen et al., 2009), the approval designated accelerated because it was done without the completion of a randomized phase III trial.

Impact of Bevacizumab on Progression Free and Overall Survival of Glioblastoma Patients

Clinical trials to date have mostly investigated bevacizumab plus topoisomerase inhibitor irinotecan (CPT-11) in recurrent glioblastoma treatment. Bevacizumab monotherapy, which has been studied less frequently, results in a 6 month progression free survival (PFS) of 33.9–42.6 %, values that are significantly ($p = 0.017$) more than the 15 % baseline PFS rates without bevacizumab (Friedman et al., 2009; Nagane et al., 2012). Radiographic response was measured at 71 %

based on Levin criteria, which considers edema and mass effect in addition to enhancement, and 35 % based on Macdonald criteria, which measures enhancing volume (Kreisl et al., 2009). Tumor shrinkage was measured to be 72.4 % in a second study, however only 27.6 % were considered responders based on MacDonald criteria (Nagane et al., 2012), with response defined as greater than 50 % decrease in tumor volume measured by the product of two diameters on the MRI scan performed more than 4 weeks after observed response.

In one study, concurrent use of corticosteroids tended to decrease response in patients treated with bevacizumab (Friedman et al., 2009; Nagane et al., 2012). While the mechanisms by which concurrent dexamethasone use lessens response in that study are not entirely clear, bevacizumab reduces cerebral edema, which should enable bevacizumab-treated glioblastoma patients to be managed on a reduced dose of dexamethasone (Kreisl et al., 2009).

Irinotecan is a topoisomerase I inhibitor that has been shown to be effective against malignant gliomas in combination with bevacizumab. Irinotecan is not very effective by itself but results of irinotecan plus bevacizumab are more promising (Vredenburgh et al., 2007b). The reason for the promising interaction between bevacizumab and irinotecan is not certain, but could involve anti-angiogenic bevacizumab increasing uptake of irinotecan into the CNS or could involve the ability of irinotecan to target differentiated tumor cells while bevacizumab targets glioma stems cells (Bao et al., 2006).

Studies combining bevacizumab and irinotecan have shown the 6 month PFS & overall survival (OS) of 38–50.3 % and 72–77 % respectively (Vredenburgh et al., 2007a, b; Friedman et al., 2009). PFS was 29 % with bevacizumab versus 46 % with the combination of bevacizumab plus irinotecan (Vredenburgh et al., 2007b; Kreisl et al., 2009). Using the Macdonald criteria, response rates for monotherapy were 35 % and dual therapy was 57 % (Vredenburgh et al., 2007b; Kreisl et al., 2009). The difference between these two studies was not statistically significant so it is unclear whether irinotecan adds additional benefit to bevacizumab. Although it has not been proven to be statistically significant, younger glioblastoma patients tend to have better PFS and OS after bevacizumab treatment (Nagane et al., 2012).

Adverse Effects of Bevacizumab

Common side effects of bevacizumab usage have included fatigue (45 %), headache (37 %), hypertension (30 %), nose bleeds (19 %), thromboembolic events (13 %), proteinuria (5 %), and intracranial hemorrhage (2 %) (Kreisl et al., 2009). Arterial and venous thromboembolic events can lead to respiratory distress with evidence of deep venous thrombosis and pulmonary emboli (Kreisl et al., 2009). In one study, 6 patients (12.5 %) suffered a thromboembolic event including 3 with pulmonary emboli and 1 with a cerebrovascular event (Kreisl et al., 2009). Related studies of bevacizumab monotherapy have established an arterial thromboembolism rate of 2.4 % and a venous thromboembolism rate of 3.2–3.6 % (Friedman et al., 2009; Nagane et al., 2012).

Would healing is critical for patients with glioblastomas who often undergo 2 or 3 craniotomies during their lifetime. In looking at 209 patients who underwent a second or third craniotomy for glioblastoma recurrence, rates of wound healing complications were significantly ($p = 0.004$) increased in patients receiving preoperative bevacizumab when compared to a non-bevacizumab-treated group (Clark et al., 2011). Of the 168 patients who did not receive bevacizumab, 17 (10 %) developed wound healing complications. Eight (35 %) of the 23 patients who received preoperative bevacizumab had impaired healing, as evidenced by infection, dehiscence, cerebrospinal fluid leakage, pseudomeningocele formation, or osteomyelitis. No significant difference was found between wound healing in patients treated with postoperative bevacizumab and the non-bevacizumab-treated group, leading to the conclusion that bevacizumab therapy significantly impairs wound healing when used preoperatively, but not when used postoperatively (Clark et al., 2011).

Resistance to Bevacizumab

Disease progression while receiving bevacizumab monotherapy for tumor recurrence can reach 37 %, suggesting the ability of this tumor to grow and obtain sufficient blood supply in the presence of this anti-VEGF antibody (Vredenburgh et al., 2007a). While bevacizumab targets only one member in the VEGF family, VEGF-A, angiogenesis could continue with the assistance of other VEGF receptors or angiogenic growth factors (Vredenburgh et al., 2007a). Proposed mechanisms of bevacizumab resistance have included recruitment of bone marrow-derived cells, increased invasion, use of alternative pro-angiogenic stimuli, and alteration of vascular architecture (Jahangiri and Aghi, 2012). In keeping with these bevacizumab resistance mechanisms, which are distinct from resistance mechanisms to conventional DNA damaging chemotherapy, imaging after bevacizumab resistance is non-enhancing and bright on FLAIR sequences (Fig. 8.2), felt by many to represent infiltrative growth (Norden et al., 2008; DeLay et al., 2012).

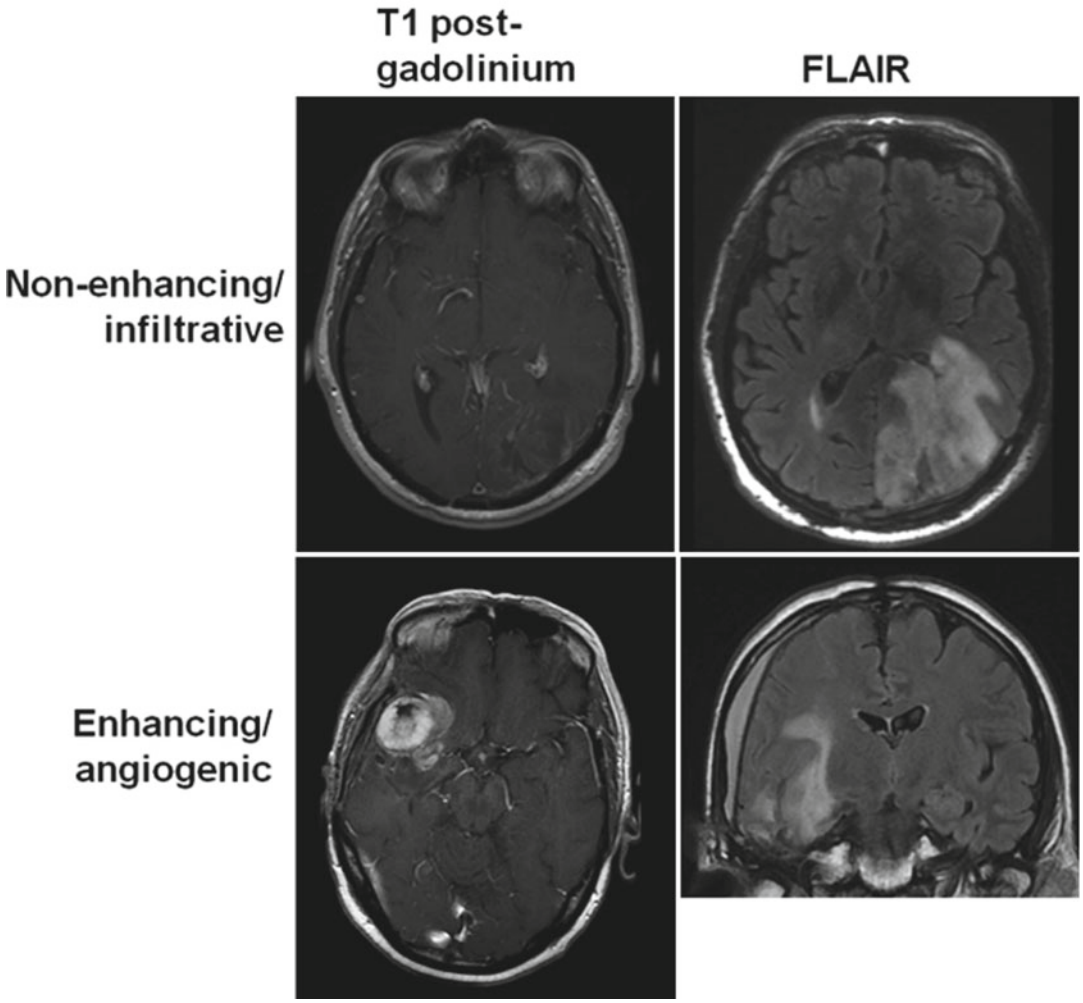

Fig. 8.2 Imaging seen during progression on bevacizumab. Magnetic resonance imaging (MRI) showing two different types of radiographic progression during bevacizumab treatment. The first is non-enhancing/infiltrative (*upper row*) with minimal enhancement seen on T1 post-gadolinium images (*upper left corner*) and FLAIR bright imaging (*upper right corner*). The second is enhancing/angiogenic (*lower row*) with robust enhancement seen on T1 post-gadolinium images (*lower left corner*) and FLAIR bright imaging matching the T1 post-gadolinium images (*lower right corner*)

Bevacizumab at Diagnosis Versus Recurrence

Progress observed with bevacizumab therapy at recurrence has led to considerations regarding whether adding it to the standard Stupp protocol at the time of diagnosis would result in better patient outcomes. Initial phase II trials have resulted in a 6 month PFS of 85–88 %, a value far exceeding the 53.9 % seen with the standard Stupp protocol and the 33.9 % observed when bevacizumab monotherapy is used at the time of recurrence (Stupp et al., 2005; Lai et al., 2011; Nagane et al., 2012; Narayana et al., 2012). OS with the addition of bevacizumab at diagnosis ranged from 19 to 23 months (Lai et al., 2011; Narayana et al., 2012). One study used the Stupp protocol at diagnosis and bevacizumab at recurrence. Results of a median OS of 21.1 months in this comparison trial and 14.6 months in the EORTC/NCIC standard protocol study emphasize minimal additional benefit of bevacizumab to OS (Lai et al., 2011). The possibility that there may be more limited benefit when using bevacizumab at diagnosis rather than at recurrence carries over when comparing the OS of 19–23 months to the 31 months seen with bevacizumab at recurrence (Kreisl et al., 2009). Using bevacizumab at the time of diagnosis has a favorable outcome when analyzing 6 month PFS, however, it fails to show any benefit to the OS of patients at this point in time. PFS improving while OS remains the same between patients with and without bevacizumab therapy is a common theme due to the criteria in which it is evaluated. Historically the MacDonald criteria have been used to identify glioblastoma progression and are based primarily on enhancing tumor volume seen on MRI but also include clinical assessment and corticosteroid dose (Wen et al., 2010). A recent advance has been the creation of the Response Assessment in Neuro-Oncology (RANO) criteria which incorporates T2/FLAIR imaging to compensate for some of the limitations of MacDonald Criteria (Wen et al., 2010). It has proven to more accurately correlate with OS in patients treated with antiangiogenic therapy because these patients have nonenhancing tumor progression that would not be documented with the MacDonald Criteria.

Surgery Alone at Recurrence

To fully understand the impact of bevacizumab treatment on recurrent glioblastoma, outcomes with surgery for recurrence need to be determined. One study suggests no additional benefit of surgery at recurrence, indicating that PFS at 6 months and OS were comparable between groups with and without surgical resection at the time of tumor progression (Clarke et al., 2011). Extent of resection (EOR) is the most important indicator of overall survival when surgical resection is used as the primary therapy at the time of recurrence (Bloch et al., 2012). In another study, further division of EOR into gross total resection (GTR) and subtotal resection (STR) was used to evaluate 107 patients with recurrent glioblastoma treated with surgery. All patients were initially managed with surgical resection and standard Stupp protocol. In this study, gross total resection (GTR) was defined as >95 % of the tumor volume removed on postoperative MRI, while subtotal resection (STR) was defined as <95 % of the tumor volume resected. The median length of survival was 20.0 months for those who received GTR at recurrence and 16.6 months for those with STR at recurrence ($p=0.01$). Obtaining GTR at recurrence maximizes survival regardless of initial EOR, however even when GTR is obtained, the majority of tumors still recur (Clarke et al., 2011).

Surgery Versus Bevacizumab for Recurrent Glioblastoma

Surgical treatment of glioblastomas at the time of progression may provide minimal benefit. When surgical resection is paired with bevacizumab at the time of recurrence, patients have an improved prognosis. There are risks to the addition of this therapy that include thromboembolic events, impaired wound healing, intracranial hemorrhage, and resistance to therapy. In order to minimize adverse outcomes, patients with intracranial

hemorrhage on imaging should not be candidates for bevacizumab therapy. In one study of bevacizumab and irinotecan in recurrent glioblastomas, after these patients with intracranial hemorrhage were excluded, no patients developed this complication after treatment was initiated (Vredenburgh et al., 2007a). Ensuring tight blood pressure control, by conservative or pharmacologic means, in all patients taking bevacizumab is also important to decrease risks of bevacizumab-induced hypertension and associated intracranial hemorrhage.

Future studies should attempt to define biomarkers predicting response or resistance to bevacizumab (Jahangiri and Aghi, 2012), as doing so would reduce the wasted expense of treating a tumor that would be unlikely to respond to bevacizumab.

With the aforementioned precautions and preemptive measures taken into account, patients can appropriately be targeted for bevacizumab therapy and minimize any risks of side effects. Regardless of these measures, the risks of bevacizumab therapy are deemed reasonable for patients with glioblastomas. Surgery alone at the time of recurrence is not sufficient. Additional therapy is needed to improve prognosis and currently bevacizumab is one such medication with multiple phase II trials in support of the benefit it provides to patients with recurrent glioblastomas.

The Future of Bevacizumab for Glioblastoma Treatment

A pair of randomized phase III clinical trial, one in Europe and one in North America, are underway looking at using the Stupp protocol with or without bevacizumab at the time of diagnosis. These trials are empowered to determine whether bevacizumab should be incorporated into the standard treatment of newly diagnosed glioblastoma. With nearly 1,000 patients per trial and incorporation of the RANO criteria, these trials could also determine if there are subsets of glioblastomas defined by patient age or tumor molecular features best served by the use of bevacizumab at the time of diagnosis.

Conclusion

A thorough understanding of tumorigenesis has proved the crucial role of angiogenesis in the aggressive progression of glioblastomas. The VEGF inhibitor bevacizumab directly targets this mechanism and phase II trials have shown that the addition of this drug has led to increased 6 month PFS and OS at the time of recurrence. Such progress has led to phase II trials looking at the effects of bevacizumab use at the time of diagnosis, in combination with radiation and temozolomide. Preliminary evidence looks promising, with increased 6 month PFS and OS. Phase III trials are currently underway to investigate the impact of bevacizumab at the time of diagnosis compared to at the time of recurrence. Bevacizumab is an important therapeutic agent for glioblastomas with the benefits outweighing any potential risks based on evidence to date.

References

Bao S, Wu Q, Sathornsumetee S, Hao Y, Li Z, Hjelmeland AB, Shi Q, McLendon RE, Bigner DD, Rich JN (2006) Stem cell-like glioma cells promote tumor angiogenesis through vascular endothelial growth factor. Cancer Res 66(16):7843–7848

Bloch O, Han SJ, Cha S, Sun MZ, Aghi MK, McDermott MW, Berger MS, Parsa AT (2012) Impact of extent of resection for recurrent glioblastoma on overall survival. J Neurosurg 117(6):1032–1038

Cohen MH, Shen YL, Keegan P, et al (2011) FDA drug approval summary: bevacizumab (Bevacizumab) as treatment of recurrent glioblastoma multiforme. Oncologist 14(11):1131–1138

Clark AJ, Butowski NA, Chang SM, Prados MD, Clarke J, Polley MY, Sughrue ME, McDermott MW, Parsa AT, Berger MS, Aghi MK (2011) Impact of bevacizumab chemotherapy on craniotomy wound healing. J Neurosurg 114(6):1609–1616

Clarke JL, Ennis MM, Yung WK, Chang SM, Wen PY, Cloughesy TF, Deangelis LM, Robins HI, Lieberman FS, Fine HA, Abrey L, Gilbert MR, Mehta M, Kuhn JG, Aldape KD, Lamborn KR, Prados MD (2011) Is surgery at progression a prognostic marker for improved 6-month progression-free survival or overall survival for patients with recurrent glioblastoma? Neuro Oncol 13(10):1118–1124

DeLay M, Jahangiri A, Carbonell WS, Hu YL, Tsao S, Tom MW, Paquette J, Tokuyasu TA, Aghi MK (2012) Microarray analysis verifies two distinct phenotypes

of glioblastomas resistant to antiangiogenic therapy. Clin Cancer Res 18(10):2930–2942

Friedman HS, Prados MD, Wen PY, Mikkelsen T, Schiff D, Abrey LE, Yung WK, Paleologos N, Nicholas MK, Jensen R, Vredenburgh J, Huang J, Zheng M, Cloughesy T (2009) Bevacizumab alone and in combination with irinotecan in recurrent glioblastoma. J Clin Oncol 27(28):4733–4740

Jahangiri A, Aghi MK (2012) Biomarkers predicting tumor response and evasion to anti-angiogenic therapy. Biochim Biophys Acta 1825(1):86–100

Kreisl TN, Kim L, Moore K, Duic P, Royce C, Stroud I, Garren N, Mackey M, Butman JA, Camphausen K, Park J, Albert PS, Fine HA (2009) Phase II trial of single-agent bevacizumab followed by bevacizumab plus irinotecan at tumor progression in recurrent glioblastoma. J Clin Oncol 27(5):740–745

Krex D, Klink B, Hartmann C, von Deimling A, Pietsch T, Simon M, Sabel M, Steinbach JP, Heese O, Reifenberger G, Weller M, Schackert G (2007) Long-term survival with glioblastoma multiforme. Brain 130(Pt 10):2596–2606

Lai A, Tran A, Nghiemphu PL, Pope WB, Solis OE, Selch M, Filka E, Yong WH, Mischel PS, Liau LM, Phuphanich S, Black K, Peak S, Green RM, Spier CE, Kolevska T, Polikoff J, Fehrenbacher L, Elashoff R, Cloughesy T (2011) Phase II study of bevacizumab plus temozolomide during and after radiation therapy for patients with newly diagnosed glioblastoma multiforme. J Clin Oncol 29(2):142–148

Michor F, Iwasa Y, Nowak MA (2004) Dynamics of cancer progression. Nat Rev Cancer 4(3):197–205

Nagane M, Nishikawa R, Narita Y, Kobayashi H, Takano S, Shinoura N, Aoki T, Sugiyama K, Kuratsu J, Muragaki Y, Sawamura Y, Matsutani M (2012) Phase II study of single-agent bevacizumab in Japanese patients with recurrent malignant glioma. Jpn J Clin Oncol 42(10): 887–895

Narayana A, Gruber D, Kunnakkat S, Golfinos JG, Parker E, Raza S, Zagzag D, Eagan P, Gruber ML (2012) A clinical trial of bevacizumab, temozolomide, and radiation for newly diagnosed glioblastoma. J Neurosurg 116(2):341–345

Norden AD, Young GS, Setayesh K, Muzikansky A, Klufas R, Ross GL, Ciampa AS, Ebbeling LG, Levy B, Drappatz J, Kesari S, Wen PY (2008) Bevacizumab for recurrent malignant gliomas: efficacy, toxicity, and patterns of recurrence. Neurology 70(10):779–787

Stupp R, Mason WP, van den Bent MJ, Weller M, Fisher B, Taphoorn MJ, Belanger K, Brandes AA, Marosi C, Bogdahn U, Curschmann J, Janzer RC, Ludwin SK, Gorlia T, Allgeier A, Lacombe D, Cairncross JG, Eisenhauer E, Mirimanoff RO (2005) Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. N Engl J Med 352(10):987–996

Vredenburgh JJ, Desjardins A, Herndon JE, Dowell JM, Reardon DA, Quinn JA, Rich JN, Sathornsumetee S, Gururangan S, Wagner M, Bigner DD, Friedman AH, Friedman HS (2007a) Phase II trial of bevacizumab and irinotecan in recurrent malignant glioma. Clin Cancer Res 13(4):1253–1259

Vredenburgh JJ, Desjardins A, Herndon JE 2nd, Marcello J, Reardon DA, Quinn JA, Rich JN, Sathornsumetee S, Gururangan S, Sampson J, Wagner M, Bailey L, Bigner DD, Friedman AH, Friedman HS (2007b) Bevacizumab plus irinotecan in recurrent glioblastoma multiforme. J Clin Oncol 25(30):4722–4729

Wen PY, Macdonald DR, Reardon DA, Cloughesy TF, Sorensen AG, Galanis E, Degroot J, Wick W, Gilbert MR, Lassman AB, Tsien C, Mikkelsen T, Wong ET, Chamberlain MC, Stupp R, Lamborn KR, Vogelbaum MA, van den Bent MJ, Chang SM (2010) Updated response assessment criteria for high-grade gliomas: response assessment in neuro-oncology working group. J Clin Oncol 28(11):1963–1972

Glioblastoma Microvesicles Transport RNA and Proteins, Promoting Tumor Growth

9

David Gonda, Amit Goyal, Johnny Akers, Clark Chen, and Bob Carter

Contents

Abstract

The recent discovery that tumor-derived proteins and nucleic acid are carried in nano-sized vesicles in the plasma of patients with brain tumors has expanded opportunities for biomarker discovery and therapeutics. Through delivery of their contents to surrounding cells, these small extra-cellular vesicles secreted by tumors including glioblastomas are able to modulate their environment to promote tumor growth and survival. In this chapter, we discuss the potential use of small microvesicles as sources of tumor-specific biomarkers, mediators of therapy, and treatment monitoring. We review the normal physiology of these vesicles, their characterization, and new directions for research in this interesting field.

Introduction

Exosomes are small endosome-derived vesicles that are 40–100 nm in diameter, and as reviewed by Cocucci et al. (2009), have been isolated from many biological fluids including blood, urine, and cerebrospinal fluid. Various methods have been used to isolate exosomes. The most commonly employed method involves serial differential centrifugation to remove large debris followed by a high-speed ultracentrifugation to pellet the nano-sized vesicles, while other methods described include the use of filters, sucrose gradient suspensions, immunoisolation employing magnetic beads

D. Gonda • A. Goyal • J. Akers • C. Chen
B. Carter (✉)
UCSD Neurosurgery, 3855 Health Science Drive #0987, San Diego, CA 92093, USA
e-mail: bobcarter@ucsd.edu

M.A. Hayat (ed.), *Tumors of the Central Nervous System, Volume 11*,
DOI 10.1007/978-94-007-7037-9_9,

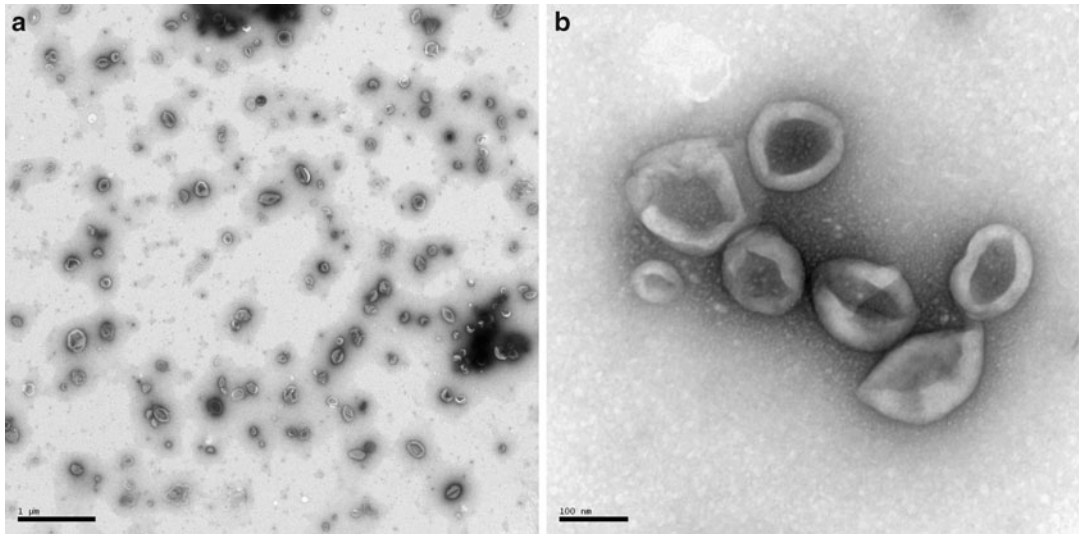

Fig. 9.1 Scanning electron microscopic images of exosomes isolated by serial centrifugation of cerebrospinal fluid at lower (**a**) and higher (**b**) magnifications. Higher magnification shows the typical cupped disc shape of the exosome

coated with specific antibodies, microfluids, or some combination of the above (Chen et al., 2010) (Fig. 9.1a, b). Exosomes are formed through the invagination of the limiting membrane of late endosomes creating intraluminal vesicles within multivesicular bodies. Multivesicular bodies then fuse with the plasma membrane to release their contents into the extracellular space through exocytosis (Fig. 9.2a). While the secretion of exosomes is ongoing in normal physiologic health, cancer cells have been observed to produce and release exosomes at a much more rapid rate than normal cells, as much as 4 times faster in the case of medulloblastoma cells with 100–300 fold more RNA content (Balaj et al., 2011).

Another group of extra-cellular vesicles are shedding microvesicles (SMVs), which are outwardly shed from the plasma membrane. Cocucci et al. (2009) reviewed some differences between exosomes and SMVs, which are larger than exosomes, measuring 100 nm–1 μm in diameter, and have distinctly different origins. SMVs do not originate from endosomal multivesicular bodies like exosomes but are formed through the direct outward budding of cytoplasmic protrusions which are released into the extracellular milieu after fission of their connecting stalk at the plasma membrane (Fig. 9.2b). Because of their closeness in size, similarity in isolation methods, and the scarcity of reliable distinguishing markers between the two, shedding microvesicles are frequently included in the analytic descriptions of exosomes. The terminology for describing shedding microvesicles to distinguish them from other extracellular vesicles such as apoptotic bodies, retro-viral like vesicle, and exosomes is controversial. For the purposes of this chapter we will use the term microvesicles to include both exosomes and shedding microvesicles together, unless otherwise specified.

Exosome Characterization

Exosomes are composed of a cytosolic fluid collection encapsulated by a lipid bilayer membrane embedded with membranous proteins in common with their cell of origin. Packaged inside of exosomes are a selected collection of cytosolic proteins and both coding and non-coding genetic material, including RNA and DNA. Though exosomes contain both proteins and genomic material they do not have the components necessary for protein synthesis. The high prevalence of certain

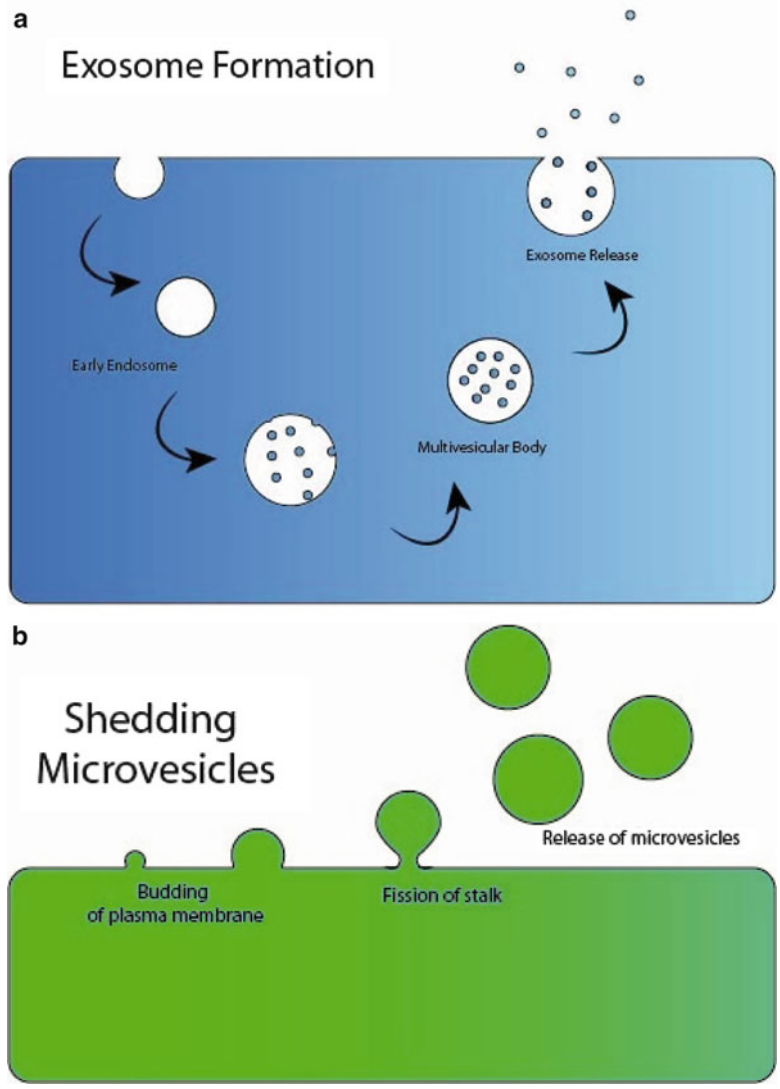

Fig. 9.2 Formation of exosomes (**a**): Invaginations of the cell plasma membrane form the early endosome. Subsequent invagination of the early endosome membrane forms multiple endosomal vesicles, creating the multivesicular body (MVB). The MVB fuses with the plasma membrane to release its vesicular contents extracellularly as exosomes. Formation of shedding microvesicles (**b**): Shedding vesicles of varying size (generally >100 nm) bud off the plasma membrane to be released into the extracellular space upon fission of the connecting stalk

transmembrane proteins such as the tetraspanins (particularly CD9 and CD63), Alix, LAMP1, LAMP2B, and TSG101 are considered exosomal markers and are sometimes used in exosome isolation and identification due to their high prevalence on exosomes (Olver and Vidal, 2007).

The processes governing the packaging of exosomal contents are not entirely understood at this time, however there is evidence for selective compartmentalization. Various protein complexes associated with the ESCRT (endosomal sorting complex required for transport) have been frequently identified in the compositional analysis of exosomes including the Annexin family of proteins, Alix, and Tsg101 suggesting one possible component of the selective sorting process (Olver and Vidal, 2007). Using microarray analysis of the mRNA from primary GBM cell lines

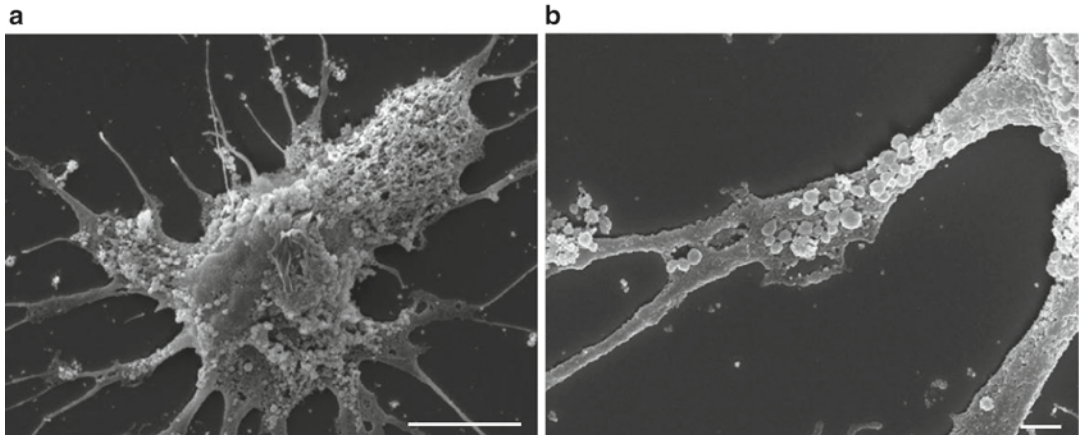

Fig. 9.3 Scanning electron microscopic image of a primary glioblastoma cell at lower (**a**) and higher (**b**) magnifications show microvesicles on the cell surface (Reprinted from Skog et al., 2008, Nat Cell Biology with permission)

and their respective exosomes, Skog et al. (2008) identified 27 k different transcripts of mRNA contained within the exosomes compared to only 22 k from the cells of origin (Fig. 9.3a, b). The additional 4,700 mRNA transcripts bundled within the exosomes highlights the enrichment process of exosome packaging.

Neoplastic cells may use this process of selective enrichment of exosomal contents to produce exosomes that enhance tumor survival and invasion. The ontology of the mRNA transcripts selectively concentrated within glioblastoma-derived exosomes showed an overrepresentation of genes that are directly related to tumor growth including angiogenesis, cell proliferation, and immune response (Skog et al., 2008). In another study, miRNAs known to be associated with angiogenesis, hematopoiesis, exocytosis and tumorigenesis were isolated from mast cell line-derived exosomes (Valadi et al., 2007). Proteomic analyses of exosomal contents reveal similar findings. Pathway analysis of proteins from brain tumor-derived exosomes revealed two leading categories of "hematologic/immunological/respiratory disease" and "cell-cell signaling/interaction, cancer, hematological system development and function" (Graner et al., 2009). Skog et al. (2008) identified the presence of seven angiogenic proteins from GBM cell line-derived exosomes. Six of the seven were differentially enriched within exosomes in comparison to the cell of origin. The functional representation of exosomal contents provides clues as to their roles in normal physiology as well as in pathological states.

The contents of exosomes vary depending on the cell of origin and the cellular physiology. In studying exosomes from three different sources of mast cells, Valadi et al. (2007) identified 271 different proteins, only 47 of which were present in all three samples. Even from the same cell type, exosomal contents may differ according to the cellular environment. Nonetheless, they retain key genomic and proteomic characteristics from their cell of origin. Notably, exosomes from EGFRvIII-positive glioblastoma cells retain the mutant transmembrane receptor expressed on the plasma membrane (Skog et al., 2008; Al-Nedawi et al., 2008). Furthermore, proteomic analysis of exosomes obtained from the media of the brain tumor cell line SMA560vIII identified 36 tumor-derived proteins, many of which were unique to the brain tumor exosomes (Graner et al., 2009). The ability to derive the origins of exosomes by their contents is an important quality that may be utilized to develop increasingly precise non-invasive biomarker studies.

As in normal cells, there is an abundance of non-coding genomic material contained within exosomes. Interestingly, non-coding RNAs makes up 98.5 % of the human genome—a far

greater amount than what is found in lesser developed organisms such as prokaryotes where ncRNAs comprise less than 25 % of the genome (van der Vos et al., 2011). The functions of most ncRNAs have not yet been determined but are known to be important for many cellular processes. ncRNAs have been shown to act as enzymes, protein binding aptamers, and to influence both gene transcription and translation—all properties that could potentially contribute to oncogenesis. miRNAs, one type of non-coding RNA prevalently found within exosomes, are short RNA sequences that play a major role in post-transcriptional gene silencing and transcript degradation. A single miRNA may be able to target over a 100 different genes. Their presence in many tumors and increased concentration within tumor-derived exosomes underlies their potential importance in tumor progression and environmental modulation (van der Vos et al., 2011).

Retrotransposons are another differentially enriched non-coding genetic element abundant within tumor exosomes (Balaj et al., 2011). Retrotransposons comprise 45 % of the human genome but their transcription is normally suppressed to maintain genomic stability (van der Vos et al., 2011). The increased expression of retrotransposons within tumor cells is thought to be at least in part due to the increased amount of reverse transcriptase activity. As reviewed by van der Vos et al. (2011), reverse transcriptase inhibitors have been shown to slow tumor proliferation in several different cancer lines inferring an oncogenic influence of retrotransposons. Since the expression of certain retrotransposon sequences is rare within normal, non-embryonic tissues, their increased presence inside tumor exosomes released into the circulation makes them a potentially valuable biomarker.

Biological Role of Exosomes

The biological roles of exosomes can be described in two broad categories as (i) cell component downregulation and remodeling and (ii) their ability to interact with other cells as mediators of intercellular communication.

Cell Component Downregulation

Numerous observations have suggested that cells use exosomes to facilitate shedding of unnecessary material for terminal differentiation and cellular regulation. Johnstone et al. (1987) provided one of the earliest examples in the context of reticulocyte maturation and remodeling during erythropoiesis. As a reticulocyte nears maturation, it uses exosomes to shed excess and unneeded cellular components. Through the release of exosomes, reticulocytes exhibit a complete loss of transferrin receptor and a 50 % reduction in acetylcholinesterase as they mature. Since its early description in erythrocytes, the use of exosomes to adjust cellular composition has been seen in numerous other cell types. Faure et al. (2006) described the exocytosis of exosomes by cortical neurons to dispose of AMPA receptors, theoretically as a means of modulating synaptic activity. Such examples have clarified the physiologic roles of exosomes in functional modulation and cellular differentiation in many types of cells.

The ability of cells to downregulate their contents through the shedding of exosomes allows tumors to use exosomes as a mechanism for drug resistance. Safaei et al. (2005) have shown that chemotherapy-resistant human ovarian cancer cells have enhanced exosomal export of cisplatin compared to chemotherapy-sensitive lines. Shedden et al. (2003) showed that the rate of microvesicle production corresponded to the degree of chemo-resistance in tumor cell lines and that the chemotherapeutic doxorubicin was accumulated within released microvesicles. Exosomes provide a selective export mechanism to escape the toxic chemotherapeutic effects of certain drugs, but whether this mechanism is exploited by glioblastoma cells has yet to be investigated.

Intercellular Communication

As mediators of intercellular communication, exosomes have been implicated in a multitude of biological processes that include (but certainly are not limited to) immunosuppression, gene transfer,

dissemination of infectious agents, and modulation of tumor microenvironments. Once released into the extracellular milieu, exosomes are capable of influencing other cells through receptor-ligand interactions or through fusing their membranes to other cells and transferring both their membranous and cytoplasmic components.

Exosomal immunomodulation is well recognized in both physiologic and pathologic conditions. An example of how exosomes suppress immune function under normal healthy conditions is their contributory role to maternal immune tolerance during pregnancy. For instance, Hedlund et al. (2009) showed how placental exosomes promote maternal immune tolerance through reduction in the cytotoxicity of natural killer, CD8(+), and gamma delta T-cells by downregulation of their NKG2D receptors. These exosomes released by the placenta carry lectin-like ligands as well as UL16-binding proteins (a family of the human NKG2D ligands) and MHC class I chain-related proteins A and B on their surface. Accordingly, exosomes contribute to physiologic immunosuppression during reproduction.

In pathologic conditions, tumor cells have been shown to use exosomes for similar immunosuppressive functions that enable their escape from immune surveillance and eradication. Exosomes isolated from tumor cells but not normal cells induce the generation and expansion of human T regulatory (T-reg) cells (Szajnik et al., 2010). T-reg cells express CD4, CD25, and Foxp3, and represent a subpopulation of T cells that downregulate the immune system by suppressing the immune responses of other cells. Szajnik et al. (2010) showed that when incubated with ovarian tumor-derived exosomes, T-reg cells demonstrated increased FasL, IL-10, TGF-beta1, CTLA-4, granzyme B, and perforin expression, which enhances the ability of T-reg cells to suppress responder cell proliferation. Furthermore, increased T-reg levels in tissue specimens of cancer patients have been linked to cancer progression and shorter survivals (Curiel et al., 2004). Another route of immune-evasion employed by tumor cells has been elucidated for glioblastoma cells; Sabin et al. (2012) have shown that glioblastoma cell-derived exosomes expressing Fas ligand are capable of inducing cytotoxic T cell apoptosis, thereby evading an important mechanism of immune surveillance. Thus through a variety of mechanisms, tumors modulate and evade the immune response via exosome release and signaling.

As intercellular messengers, exosomes not only influence other cells through ligand-receptor interactions but are able to deliver genetic contents from one cell into another. It is not known how often this method of genetic transfer occurs under normal physiologic circumstances, but the genetic communication between cells may occur in the microenvironment or at a distance as exosomes are carried by the circulating bodily fluids. Encapsulated and protected within the exosomal membranes, mRNA is delivered into target cells when the exosome fuses with the recipient cell outer membrane, spilling its genomic contents into that cell. In vitro studies have demonstrated the effectiveness of exosomal delivery of mRNA from one cell type to another with subsequent protein translation. Valadi et al. (2007) cultured human mast cells with mouse mast cell-derived exosomes and demonstrated the new and enhanced production of mouse protein within the human cells. Skog et al. (2008) showed that exosomes from glioblastoma cells could deliver a specific mRNA transcript to another cell type (endothelial cells) which was then incorporated into the recipient cells, generating functional proteins. Exosomal transfer of genomic material is therefore a plausible mode of intercellular communication.

Exosomes have also been implicated in the transfer of non-coding genomic material such as ribosomal RNA, small nuclear RNA, short interspersed RNA, miRNAs, siRNAs, and mitochondrial DNA (van der Vos et al., 2011). Non-coding RNAs make up a large portion of the genomic material contained within exosomes and may prove to be one of the more important intermediaries of exosomal intercellular interactions. Interestingly, Pegtel et al. (2010) have confirmed the ability of EBV-infected B lymphocytes to modulate the gene expression of recipient cells via exosomal transfer of miRNA. Specifically, EBV-encoded miRNA in exosomes released by

EBV-infected cells have been shown to down regulate the target CXCL11/ITAC immunoregulatory genes in non-infected recipient cells, thereby fostering the development of primary EBV-associated lymphomas. Furthermore, in comparing serum exosomes from GBM patients with that from normal controls, Noerholm et al. (2012) discovered that the GBM-associated exosomes had a significant upregulation of the total RNA amount. Notably, the largest fraction of this upregulated RNA was comprised of short non-coding RNA species less than 300nt in length. Further study is necessary to elucidate the various functions of the abundant exosomal non-coding genomic information associated with tumor pathophysiology.

The process of intercellular communication via exosomes is employed by tumor cells to modulate their surrounding microenvironment, thereby facilitating enhanced tumor invasion and promoting angiogenesis. Microvesicles shed by tumor cells are loaded with proteases capable of matrix degradation, such as MMP2, MMP9, MTI-MMP, and urokinase-type plasminogen activator (tPA) and eMMPRIN (Muralidharan-Chari et al., 2010). As an example, prostate cancer cells release microvesicles that interact with surrounding stroma to increase fibroblast motility, resistance to apoptosis, and up-regulate MMP expression (Castellana et al., 2009). In turn, the fibroblasts release additional microvesicles that reciprocally facilitate the prostate carcinoma cellular migration and invasion.

Exosomes from glioblastoma cells are enriched in angiogenic proteins and stimulate tubule formation and growth of endothelial cells when combined in culture. Other cancer cell lines have been shown to transfer the oncogenic receptor EGFR to adjacent endothelial cell membranes via fusion of EGFR-bearing exosomes, thereby promoting an angiogenic environment (Al Nedawi et al., 2009). Al Nedawi et al. (2008) previously showed that EGFRvIII-expressing GBM cells release microvesicles bearing the mutant receptor which are then taken up by wild-type EGFR GBM cells and subsequently expressed. GBM microvesicles demonstrate the ability to both promote peri-tumor angiogenesis as well as to transfer oncogenic activity in a horizontal manner endowing nearby cells with increased anchorage independent growth capacity.

Exosomes as Biomarkers

Rapid advances in genomic sequencing are expanding the knowledge of the different somatic mutations that take place in tumorigenesis and the realization that, although many mutations may be shared among tumors, each patient's tumor contains a specific pattern of these genetic variations. Many of these mutations predict which drugs would be effective in treatment of individual patients based on the profile of their specific tumors. Stratification of cancer patients, including those with brain tumors, into treatment groups based on their molecular profile has already begun.

The genomic profile of a tumor is not a static condition and changes with tumor progression and in response to therapy. As tumor genotype changes, so should the directed therapies. The ability to follow longitudinal molecular changes within a tumor throughout treatment and remission has been limited by the need to obtain direct tissue specimens for tumor characterization. Taking serial repeat biopsies, especially in difficult-to-access tumors such as in the brain, is not practical. There is an urgent need for non-invasive yet reliable genotyping of tumors to identify genetic markers for rapid and longitudinal analysis. The analysis of serum or other body fluid derived exosomes may provide us with this opportunity. The ability of exosomes to shelter proteins and genomic material from the harsh and destructive environment of the extracellular space makes them a promising source of potential biomarkers.

Genomic Profiling

Tumor-related microvesicles were first discovered in the blood of women with ovarian cancer in 1979 (Taylor and Doellgast, 1979). Since then, there have been an abundance of reports describing the

isolation of tumor-derived genetic and proteomic markers from microvesicles. Taylor and Gercel-Taylor (2008) demonstrated the value of serum exosomal miRNA as a biomarker from ovarian carcinoma. Microvesicles contain a select population of miRNAs secreted from tumor cells that differs from the miRNA bound in protein complexes in the circulating serum (Arroyo et al., 2011). The quantity of both exosomes and exosomal miRNA are increased in patients with malignant disease compared to normal or benign tissues and carries a miRNA profile that mirrors that of the cells from tissue biopsies. In fact, Rabinowits et al. (2009) detected significant increases in total exosome and miRNA levels in the serum of lung adenocarcinoma patients compared to normal as well as a similarity in circulating exosomal miRNA patterns with the miRNA profile of the tumor tissue. These findings provide proof of concept that miRNA profiling from serum exosomes can be done in the absence of a tissue biopsy and accurately reflect a tumor's profile.

Protein markers embedded in exosomal membranes may also be used as potential biomarkers. Koga et al. (2005) detected elevated Her2 oncoprotein on serum exosomes of breast carcinoma patients. Balaj et al. (2011) identified elevated levels of specific coding and non-coding RNA and DNA, mutated and amplified oncogene sequences, and transposable elements, all of which have potential use as blood biomarkers for cancer. Specifically, c-Myc amplification was identifiable in exosomes from the serum of human medulloblastoma-xenografted mice and not in control epidermoid carcinoma-bearing mice. Balaj et al. (2011) further expanded the list of potential genomic biomarkers as they identified an increased expression of certain retrotransposon elements, especially from human endogenous retroviruses, such as LINE-1 and Alu contained within tumor exosomes. Levels of specific retrotransposon sequences may be indicative of specific cells-of-origin in future studies of serum based biomarkers. These studies support the concept of using fluid-derived exosomes as sources of both proteomic as well as various forms of genomic biomarkers for neoplastic processes.

A challenge of exosomal genomic profiling from serum samples or other bodily fluids is the degree of background noise that must be sorted through. Even in oncologic cases when exosome production is upregulated, the representative number of tumor-derived exosomes isolated from serum samples is still only a small minority of the total exosome population obtained, the large majority of which are from hematologic origins. Noerholm et al. (2012) demonstrated the ability to differentiate between glioblastoma patients and normal controls through microarray analysis of sera exosomal mRNA profiles. However, when a Gene ontology analysis of the differentially expressed genes was done, the most differentially expressed genes were downregulated and were associated with ribosomal proteins. The finding of downregulated ribosomal protein-related genes is most likely attributable to the number of circulating lymphocytes which are the most abundant producers of exosomes with ribosomal-related genes, and in fact were significantly lower in the GBM patient's blood in comparison to normal patients. The distinct mRNA profiles of the two groups then, were more likely from hematologic background changes rather than detectable tumor genomic signatures. In order to obtain a desired 'snapshot' of a tumor's genome from serum sampling, these extraneous changes of a dynamic exosomal background will need to be filtered out. Exosome analysis will be improved in the future as different methods for exosome isolation are developed that target specific tissue-derived exosomes by surface markers through magnetic activated sorting and microfluidic capture (Chen et al., 2010).

Specific Biomarkers

Whole genome profiling of glioblastomas from serum samples requires further advances in exosome isolation to garner tissue-specific materials. On the other hand certain gene mutations, when present, even in a sea of background noise can by themselves have prognostic and diagnostic value. Exosomes may provide a protected source of these genetic mutations being carried throughout

the circulating body fluids that can be used as biomarkers even now.

Epidermal growth factor receptor variant III (EGFRvIII) is a mutation that is highly specific for GBM consisting of exon 2–7 deletion that is found in about 20–25 % of GBM cases. Skog et al. (2008) examined the serum of 30 GBM patients, in 14 of whom the EGFRvIII mutation was present within matched tissue samples. Using nested RT-PCR, they were able to identify the EGFRvIII mutation in 7 of the 30 serum samples demonstrating proof that EGFRvIII could be detected as a potential diagnostic marker in serum samples, although not currently with the desired sensitivity to be used in routine clinical practice. Interestingly, 2 of 7 serum samples where EGFRvIII was detected had matched tissue samples that had been negative for the mutation, suggesting that analysis of serum-based biomarkers may provide a more comprehensive test of tumor characteristics than tissue specimens. A small tissue sample from a tumor such as GBM may miss key genetic mutations due to the underlying heterogeneity of GBMs cellular distribution but a serum sample would presumably receive exosomes from the entire tumor. Exosomes from the serum of 30 normal control patients were all negative for EGFRvIII. Five serum samples were tested from patients 2 weeks after tumor resection and were all negative for EGFRvIII which suggests the possibility that following serum exosomes for return of biomarker positivity could be used as a marker of tumor recurrence. The ability to assess the presence or recurrence of tumor through non-invasive methods would be a valuable adjunct to long-term patient monitoring, especially after other treatments such as stereotactic radiosurgery when the difference between radiation necrosis and tumor progression are not always discernible by imaging methods. While exosomes may play a role in obtaining such biomarkers, in the case of GBMs, we will likely have to identify new and additional biomarkers to EGFRvIII for this purpose due to its rather low prevalence, and the tendency for recurrent tumors to no longer express the mutation.

The gene encoding the enzyme isocitrate dehydrogenase 1 (IDH1) is frequently mutated in glioma tumors and offers another potential biomarker source to be identified in exosomes. This mutated gene is a characteristic of secondary astrocytic tumors and is associated with the CpG-island methylator phenotype, a phenotype which remains stable for many years even after treatment and recurrence (Noushmehr et al., 2010). The subset of GBM patients with IDH1 mutations have significantly improved survival duration compared to other primary GBM patients. Chen et al. (2010) demonstrated the ability to detect IDH1 mRNA transcript within the exosomes from sera of both healthy individuals and of GBM patients. The quantity of mRNA transcript found within exosomes was judged to be sufficient for mutation-specific PCR or sequence analysis. Analysis of exosomes to detect the mutated version of IDH1 has yet to be performed. Other potential biomarkers that may be identifiable in serum-derived exosomes include the BRAF V600E missense mutation frequently found in gangliogliomas and xanthoastrocytomas, as well as the KIAA 1549-BRAF fusion gene present in up to 80 % of pilocytic astrocytomas (Jeuken and Wesseling, 2010). The increasing array of tumor-specific biomarkers being identified will likely increase the accuracy and reliability of non-invasive exosome-based assays.

Therapeutic Potentials of Exosomes

The understanding of exosomal function opens at least two new therapeutic directions of investigation for neurologic diseases. The first therapeutic direction being explored focuses on preventing exosomal intercellular communication either through targeting exosomal production or by impairing the ability of exosomes to bind and affect other cells. The second direction explores the use of exosomes as delivery vehicles for targeted drug or gene delivery.

Inhibiting Exosomal Communication

The first direction stems from the concept that exosome production is markedly increased in

several pathologic conditions including many cancers. Neoplastic cells use exosome-encapsulated proteins, mRNA, and non-coding RNAs to modulate their microenvironment and enhance their invasive abilities. As discussed, exosomes may also play a role in suppressing the body's natural immunologic mechanisms for combatting tumor growth. Strategies that prevent effective exosomal communication can potentially combat the tumor's devices for immune system evasion and tissue invasion. Inhibiting exosomal production may also impair a tumor's drug resistance mechanisms.

Chalmin et al. (2010) showed that cancer patients treated with amiloride, an antihypertensive drug that also decreases exosome production, exhibited decreased signs of tumor mediated immunosuppression. They also demonstrated in three different mouse models, that a related drug dimethyl amiloride enhanced in vivo antitumor efficacy of the chemotherapeutic drug cyclophosphamide. Proton pump inhibitors used for their antacid effects in the gastrointestinal tract are another drug with secondary effects of reducing exosome formation through an unknown mechanism (Iero et al., 2008). In fact, mice with xenografted melanomas that were pretreated with proton pump inhibitors showed improved chemosensitivity to cisplatin through reduced drug efflux at the tumor's cellular level (Luciani et al., 2004).

The transference of drug resistance through exosomes, as has been observed in drug-sensitive cell lines co-cultured with exosomes bearing the multi-drug efflux transporter P-glycoprotein from drug-resistant lines, may also be targeted by decreasing exosomal production (Bebawy et al., 2009). Al-Nedawi et al. (2008) demonstrated that incubation of microvesicles with annexin V, a scaffolding protein that blocks phosphatidylserine and thus inhibits exosome fusion, effectively blocked exosome uptake into U323 cells and reduced horizontal propagation of the EGFRvIII oncogene. Exosome secretion in vivo has also been reduced by silencing genes associated with exosome secretion, SYTL4 and EXPH5 (Ostrowski et al., 2010). As the mechanisms of exosomal production become better understood, it is easy to anticipate the development of additional therapeutics to inhibit exosomal communication.

Exosomes as Delivery Vehicles

As endogenous nano-vesicles that transport RNA and proteins between cells, exosomes have the therapeutic potential of serving as efficient, tissue-specific and non-immunogenic delivery vehicles. One of the most significant obstacles in developing new drug and gene therapies for primary brain tumors is employing a delivery system able to target specific cell types and can cross the blood brain barrier. Alvarez-Erviti et al. (2011) showed that exosomes from self-derived dendritic cells could be engineered to express a tissue-specific membrane protein for targeted delivery within the CNS, loaded with siRNA, and used to effectively knock down a specific gene with therapeutic benefits and do so without inducing an immune response. To accomplish this, rabies viral glycoprotein (RVG) was fused to the Lamp2b protein, an endogenous and abundant exosomal membrane constituent. Exosomes engineered with the RVG fusion protein were then loaded with siRNA targeting the BACE1 gene, a proposed target for Alzheimer's disease which forms a protease responsible for the cleavage of the amyloid precursor protein (APP), resulting in production of the pathologic aggregate-forming beta-amyloid peptide. The exosome-mediated siRNA delivery successfully crossed the blood brain barrier and resulted in a significant decrease in both BACE1 mRNA levels and beta-amyloid levels within the brains of injected mice.

The demonstration that exosomes can be exploited for targeted RNAi delivery to the brain after systemic injection provided the first proof-of concept for the potential of these naturally occurring vesicles as vehicles of drug delivery. As new drugs and gene therapies are discovered for treating glioblastomas, exosomes engineered for tissue-specific targeting have the potential to serve as effective non-immunogenic carriers able to cross the blood brain barrier.

In conclusion, exosomes are endosome-derived nano-sized vesicles secreted by many cell types including glioblastoma cells. They are a newly recognized system of intercellular communication enabling glioblastomas to safely deliver encapsulated proteomic and genetic material to surrounding tissues, thus promoting their growth and existence. Exosomes originating from glioblastoma cells have been identified in the serum and CSF of tumor-bearing patients and maintain characteristics of their cell of origin making them a potentially valuable source of biomarkers for tumor diagnostics and profiling. Modulation of exosome production and their ability to bind and uptake to other cells may serve as a therapeutic modality for impairing mechanisms of tumor progression. Their ability to be engineered for targeted tissue delivery and to be loaded with genes or drugs with effective transport across the blood brain barrier makes them a promising delivery vehicle for future targeted therapies. Neurosurgeons should be aware of the new developments in exosome research that may one day improve the care of glioblastoma patients.

References

Al-Nedawi K, Meehan B, Micallef J, Lhotak V, May L, Guha A, Rak J (2008) Intercellular transfer of the oncogenic receptor EGFRvIII by microvesicles derived from tumour cells. Nat Cell Biol 10:619–624

Al-Nedawi K, Meehan B, Kerbel RS, Allison AC, Rak J (2009) Endothelial expression of autocrine VEGF upon the uptake of tumor-derived microvesicles containing oncogenic EGFR. Proc Natl Acad Sci U S A 106:3794–3799

Alvarez-Erviti L, Seow Y, Yin H, Betts C, Lakhal S, Wood MJ (2011) Delivery of siRNA to the mouse brain by systemic injection of targeted exosomes. Nat Biotechnol 29:341–345

Arroyo JD, Chevillet JR, Kroh EM, Ruf IK, Pritchard CC, Gibson DF, Mitchell PS, Bennett CF, Pogosova-Agadjanyan EL, Stirewalt DL, Tait JF, Tewari M (2011) Argonaute2 complexes carry a population of circulating microRNAs independent of vesicles in human plasma. Proc Natl Acad Sci U S A 108: 5003–5008

Balaj L, Lessard R, Dai L, Cho YJ, Pomeroy SL, Breakefield XO, Skog J (2011) Tumour microvesicles contain retrotransposon elements and amplified oncogene sequences. Nat Commun 2:180

Bebawy M, Combes V, Lee E, Jaiswal R, Gong J, Bonhoure A, Grau GE (2009) Membrane microparticles mediate transfer of P-glycoprotein to drug sensitive cancer cells. Leukemia 23:1643–1649

Castellana D, Zobairi F, Martinez MC, Panaro MA, Mitolo V, Freyssinet JM, Kunzelmann C (2009) Membrane microvesicles as actors in the establishment of a favorable prostatic tumoral niche: a role for activated fibroblasts and CX3CL1-CX3CR1 axis. Cancer Res 69:785–793

Chalmin F, Ladoire S, Mignot G, Vincent J, Bruchard M, Remy-Martin JP, Boireau W, Rouleau A, Simon B, Lanneau D, De Thonel A, Multhoff G, Hamman A, Martin F, Chauffert B, Solary E, Zitvogel L, Garrido C, Ryffel B, Borg C, Apetoh L, Rébé C, Ghiringhelli F (2010) Membrane-associated Hsp72 from tumor-derived exosomes mediates STAT3-dependent immunosuppressive function of mouse and human myeloid-derived suppressor cells. J Clin Invest 120:457–471

Chen C, Skog J, Hsu CH, Lessard RT, Balaj L, Wurdinger T, Carter BS, Breakefield XO, Toner M, Irimia D (2010) Microfluidic isolation and transcriptome analysis of serum microvesicles. Lab Chip 10:505–511

Cocucci E, Racchetti G, Meldolesi J (2009) Shedding microvesicles: artefacts no more. Trends Cell Biol 19:43–51

Curiel TJ, Coukos G, Zou L, Alvarez X, Cheng P, Mottram P, Evdemon-Hogan M, Conejo-Garcia JR, Zhang L, Burow M, Zhu Y, Wei S, Kryczek I, Daniel B, Gordon A, Myers L, Lackner A, Disis ML, Knutson KL, Chen L, Zou W (2004) Specific recruitment of regulatory T cells in ovarian carcinoma fosters immune privilege and predicts reduced survival. Nat Med 10:942–949

Fauré J, Lachenal G, Court M, Hirrlinger J, Chatellard-Causse C, Blot B, Grange J, Schoehn G, Goldberg Y, Boyer V, Kirchhoff F, Raposo G, Garin J, Sadoul R (2006) Exosomes are released by cultured cortical neurones. Mol Cell Neurosci 31:642–648

Graner MW, Alzate O, Dechkovskaia AM, Keene JD, Sampson JH, Mitchell DA, Bigner DD (2009) Proteomic and immunologic analyses of brain tumor exosomes. FASEB J 23:1541–1557

Hedlund M, Stenqvist AC, Nagaeva O, Kjellberg L, Wulff M, Baranov V, Mincheva-Nilsson L (2009) Human placenta expresses and secretes NKG2D ligands via exosomes that down-modulate the cognate receptor expression: evidence for immunosuppressive function. J Immunol 183:340–351

Iero M, Valenti R, Huber V, Filipazzi P, Parmiani G, Fais S, Rivoltini L (2008) Tumour-released exosomes and their implications in cancer immunity. Cell Death Differ 15:80–88

Jeuken JW, Wesseling P (2010) MAPK pathway activation through BRAF gene fusion in pilocytic astrocytomas; a novel oncogenic fusion gene with diagnostic, prognostic, and therapeutic potential. J Pathol 222:324–328

Johnstone RM, Adam M, Hammond JR, Orr L, Turbide C (1987) Vesicle formation during reticulocyte maturation. Association of plasma membrane activities with released vesicles exosomes. J Biol Chem 262:9412–9420

Koga K, Matsumoto K, Akiyoshi T, Kubo M, Yamanaka N, Tasaki A, Nakashima H, Nakamura M, Kuroki S, Tanaka M, Katano M (2005) Purification, characterization and biological significance of tumor-derived exosomes. Anticancer Res 25:3703–3707

Luciani F, Spada M, De Milito A, Molinari A, Rivoltini L, Montinaro A, Marra M, Lugini L, Logozzi M, Lozupone F, Federici C, Iessi E, Parmiani G, Arancia G, Belardelli F, Fais S (2004) Effect of proton pump inhibitor pretreatment on resistance of solid tumors to cytotoxic drugs. J Natl Cancer Inst 96:1702–1713

Muralidharan-Chari V, Clancy JW, Sedgwick A, D'Souza-Schorey C (2010) Microvesicles: mediators of extracellular communication during cancer progression. J Cell Sci 123:1603–1611

Noerholm M, Balaj L, Limperg T, Salehi A, Zhu LD, Hochberg FH, Breakefield XO, Carter BS, Skog J (2012) RNA expression patterns in serum microvesicles from patients with glioblastoma multiforme and controls. BMC Cancer 12:22

Noushmehr H, Weisenberger DJ, Diefes K, Phillips HS, Pujara K, Berman BP, Pan F, Pelloski CE, Sulman EP, Bhat KP, Verhaak RG, Hoadley KA, Hayes DN, Perou CM, Schmidt HK, Ding L, Wilson RK, Van Den Berg D, Shen H, Bengtsson H, Neuvial P, Cope LM, Buckley J, Herman JG, Baylin SB, Laird PW, Aldape K, Network CGAR (2010) Identification of a CpG island methylator phenotype that defines a distinct subgroup of glioma. Cancer Cell 17:510–522

Olver C, Vidal M (2007) Proteomic analysis of secreted exosomes. Subcell Biochem 43:99–131

Ostrowski M, Carmo NB, Krumeich S, Fanget I, Raposo G, Savina A, Moita CF, Schauer K, Hume AN, Freitas RP, Goud B, Benaroch P, Hacohen N, Fukuda M, Desnos C, Seabra MC, Darchen F, Amigorena S, Moita LF, Thery C (2010) Rab27a and Rab27b control different steps of the exosome secretion pathway. Nat Cell Biol 12:19–30; sup pp 11-13

Pegtel DM, Cosmopoulos K, Thorley-Lawson DA, van Eijndhoven MA, Hopmans ES, Lindenberg JL, de Gruijl TD, Würdinger T, Middeldorp JM (2010) Functional delivery of viral miRNAs via exosomes. Proc Natl Acad Sci U S A 107:6328–6333

Rabinowits G, Gerçel-Taylor C, Day JM, Taylor DD, Kloecker GH (2009) Exosomal microRNA: a diagnostic marker for lung cancer. Clin Lung Cancer 10:42–46

Sabin KZ, Rovin RA, Lawrence JE, Belton RJ, Winn RJ (2012) 190 glioblastoma derived exosomes induce apoptosis in cytotoxic T cells through a Fas ligand mediated mechanism. Neurosurgery 71:E574

Safaei R, Larson BJ, Cheng TC, Gibson MA, Otani S, Naerdemann W, Howell SB (2005) Abnormal lysosomal trafficking and enhanced exosomal export of cisplatin in drug-resistant human ovarian carcinoma cells. Mol Cancer Ther 4:1595–1604

Shedden K, Xie XT, Chandaroy P, Chang YT, Rosania GR (2003) Expulsion of small molecules in vesicles shed by cancer cells: association with gene expression and chemosensitivity profiles. Cancer Res 63:4331–4337

Skog J, Würdinger T, van Rijn S, Meijer DH, Gainche L, Sena-Esteves M, Curry WT, Carter BS, Krichevsky AM, Breakefield XO (2008) Glioblastoma microvesicles transport RNA and proteins that promote tumour growth and provide diagnostic biomarkers. Nat Cell Biol 10:1470–1476

Szajnik M, Czystowska M, Szczepanski MJ, Mandapathil M, Whiteside TL (2010) Tumor-derived microvesicles induce, expand and up-regulate biological activities of human regulatory T cells Treg. PLoS One 5:e11469

Taylor DD, Doellgast GJ (1979) Quantitation of peroxidase-antibody binding to membrane fragments using column chromatography. Anal Biochem 98:53–59

Taylor DD, Gercel-Taylor C (2008) MicroRNA signatures of tumor-derived exosomes as diagnostic biomarkers of ovarian cancer. Gynecol Oncol 110:13–21

Valadi H, Ekström K, Bossios A, Sjöstrand M, Lee JJ, Lötvall JO (2007) Exosome- mediated transfer of mRNAs and microRNAs is a novel mechanism of genetic exchange between cells. Nat Cell Biol 9:654–659

van der Vos KE, Balaj L, Skog J, Breakefield XO (2011) Brain tumor microvesicles: insights into intercellular communication in the nervous system. Cell Mol Neurobiol 31:949–959

MicroRNA in the Pathophysiology of Glioblastoma

10

Jessian Munoz, Steven J. Greco, and Pranela Rameshwar

Contents

Abstract

Glioblastoma Multiforme (GBM) is the most common and aggressive adult intracranial malignancy; with a ~11-month medial survival rate. Radio- and chemo-resistance is a common feature of GBM. The experimental evidence indicates that the currently used anti-neoplastic treatment for GBM can be counteracted by the activation of particular cellular signalling pathways such as p53, PTEN. These pathways can be partly regulated by microRNA (miRNA) through both positive and negative regulatory functions. MiRNA are 18–22 nt small RNA molecules, which bind the 3′ untranslated region (UTR) of specifically targeted mRNA to mediate translational repression. This chapter focuses on the role of specific miRNA molecules on GBM cell signalling and the overall effect on cellular proliferation, viability and treatment resistance.

Introduction – Overview

The prognosis of glioblastoma is severe, with less than 2 years survival (Stupp et al., 2006). Treatment options for patients with GBM are limited to surgery, radiation and temozolamide (Dunn et al., 2012). This combination of therapies is the result of years of clinical trials with various classes of drugs (Galanis et al., 2012). In 2009, the United States Food and Drug Administration approved Bevacizumab, also

J. Munoz • S.J. Greco • P. Rameshwar (✉)
UMDNJ-New Jersey Medical School,
MSB, Room E-579, 185 South Orange Avenue,
Newark, NJ 07103, USA
e-mail: rameshwa@umdnj.edu

M.A. Hayat (ed.), *Tumors of the Central Nervous System, Volume 11*,
DOI 10.1007/978-94-007-7037-9_10,

known as Avastin (Cohen et al., 2009). However, Avastin was only approved for cases that continue to progress after the standard care, which included surgery, radiotherapy and temozolamide (Cohen et al., 2009). GBM comprises of oligodendroglioma and oligoastrocytoma (Stupp et al., 2006). Patients with both subtypes of GBM respond to temozolomide, but with little effect during recurrence (Stupp et al., 2005).

Epigenetic silencing of the DNA repair enzyme O(6)-methylguanine-DNA-methyltransferase (MGMT) is a key molecular diagnostic in predicting response to temozolomide (Fukushima et al., 2009). Despite the prediction by MGMT, this does not affect the recurrence of GBM, underscoring the need for an interdisciplinary team to study GBM resistance. It is equally important to identify the subtypes of GBM and to determine if a hierarchy of cancer cells exist, further enabling identification of the relative maturity of cells. A hierarchy of GBM will incorporate the research findings for a comprehensive understanding of GBM. Additionally, it is important to study the brain microenvironment and invading cells on the development and progression of GBM.

Intercellular communication among tumor cells and adhesion molecules contributes to the metastasis of GBM (Hotz-Wagenblatt and Shalloway, 1993). Gap junctional intercellular communication between cancer cells such as GBM has been linked to the pathophysiology of cancer development (Strale et al., 2012). Small second messenger molecules and microRNAs (miRNAs) can pass through gap junctions to regulate intercellular communications (Lim et al., 2011). This review discusses the role of miRNAs in intercellular communication among GBMs and also investigates how the miRNAs regulate intracellular signalling pathways. The implication for treatment is discussed.

MicroRNA – General

MiRNAs are small, non-coding RNAs that constitute ~1–2 % of mammalian genes (Bartel, 2009). Since their discovery in 2000, miRNAs have been implicated in a number of biological processes including neural patterning, neurodevelopment and oncogenesis. Despite their relatively small size, miRNAs are stable in the normal circulation, thus enabling their utilization as a biomarker in oncology (Zen and Zhang, 2012).

MiRNAs represent a diverse family of RNA molecules that can be found inter-, and intragenetically (intronic and exonic). Primary miRNAs are transcribed by RNA polymerase II, and then cleaved by Drosha, a RNase type III. Exportin 5 transports the precursor miRNA in a RAN-GTP-dependent manner from the nuclei to the cytoplasm where RNase type III, Dicer, cleaves the precursor miRNA into mature 18–22 double stranded nucleotides. It is believed that the more stable of the two stands recruits the RNA Induced Silencing Complex (RISC) to degrade the complementary strand. After integration to the RISC, the miRNA may bind to the 3′ untranslated region (UTR) of its target mRNA. Depending on complementarity, the target mRNA may be degraded by RISC-associated Argonaute (Ago) proteins or the translation of the targeted mRNA could be suppressed.

In general, miRNAs are considered as regulators of genes, post-transcriptionally (Ebert and Sharp, 2012). This occurs through interactions with the 3′ UTR of transcripts (mRNA) to suppress translation. Interestingly, miRNAs and their targets are generally conserved, suggesting their critical functions in development (Bartel, 2009). Interestingly, a single miRNA has been reported to suppress target genes. In most instances, outcomes of a single miRNA are generally modest. The efficiency of miRNAs in regulating gene expression appears to require one or more miRNAs at clusters at multiple sites within the transcript (Arvey et al., 2010). Although the role of miRNAs in development has been exhaustively studied, it is yet to be determined if the miRNAs are involved in ‘fine-tuning’ the developmental processes or if they mediate a central role in development.

MicroRNA-Glioblastoma

The body of literature linking miRNA to cancer is growing at an exponential rate. The literature includes an exhaustive report on GBM in which

miRNAs were shown to have oncogenic functions, referred to as oncomirs. The role of miRNA includes diagnostic and perhaps prognostic value since profiles of miRNAs have been reported in cerebrospinal fluid (Teplyuk et al., 2012). Specific miRNAs have been shown to regulate the invasion, migration and proliferation of GBM, leading to poor prognosis (Loftus et al., 2012; Ma et al., 2012). Interestingly, the signal transducer and activator of transcription (STAT3), through miRNA21, maintained telomerase reverse transcriptase (TERT), which suggested an anti-aging mechanism by miR21 in GBM (Wang et al., 2012b). The next sections will highlight specific signaling pathways and discuss the role of miRNAs.

MicroRNA – Cytokines in Glioblastoma

Cytokines are growth-promoting factors which are known to mediate cancer growth; although the mechanisms by which miRNAs regulate the production of cytokines in GBM are still to be determined. MiRNA34a regulates the pathways leading to TGFβ1 production in GBM and its expression has been suggested as a prognostic gene (Genovese et al., 2012). Other miRNAs that would otherwise decrease TGFβ1-mediated angiogenic factors might be decreased in GBM and should be examined (Dews et al., 2010). MiR196b has also been suggested as a prognostic marker and its expression has been linked to cell proliferation (Ma et al., 2012). Although miR196b has not been shown to regulate particular cytokines, its role in the production of cytokines is implied since proliferation is mediated by cytokines.

As compared to the other miRNAs, miRNA21 has been extensively studied in GBM. MiR21 mediates phosphorylation of STAT3 in GBM (Wang et al., 2012b). Since STAT3 is relevant to cytokine signalling, this places a relevant role for miR21 in cytokine production in GBM. To this end, inhibition of miR21 has been shown to sensitize GBM to temozolomide (Zhang et al., 2012). MiR21 has been shown to target multiple pathways involving p53 and apoptosis (Papagiannakopoulos et al., 2008). These studies on miR21 supported the intimate relationship among cytokines, miRNAs and treatment sensitivity. Indeed, miRNA with oncogenic and tumor suppressor roles in GBM are involved in maintaining different subsets of GBM cells, including the stem cell population (Chistiakov and Chekhonin, 2012). As suggested by Chistiakov and Chekhonin, miRNAs are central to the future treatments of GBM to sensitize the cells to radio- and chemo-therapy.

Signalling – Glioblastoma

A number of parallels exist between human developmental pathways and oncogenic transformation/maintenance. The Epidermal Growth Factor/Epidermal Growth Factor Receptor (EGF/EGFR) pathway represents such overlap. EGF is a 6-kDa protein with 53 amino acids, stabilized by three disulfide bonds. EGF binds with very high affinity to the EGFR, thereby inducing cellular proliferation, differentiation and survival.

In the absence of ligand, EGFR is a non-active monomeric transmembrane protein; although some evidence has suggested the existence of ligand independent dimerization. After activation with EGF, the monomeric EGFR undergoes homodimerization to activate protein-tyrosine kinase to auto-phosphorylate at least five residues (Y992, Y1045, Y1068, Y1148 and Y1173). Downstream proteins then interact with the phosphorylated EGFR through SH2-phosphotyrosine binding domains. EGFR binds and phosphorylates phospholipase C (PLC), which activates inositol trisphosphate (IP3) – diacylglycerol (DAG) pathway, leading to the release of stored calcium and the activation of the anti-apoptotic Akt/PKB pathway. The activated EGFR can also form the Grb2/SOS complex to activate the p21 RAS pathway and MAPK/ERK activation (Zhou et al., 2010b). Pathway "cross-talk" and activation of MAPK/AKT/PLC as well as other EGFR induced pathways leads to the signalling of EGFR.

EGFR is amplified in ~60 % of primary GBM tumors (Wang et al., 2012a), resulting in the worst clinical prognosis for patients. The EGFR serves as an attractive target to pharmacologically inhibit GBM signalling. Recent clinical trials have shown some improvement in patients treated with tyrosine-kinase inhibitors. EGFR has intrinsic protein-tyrosine kinase activity, which leads to canonical receptor tyrosine kinase pathways.

The *TP53* gene is one of the most frequently mutated genes in human malignancy. The *TP53* gene product, p53 is important for proper cellular functions. These include inhibition of cellular proliferation and activation of apoptosis. The functions of p53 are tightly regulated by a feedback loop mediated through the p53 target, *Mdm2*. Mdm2 is an E3 ubiquitin ligase that targets the amino terminal of p53 for proteasomal degradation (Stark et al., 2003). MiRNAs provide an additional mechanism for p53 regulation.

GBM cell lines were analyzed for p53-regulated microRNAs, in the presence and absence of the Mdm2/p53 complex inhibitor, Nutilin-3a (Suh et al., 2012). The analyses indicated >2 fold repression of mir-25 when p53 was activated with Nutilin-3a. Mir-32, which shares the same seed sequence as mir-25, was also repressed by p53. In situ hybridization indicated that p53 expressing GBM lacked mir-25/-32. MiR-25 is part of a larger cluster of miRNAs located in the 13th intronic region of the *MCM7* gene. Transcriptional regulation of the miRNA cluster has been shown to be E2F1 and MYC dependent. Not surprisingly, p53-expressing GBM cells showed reduced expression of E2F1 and MYC, as well as mir-25/32. However, the mir-32 host gene, *C9orf5*, was not repressed, leading to the discovery of a novel mir-32 promoter, which is regulated by MYC. Interestingly, ectopic expression of mir-25/32 lead to prolonged p53 protein expression through stabilization, through targeting of Mdm2. *In vivo* studies using an intracranial xenograft model showed that mir-25/32 expression increased the overall survival through the accumulation of p53. Taken together, this series of data showed a feedback loop in which mir-25/32 are repressed by p53 activation, resulting in increased Mdm2, which allows for p53 degradation and impaired function.

Phosphatase and tensin homolog (*PTEN*) is a well-characterized and commonly mutated human tumor suppressor gene. MiRNA 21 is commonly upregulated in tumors and seems to maintain malignancy. Mir-21 expression has been mostly reported in tumors of glial origin to decrease apoptosis (Zhou et al., 2010a). Mir-21 can repress p53-mediated apoptosis and prolong cell cycling; thus contributing to chemoresistance. Mir-21 regulates the expression of several genes such as Programmed Cell Death 4 (PDCD4) (Lu et al., 2008). In other studies, mir-21 has been shown to regulate the migration of GBM, indirectly through matrix metalloprotease inhibitors such as TIMP3 and RECK 9 (Gabriely et al., 2008).

MicroRNA – Potential Therapy/Glioblastoma

This chapter briefly discusses miRNA in the biology of GBM. The question remains whether the miRNAs will be directly targeted or whether the pathways mediated by the signalling of the miRNAs will be the target. For example, miRNA has been shown to affect other genes to alter the migration of GBM (Loftus et al., 2012). These and other studies suggest that further investigation into the role of miRNAs in the biology of GBM might identify drugable targets. Experimental evidence suggests that inhibition of miR10b and miR21 acts synergistically to blunt the proliferation and invasion of GBM (Dong et al., 2012).

Although the identity of the stem cells within GBM remains as a subject of discussion, there are several reports that the pluripotent subset might be identified based on CD133 (Shi et al., 2012). MiR125b has been shown to exert different effects on the migration of CD133(+) and CD133(−) cells (Shi et al., 2012), indicating that the treatment of miRNA will require studies to develop a hierarchy of GBM (discussed above).

References

Arvey A, Larsson E, Sander C, Leslie CS, Marks DS (2010) Target mRNA abundance dilutes microRNA and siRNA activity. Mol Syst Biol 6:363

Bartel DP (2009) MicroRNAs: target recognition and regulatory functions. Cell 136:215–233

Chistiakov DA, Chekhonin VP (2012) Contribution of microRNAs to radio- and chemoresistance of brain tumors and their therapeutic potential. Eur J Pharmacol 684:8–18

Cohen MH, Shen YL, Keegan P, Pazdur R (2009) FDA drug approval summary: Bevacizumab (Avastin) as treatment of recurrent glioblastoma multiforme. Oncologist 14:1131–1138

Dews M, Fox JL, Hultine S, Sundaram P, Wang W, Liu YY, Furth E, Enders GH, El-Deiry W, Schelter JM, Cleary MA, Thomas-Tikhonenko A (2010) The Myc-miR-17 92 axis blunts TGF-beta signaling and production of multiple TGFβ-dependent antiangiogenic factors. Cancer Res 70:8233–8246

Dong CG, Wu WK, Feng SY, Wang XJ, Shao JF, Qiao J (2012) Co-inhibition of microRNA-10b and microRNA-21 exerts synergistic inhibition on the proliferation and invasion of human glioma cells. Int J Oncol 41:1005–1012

Dunn GP, Rinne ML, Wykosky J, Genovese G, Quayle SN, Dunn IF, Agarwalla PK, Chheda MG, Campos B, Wang A, Brennan C, Ligon KL, Furnari F, Cavenee WK, Depinho RA, Chin L, Hahn WC (2012) Emerging insights into the molecular and cellular basis of glioblastoma. Genes Dev 26:756–784

Ebert M, Sharp P (2012) Roles for microRNAs in conferring robustness to biological processes. Cell 149:515–524

Fukushima T, Takeshima H, Kataoka H (2009) Antiglioma therapy with temozolomide and status of the DNA-repair gene MGMT. Anticancer Res 29:4845–4854

Gabriely G, Wurdinger T, Kesari S, Esau CC, Burchard J, Linsley PS, Krichevsky AM (2008) MicroRNA 21 promotes glioma invasion by targeting matrix metalloproteinase regulators. Mol Cell Biol 28:5369–5380

Galanis E, Wu W, Cloughesy T, Lamborn K, Mann B, Wen PY, Reardon DA, Wick W, Macdonald D, Armstrong TS, Weller M, Vogelbaum M, Colman H, Sargent DJ, van den Bent MJ, Gilbert M, Chang S (2012) Phase 2 trial design in neuro-oncology revisited: a report from the RANO group. Lancet Oncol 13:e196–e204

Genovese G, Ergun A, Shukla SA, Campos B, Hanna J, Ghosh P, Quayle SN, Rai K, Colla S, Ying H, Wu CJ, Sarkar S, Xiao Y, Zhang J, Zhang H, Kwong L, Dunn K, Wiedemeyer WR, Brennan C, Zheng H, Rimm DL, Collins JJ, Chin L (2012) MicroRNA regulatory network inference identifies miR-34a as a novel regulator of TGF beta signaling in GBM. Cancer Discov 2(8):736–749

Hotz-Wagenblatt A, Shalloway D (1993) Gap junctional communication and neoplastic transformation. Crit Rev Oncog 4:541–558

Lim PK, Bliss SA, Patel SA, Taborga M, Dave MA, Gregory LA, Greco SJ, Bryan M, Patel PS, Rameshwar P (2011) Gap junction-mediated import of microRNA from bone marrow stromal cells can elicit cell cycle quiescence in breast cancer cells. Cancer Res 71:1550–1560

Loftus JC, Ross JTD, Paquette KM, Paulino VM, Nasser S, Yang Z, Kloss J, Kim S, Berens ME, Tran NL (2012) miRNA expression profiling in migrating glioblastoma cells: regulation of cell migration and invasion by miR-23b via targeting of Pyk2. PLoS One 7:e39818

Lu Z, Liu M, Stribinskis V, Klinge CM, Ramos KS, Colburn NH, Li Y (2008) MicroRNA-21 promotes cell transformation by targeting the programmed cell death 4 gene. Oncogene 27:4373–4379

Ma R, Yan W, Zhang G, Lv H, Liu Z, Fang F, Zhang W, Zhang J, Tao T, You Y, Jiang T, Kang X (2012) Upregulation of miR-196b confers a poor prognosis in glioblastoma patients via inducing a proliferative phenotype. PLoS One 7:e38096

Papagiannakopoulos T, Shapiro A, Kosik KS (2008) MicroRNA-21 targets a network of key tumor-suppressive pathways in glioblastoma cells. Cancer Res 68:8164–8172

Shi L, Wan Y, Sun G, Gu X, Qian C, Yan W, Zhang S, Pan T, Wang Z, You Y (2012) Functional differences of miR-125b on the invasion of primary glioblastoma CD133-negative cells and CD133-positive cells. Neuromolecular Med 14(4):303–316

Stark AM, Witzel P, Strege RJ, Hugo HH, Mehdorn HM (2003) p53, mdm2, EGFR, and msh2 expression in paired initial and recurrent glioblastoma multiforme. J Neurol Neurosurg Psychiatry 74:779–783

Strale PO, Clarhaut J, Lamiche C, Cronier L, Mesnil M, Defamie N (2012) Down-regulation of connexin43 expression reveals the involvement of caveolin-1 containing lipid rafts in human U251 glioblastoma cell invasion. Mol Carcinog 51(11):845–860. doi:10.1002/mc.20853

Stupp R, van den Bent MJ, Hegi ME (2005) Optimal role of temozolomide in the treatment of malignant gliomas. Curr Neurol Neurosci Rep 5:198–206

Stupp R, Hegi ME, van den Bent MJ, Mason WP, Weller M, Mirimanoff RO, Cairncross JG, on behalf of the European Organisation for research and treatment of cancer brain Tumor and Radiotherapy groups and the national cancer institute of Canada clinical trials group (2006) Changing paradigms-an update on the multidisciplinary management of malignant glioma. Oncol 11:165–180

Suh SS, Yoo JY, Nuovo GJ, Jeon YJ, Kim S, Lee TJ, Kim T, Bakács A, Alder H, Kaur B, Aqeilan RI, Pichiorri F,

Croce CM (2012) MicroRNAs/TP53 feedback circuitry in glioblastoma multiforme. Proc Natl Acad Sci 109:5316–5321

Teplyuk NM, Mollenhauer B, Gabriely G, Giese A, Kim E, Smolsky M, Kim RY, Saria MG, Pastorino S, Kesari S, Krichevsky AM (2012) MicroRNAs in cerebrospinal fluid identify glioblastoma and metastatic brain cancers and reflect disease activity. Neuro Oncol 14:689–700

Wang Y, Wang X, Zhang J, Sun G, Luo H, Kang C, Pu P, Jiang T, Liu N, You Y (2012a) MicroRNAs involved in the EGFR/PTEN/AKT pathway in gliomas. J Neurooncol 106:217–224

Wang YY, Sun G, Luo H, Wang XF, Lan FM, Yue X, Fu LS, Pu PY, Kang CS, Liu N, You YP (2012b) MiR-21 modulates hTERT through a STAT3-dependent manner on glioblastoma cell growth. CNS Neurosci Ther 18(9):722–728

Zen K, Zhang CY (2012) Circulating microRNAs: a novel class of biomarkers to diagnose and monitor human cancers. Med Res Rev 32:326–348

Zhang S, Wan Y, Pan T, Gu X, Qian C, Sun G, Sun L, Xiang Y, Wang Z, Shi L (2012) MicroRNA-21 inhibitor sensitizes human glioblastoma U251 stem cells to chemotherapeutic drug temozolomide. J Mol Neurosci 47:346–356

Zhou X, Zhang J, Jia Q, Ren Y, Wang Y, Shi L, Liu N, Wang G, Pu P, You Y, Kang C (2010a) Reduction of miR-21 induces glioma cell apoptosis via activating caspase 9 and 3. Oncol Rep 24:195–201

Zhou X, Ren Y, Moore L, Mei M, You Y, Xu P, Wang B, Wang G, Jia Z, Pu P, Zhang W, Kang C (2010b) Downregulation of miR-21 inhibits EGFR pathway and suppresses the growth of human glioblastoma cells independent of PTEN status. Lab Invest 90:144–155

Surgical Management of Incidentally Discovered Diffuse Low-Grade Gliomas

11

Johan Pallud and Emmanuel Mandonnet

Contents

Abstract

An incidental diffuse low-grade glioma (DLGG) is a previously undetected and asymptomatic tumor at the time of imaging diagnosis that was unexpectedly discovered and unrelated to the purpose of the MR examination. The reported prevalence of incidental DLGGs ranges from 0.025 to 0.2 %. The occurrence of incidentally discovered DLGGs will increase in the future due to the rising frequency of brain imaging in addition to recent advances in imaging technology. Incidental DLGGs are progressive tumors that develop at a similar rate to those for the symptomatic DLGGs, and represent an earlier step than symptomatic DLGGs in the tumor natural course. Incidental diffuse gliomas can remain silent until malignant transformation occurs. Thus, incidental DLGGs should be considered as progressive tumors with the same potential for progression than that for symptomatic DLGGs. Because incidental DLGGs are not benign tumors and because the natural course of DLGGs during the silent and symptomatic periods are similar, incidental DLGGs should be managed as symptomatic DLGGs. Surgical resection of incidental DLGGs is feasible with a minimal morbidity and larger amount of resection can be carried out comparing with that from symptomatic DLGGs. These data argue for an early surgical treatment in asymptomatic patients to maximize the extent of DLGG resection before glioma growth and migration,

J. Pallud (✉)
Department of Neurosurgery, University Paris Descartes – Sainte-Anne Hospital Center, 1 rue Cabanis, 75674 Paris cedex 14, France
e-mail: j.pallud@ch-sainte-anne.fr

E. Mandonnet
Department of Neurosurgery, Lariboisière Hospital, 2 rue Ambroise Paré, 75010 Paris, France

M.A. Hayat (ed.), *Tumors of the Central Nervous System, Volume 11*,
DOI 10.1007/978-94-007-7037-9_11,

even in critical brain regions. Hence, surgical removal with functional intraoperative mapping should be proposed as soon as progression is demonstrated on close imaging follow-up.

Introduction

World Health Organisation (WHO) supratentorial and hemispheric diffuse low-grade gliomas (DLGGs) in adults, i.e., WHO grade II gliomas, are progressive tumors (Mandonnet et al., 2003; Pallud et al., 2006). Their primary therapeutic management consists in a functional-based maximal surgical resection (Soffietti et al., 2010). The main presenting symptoms are epileptic seizures, but rarely a DLGG is discovered incidentally (Pallud et al., 2010c). Little is known regarding the natural history of incidental DLGGs. Do they differ from symptomatic DLGGs or do they represent the same tumor discovered earlier, before clinical revelation? The frequency of brain imaging leads to an increase of incidentally discovered DLGGs. As a consequence, it is time to raise the question of management of incidental DLGGs. However, little is known about their natural history, prognosis, and optimal management strategies.

Therefore, the aim of the present chapter is to review data regarding incidental DLGGs. We will show that incidental DLGGs are progressive tumors that become symptomatic with time, and we will confirm that they behave like symptomatic DLGGs do. In addition, we will show that incidental diffuse gliomas can remain silent until malignant transformation occurs. The practical implications regarding therapeutic management will be detailed, mainly the place of surgical resection. We will show that the surgical management of incidental DLGGs is safe and shares better outcomes as compared with symptomatic DLGGs. This suggests that surgical removal should be proposed as soon as progression is demonstrated on close imaging follow-up (Pallud et al., 2010b; Potts et al., 2012; Duffau, 2012a, b).

Definition and Epidemiology of Incidental Diffuse Low-Grade Gliomas

The incidental discovery of a DLGG can be defined as a previously undetected tumor at the time of imaging diagnosis that was unexpectedly discovered and unrelated to the purpose of the MR examination (Pallud et al., 2010b). Hence, incidental DLGGs are diagnosed due to MR imaging for nonspecific symptoms in ~70 % of cases (headaches, dizziness, mood disorders, hearing loss, gait disturbance, infection), through workup of other intracranial lesions in ~15 % (other primary brain tumor, schwannoma, meningioma, pituitary adenoma, aneurysm, arteriovenous malformation, cerebellar atrophy, Chiari malformation), through MRI screening of healthy volunteers under investigational protocols in ~11 % and following head trauma in ~5 % (Pallud et al., 2010b; Potts et al., 2012; Duffau, 2012a, b).

In literature, the reported prevalence of incidental DLGGs ranges from 0.025 to 0.2 %: Katzman et al. (1999) identified one histologically proven DLGG and one suspected DLGG in 1,000 healthy volunteers that underwent a MRI for an investigational protocol; Onizuka et al. (2001) identified one histologically proven DLGG in 4,000 patients that underwent a MRI for a brain check-up; Vernooij et al. (2007) identified one suspected DLGG in 2,000 healthy volunteers that underwent a MRI for an investigational protocol. Weber and Knopf (2006) identified five suspected primary brain tumors in 2,536 applicants for military flying duties in the German Air Force. More recently, Morris et al. (2009) estimated the prevalence of incidental DLGG on MRI at 0.05 % from a meta-analysis of observational studies. In a prospective cohort study, Floeth et al. (2008) followed 21 patients with an incidental, non-enhancing, supratentorial, lobar and small volume mass. In fives cases (23.8 %), MRI abnormalities regressed completely; in ten cases (47.6 %), MR abnormalities were stable and asymptomatic; in two cases (9.6 %), MR

abnormalities grew over years at known ranges for DLGGs, leading to a surgical management that demonstrated a DLGG in both cases; in four cases (19 %), MR abnormalities grew rapidly, leading to a surgical management that demonstrated a malignant glioma in all cases. This interesting study shows that incidental MR abnormalities are an actual incidental diffuse glioma in, at least, 30 % of cases. Moreover, it shows that incidental diffuse gliomas can be revealed during the "low-grade" period, leading to a symptomatic DLGG or can remain silent until malignant transformation occurs, leading to a symptomatic malignant glioma (WHO grade III and IV gliomas, including the so-called secondary glioblastomas) (Nobusawa et al., 2009). In addition, this partly explains the gap we observe between the prevalence of incidental DLGGs (0.05 %) and those of symptomatic DLGGs (0.01 %) (Davis et al., 2001; Zouaoui et al., 2012).

In published series of diffuse gliomas, the reported rates of incidentally discovered tumors range from ~3 to 5 % (Bauchet et al., 2007; Kamiguchi et al., 1996). Regarding DLGGs, Olson et al. (2000) reported a 4.7 % rate of incidentally discovered tumors from a series of DLGGs with an oligodendroglial component, Pallud et al. (2010b) reported a 3.8 % rate incidentally discovered tumors in a multicentre French database of DLGGs (Réseau d'Etude des Gliomes, REG), and Potts et al. (2012) reported a 9.6 % rate of incidentally discovered tumors from a surgical series of DLGGs. Hence, the incidental discovery of DLGG remains rare in clinical practice. To our knowledge, 118 cases of incidental DLGGs have been reported in literature (Potts et al., 2012; Duffau, 2012a, b; Shah et al., 2012), the largest series comprising 47 cases (Pallud et al., 2010b). The frequency of brain imaging for a wide variety of unrelated complaints in addition to recent advances in imaging technology with increased sensitivity will increase the occurrence of incidentally discovered DLGGs, and will increase the probability for a neurosurgeon to encounter DLGGs in the future.

Natural Course of Incidental Diffuse Low-Grade Gliomas

The natural course of DLGGs, as observed in clinical practice, can be summarized as a three-step process (Pallud and Mandonnet, 2011). The first two steps correspond to the histological "low-grade" of malignancy with an initial silent period before clinical revelation followed by a symptomatic period. The third step corresponds to the progression to a higher grade of malignancy. Beyond this artificial clustering of the DLGG natural course, there is an actual continuum from "low-grade" to "high-grade" malignancy.

The beginning of the silent period, i.e., the "birthdate" of DLGGs is not known. Hence, the tumor genesis is still a matter of debate. Tumors probably occur during the young adult period as suggested by rare reports of a normal MRI examination several years before the DLGG discovery (Duffau et al., 2011) (Fig. 11.1). This finding is in agreement with the fact that DLGGs are distinct entities in pediatric and adult populations with different natural courses and prognoses (Bristol, 2009). A recent study addressed the question of the DLGGs birthdate using modeling (Gérin et al., 2011). Gérin et al. (2011) extrapolate the imaging tumor growth during the silent period from available data obtained during the symptomatic period in a selected population of 144 adult patients harboring a supratentorial and hemispheric histologically proven DLGGs with an available MRI follow-up before any oncological treatment without clinical, imaging and pathological evidence of malignant transformation. Based on the assumptions of this model, they concluded that the mean age of the patient at the onset of the tumour was ~18 years. They identified two populations of DLGGs (Fig. 11.1). The first population corresponds to very slow growing tumors (with a rate of diametric expansion between 1 and 4 mm/year) that appear during adolescence, at a mean 15 years. The second population corresponds to slow growing tumors (with a rate of diametric expansion between 4 and

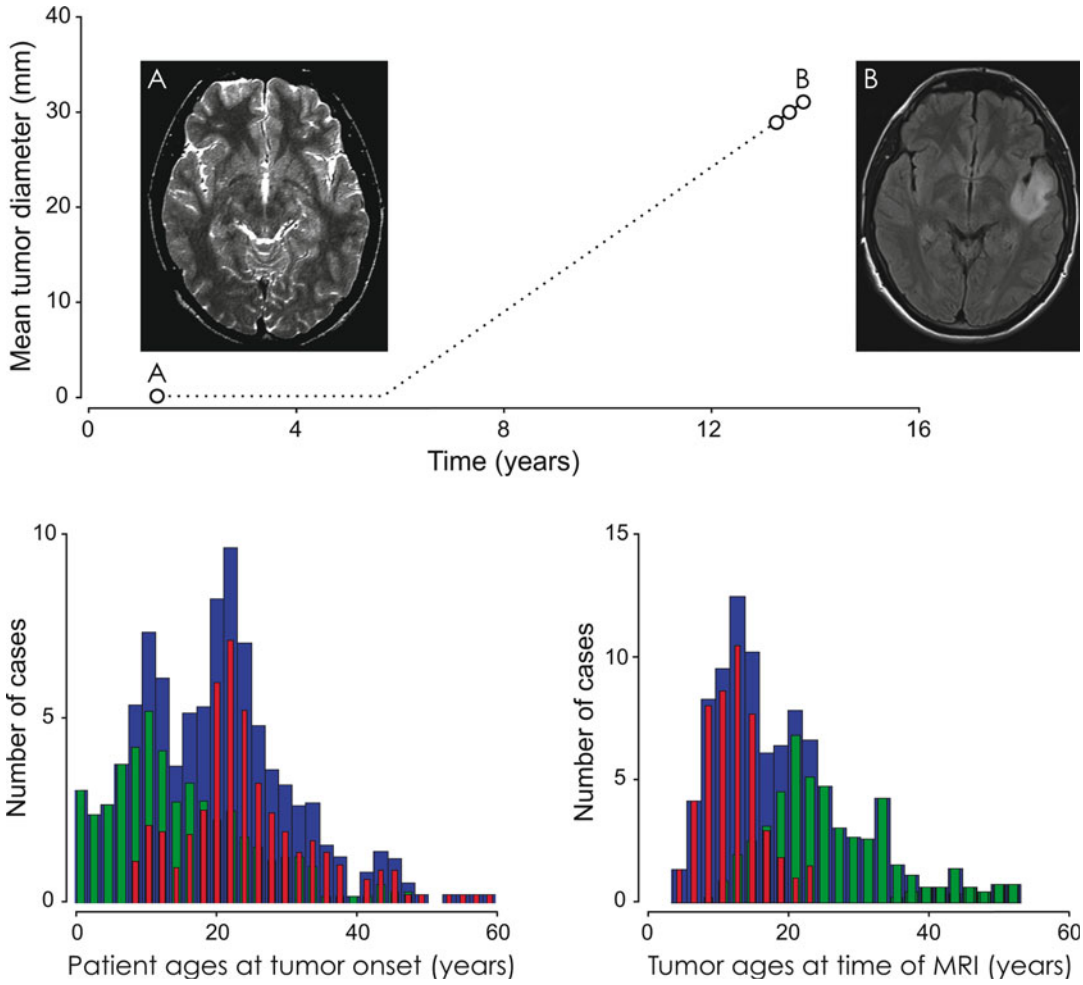

Fig. 11.1 Birthdate of diffuse low-grade gliomas. *Up*: Illustration of the diffuse low-grade glioma tumorigenesis (Adapted from Duffau et al., 2011). Example of a left temporo-insular diffuse low-grade glioma discovered incidentally in a 31-year-old right-handed man that underwent MRIs for a Chiari malformation. The first MRI, performed 12 years earlier, did not detect signal abnormality. *Down*: Estimation of the birthdates of diffuse low-grade gliomas by modeling (Adapted from Gérin et al., 2011). Distribution of the patient ages at the onset of the tumor (*left*): all patients (*blue histogram*, mean 18 years). Patients with tumor imaging velocities between 1 and 4 mm/year (*green histogram*, mean 15 years). Patients with tumor imaging velocities between 4 and 8 mm/year (*red histogram*, mean 25 years). Distributions of the tumor ages at the time of MRI examination (*right*): all patients (*blue histogram*, mean 18 years). Patients with tumor imaging velocities between 1 and 4 mm/year (*green histogram*, mean = 25 years). Patients with tumor imaging velocities between 4 and 8 mm/year (*red histogram*, mean = 11.5 years)

8 mm/year) that appear during early adulthood, at a mean 25 years. As a consequence, all of the studied tumors were detectable at an approximate patient age of 30 years. In parallel, they demonstrated that the mean age of DLGGs at the time of first MR examination was 17.6 years; thus, suggesting a very long silent period before clinical revelation of a DLGG.

Three recent studies addressed the natural course of incidental DLGGs: Pallud et al. (2010b) reported 47 cases of both treated and untreated incidental DLGGs with a mean follow-up of 6.6 years, whereas Potts et al. (2012) and Duffau (2012b) reported 35 cases and 11 cases, respectively, of incidental DLGGs operated on while asymptomatic with a mean follow-up of

5.1 and 5.0 years, respectively. They showed that DLGGs present a spontaneous imaging tumor growth before treatment in all available cases, that can be quantified by the rate of diametric expansion, at a median range ~4 mm/year (Pallud et al., 2010b, c, 2012; Potts et al., 2012; Floeth et al., 2008) (Fig. 11.2). When not treated, incidental DLGGs become symptomatic with time at a median 4.0 years since radiological discovery and can turn towards a higher grade of malignancy at a median 5.7 years since radiological discovery (Pallud et al., 2010b). After oncological treatment while asymptomatic, DLGGs can present tumor recurrence in 18–36 % of cases at a median 2.1–4.8 years, even after complete surgical resection (Pallud et al., 2010b; Potts et al., 2012; Duffau, 2012b). Similarly, malignant transformation have been documented after oncological treatment while asymptomatic in 11–27 % of cases at a median 3.2–5.7 years, leading ultimately to death in 2.8–8.5 % of cases (Pallud et al., 2010b; Potts et al., 2012; Duffau, 2012b). Tumor progression, malignant transformation, and death rates will likely increase with the follow-up of such incidental DLGGs. Finally, one study showed that incidental diffuse gliomas can remain silent until malignant transformation occurs, leading to a symptomatic malignant glioma (Floeth et al., 2008).

Do Incidental DLGG Differ from Symptomatic Diffuse Low-Grade Gliomas?

Incidental DLGGs differ from symptomatic DLGGs in several respects. There is a female predominance, while DLGGs are generally most common in men, and age at radiological discovery is lower (Pallud et al., 2010b; Potts et al., 2012). In addition, incidental DLGGs present with smaller tumour volumes at the time of discovery as compared to symptomatic DLGGs (Pallud et al., 2010b; Potts et al., 2012). Accordingly, tumors are limited to one lobe in most of the cases, with rare corpus callosum involvement and midline crossing. The absence of clinical symptoms at the time of imaging discovery can be explained by a combination of limited mass effect, primarily frontal lobe involvement, tumor location in non-dominant hemisphere, and in non-eloquent areas (Pallud et al., 2010b; Potts et al., 2012). Contrast enhancement is less frequent in incidental DLGGs than in symptomatic DLGGs (Pallud et al., 2009, 2010b; Potts et al., 2012). On the other side, the imaging tumor rate, the histological subtypes, and the proliferation rates of incidental DLGG are similar to those of symptomatic DLGGs. Indeed, the rate of diametric expansion of incidental DLGGs was measured at 2–4 mm/year (Floeth et al., 2008; Potts et al., 2012; Pallud et al., 2010b) and was within the range of symptomatic DLGGs. The data suggest that incidental DLGGs are progressive tumors that develop at a similar range to that for symptomatic DLGGs and suggest that incidental DLGGs represent an earlier step than symptomatic DLGGs in the natural tumor course. Thus, incidental DLGGs should be considered as progressive tumors with the same potential for progression as symptomatic DLGGs (Pallud et al., 2010b). This is supported by the occurrence of clinical symptoms and of malignant transformation in incidental DLGGs.

Surgical Management of Incidental Diffuse Low-Grade Gliomas

The surgical management of symptomatic DLGGs is now well established, and an early maximal safe functional-based surgical resection, while preserving eloquent brain areas using peroperative mapping, is currently the first treatment option to consider, as recommended by the European Guidelines (Duffau, 2009; Soffietti et al., 2010). Indeed, there is a growing trend, supported by large series, that the extent of resection is a significant prognostic factor for malignant progression-free survival and overall survival for DLGGs (Mcgirt et al., 2008; Sanai and Berger, 2008; Sanai et al., 2008; Smith et al., 2008). In patients harboring a symptomatic DLGG, the risk of any surgical complication is largely overshadowed by the survival and functional benefits. Epileptic seizures and/or anti-epileptic drugs

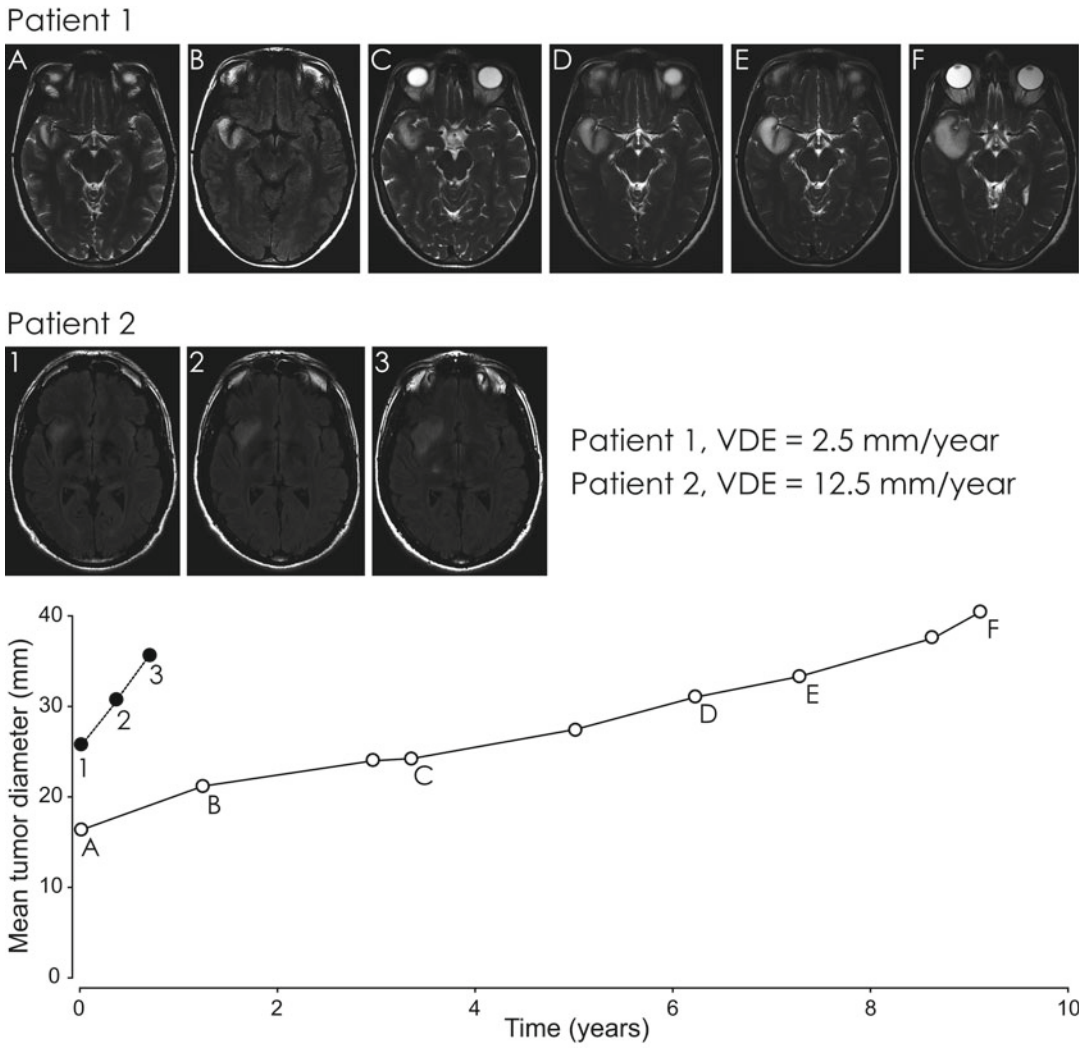

Fig. 11.2 Natural history of incidental diffuse low-grade gliomas. Patient 1. Example of a right temporo-insular diffuse low-grade glioma discovered incidentally in a 33-year-old right-handed woman that underwent a MRI of the head and the neck for the preoperative workup of a thoraco-brachial outlet syndrome. She was followed in an outside institution that proposed a wait-and-watch strategy with control MRIs. Astonishingly, they concluded to a stable disease on repeat control MRIs after qualitative images analysis. Contrarily, the quantitative follow-up demonstrated a spontaneous and continuous growth of the mean tumor diameter with a velocity of diametric expansion (VDE) at 2.5 mm/year with a tumor volume of 2 cc at the time of discovery and 32 cc at the time of surgery. On the last MR examination, a faint and patchy contrast enhancement appeared on the insular part of the tumor. The patient asked for a second advice in our institution. Although the patient was asymptomatic, we proposed and performed a complete resection of the tumor using intraoperative cortical and subcortical mapping. Neuropathological examination confirmed a World Health Organization (WHO) grade II mixed glioma, with anaplastic microfoci, with IDH1-positive immunoexpression and p53-positive immunoexpression but with no 1p19q codeletion. Patient 2. Example of a right insular diffuse glioma discovered incidentally in a 48-year-old right-handed man that underwent a MRI for a tinnitus. The follow-up at 5 and 9 months evidenced a rapidly growing mass with a spontaneous VDE higher than 12 mm/year, with extension along acoustic radiations. The patient was operated on, evidencing a WHO grade III glioma. Tinnitus resolved after surgery. Considering the high growth rate (hampering functional compensation by plasticity mechanisms) and the resolution after surgery, tinnitus should be retrospectively probably associated with this lesion. The incidental discovery is thus questionable in this situation

usually affect the quality of life of these patients (Klein et al., 2003). Hence, the functional benefit for symptomatic patients comes as an additional bonus to the survival benefit of surgical resection, leading to the concept of functional surgical neurooncology (Duffau, 2009).

This makes the difference when managing a patient with an incidental DLGG and raises a fundamental ethical question: is it legitimate to take the (minimal) risk to harm a patient, as there is no symptoms to relieve and there is no guarantee that the patient will be definitely cured, even after supratotal resection? The surgical management of incidental DLGGs can be guided by their natural history: (1) they are progressive tumors; (2) they evolve toward symptomatic DLGGs; (3) they can contain microfoci of malignancy (Duffau, 2012b) and can transform toward a malignant glioma (Pallud et al., 2010b); (4) they may become symptomatic only after malignant transformation (Floeth et al., 2008). Thus, incidental DLGGs are not a benign tumor, but an entity that will progress. The similarity of the natural course of DLGGs during the silent and symptomatic period supports a "preventive" resection, and therapeutic management of incidental DLGGs should be inspired by the same principles guiding the active attitude for symptomatic DLGGs.

The surgical management of incidental DLGGs has been addressed in recent studies. A higher rate of gross total resection was achieved in the group of incidental DLGGs in comparison with a control group of symptomatic DLGGs: 38 % versus 15 % (Pallud et al., 2010b), 60 % vs. 31.5 % (Potts et al., 2012), 60 % vs. 32 % (including 28 % of supratotal resections) (Duffau, 2012a, b). It is likely that such high rate of maximal resection in incidental DLGGs was made possible because the tumor volume was smaller and with a lower frequency of involvement of functional brain areas (Pallud et al., 2010b; Potts et al., 2012; Duffau, 2012b). This makes surgical resection easier and allows functional-based resection beyond MRI-defined abnormalities, the so-called supratotal resection (Pallud et al., 2010a, b; Yordanova et al., 2011) (Fig. 11.3). In addition, these studies showed that surgical morbidity was actually lower in patients with incidental DLGGs, and that surgery can be performed with a high rate of preservation of quality of life (Potts et al., 2012; Duffau, 2012b). Indeed, Duffau (2012b) reported a transient neurological worsening in 63 % of cases, with no permanent neurological deficit and a return to a normal social and professional life in all cases. Pallud et al. (2010b) and Potts et al. (2012) demonstrated that patients operated on for incidental DLGGs had an improved overall survival in comparison with a control group of symptomatic DLGGs. Therefore, taken together, these data plead for an early surgical treatment in asymptomatic patients to maximize the extent of resection before glioma growth and migration, even in critical brain regions. This was previously suggested by Kelly (2010) who claimed it could be important to find DLGGs when they are small, before they turn malignant and ideally in their silent period, when they may still be "curable" by some minimally invasive surgical method, because it is easier and safer to operate on a small lesion.

Practical Implications

An initial longitudinal follow-up is needed. Proven progression on imaging is the "sine qua non" condition before offering a proactive attitude to a patient harboring an incidental DLGG. Indeed, even if multimodal MRI suggests the diagnosis of DLGG with a high level of confidence, differential diagnosis cannot be excluded on a single time point examination, and MR abnormalities can regress spontaneously (Floeth et al., 2008). Sequential MRI follow-up allows measuring the spontaneous velocity of diameter expansion (i.e., the imaging tumor growth), a pivotal parameter characterizing the tumor aggressiveness (Pallud et al., 2006, 2012) together with the initial tumor volume (Pallud et al., 2010b). The second MRI should be performed 3–4 months after the first one, to make sure that the tumor is not growing fast, which would lead to reconsider the diagnosis of incidental DLGG and to envision the diagnosis of incidental

malignant glioma (Floeth et al., 2008) or to reconsidering the incidental nature of the discovery (Fig. 11.2). A third MRI should eventually be done 9–12 months after initial MRI. With MRI follow-up spanning over a 3–12-month period, one can accurately measure the rate of diameter expansion (Pallud et al., 2012). During this preoperative period, it is recommended to perform an extensive neuropsychological assessment as advised for symptomatic DLGGs and a preoperative functional as well as metabolic neuroimaging. Indeed, positron emission tomography with the 18F-labeled amino acid fluoroethyl-L-tyrosine seems to detect growth of incidentally discovered diffuse gliomas and could be integrated in the follow-up of incidentally discovered MRI abnormalities (Floeth et al., 2008).

Once evolutivity is proven, the timing of the treatment should be adapted to both the tumors characteristics (rate of diameter evolution and initial diameter) and the personal wishes of the patient (Fig. 11.3).

- For very small (diameter <3 cm) *and* very slow (rate <1–2 mm/year) tumors, the timing of the surgical resection is not very urgent, especially for those tumors located in non-eloquent areas. In such situation, if the patient asks to delay surgery for personal reasons, an initial "wait-and-watch" policy should be accepted. During this conservative follow-up, surgery should be triggered whenever it is believed that further growth would preclude to perform a complete resection : the benefit of a complete resection would then clearly override the functional risk. Ideally, an early surgery should be offered, with the aim to perform a supratotal resection (Yordanova et al., 2011).
- For larger (diameter >3 cm) or faster (>3 mm/year) tumors, immediate surgery is preferred.

Of course, it seems reasonable to allow some time to the patient after the incidental diagnosis and before surgery. When recommending surgery for an incidental DLGG, the patient should be informed that while there is no definitive data in the literature supporting this proactive attitude, it can be built on the following reasoning : (1) the more extensive the surgery of a DLGG, the better the overall prognosis; (2) incidental DLGGs are progressive tumors that become symptomatic; (3) the sooner the surgery, the higher the chances to perform a complete or a supratotal resection, and hence the better the overall prognosis. Of course, the (minimal) functional risks should be discussed with the patient.

Conclusion

Incidental DLGGs are progressive tumors that become symptomatic with time and can be transformed into malignant gliomas. The latter behave like symptomatic DLGGs and represent an earlier step in the natural history of a diffuse glioma. In addition, incidental diffuse gliomas can remain silent until malignant transformation occurs. The similarity of the natural course of DLGGs during the silent and symptomatic period supports a "preventive" approach for incidental DLGGs that should be managed as symptomatic DLGGs. Surgical resection of incidental DLGGs is feasible with a minimal morbidity and larger amount of resections can be obtained compared with symptomatic DLGGs. These data argue for an early surgical treatment in asymptomatic patients, and surgical removal with functional peroperative mapping can be proposed as soon as progression is demonstrated on close imaging follow-up.

Fig. 11.3 (continued) Complete resection was performed. Post-operative MRI revealed a small infarct surrounding the depth of the cavity, probably in keeping with bipolar coagulation of a small artery in the F2-F3 sulcus that was bleeding after subpial dissection. At last follow-up, patient had a normal life, except that difficulties in multitasking prevented him to resume his professional activity. He felt indeed unable to sustain the high cognitive load required by his job. Retrospectively, opting for an initial "wait and watch" strategy in this patient and offering surgery 2 years later at the moment of his retirement could have been a better strategy, at the condition the patient would have accepted the unquantified, but probably low, risk that the tumor became malignant within this 2-year long period

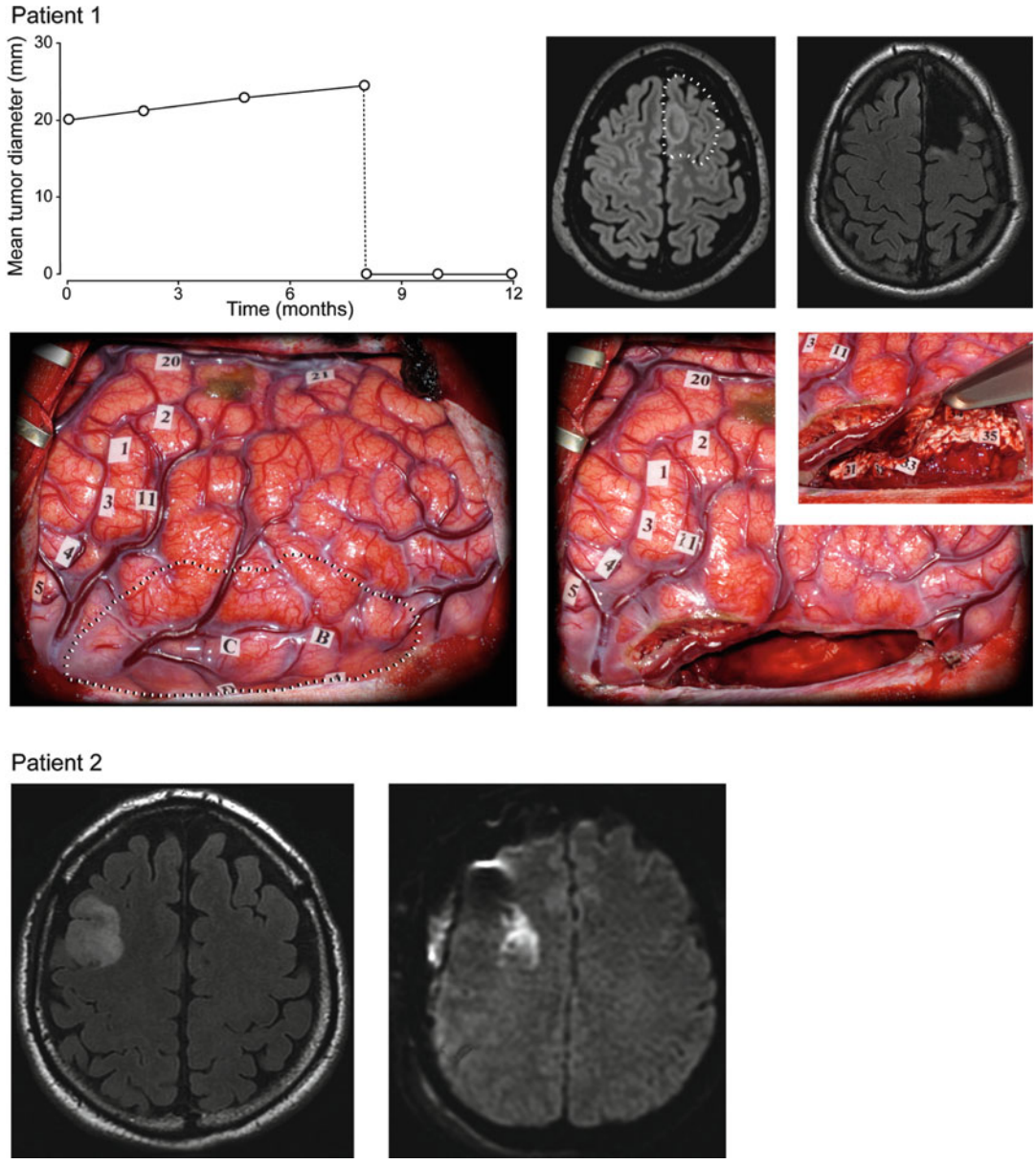

Fig. 11.3 Surgical management of incidental diffuse low-grade gliomas. Patient 1. Example of a left frontal diffuse low-grade glioma discovered incidentally in an asymptomatic 35-year-old right-handed man that underwent a research MRI for an investigational protocol (*up middle*). The preoperative MRI follow-up (*up left*) demonstrated a spontaneous and continuous growth of the mean tumor diameter with a velocity of diametric expansion (VDE) at 6.7 mm/year with a tumor volume of 4 cc at the time of discovery and 7 cc at the time of surgery. A complete resection of the tumor associated with a resection of a margin of security within the surrounding brain parenchyma (the so-called supratotal resection) was performed under awake condition according to functional boundaries (*number tags*) provided by intraoperative cortical and subcortical electrostimulation mapping (*down left* and *right*). The postoperative MRI confirmed the large resection (*up right*). Neuropathological examination confirmed a World Health Organization grade II oligodendroglioma with IDH1-positive immunoexpression and p53-positive immunoexpression but with no 1p19q codeletion. Patient 2. Example of a right frontal diffuse low-grade glioma discovered incidentally in a 58-year-old right-handed man that underwent a MRI of the head and the neck for the preoperative workup of a benign angiofibroma of the nasopharynx. The lesion was small with a tumor volume of 2.5 cc and, looking back at 10 years of follow-up, very slowly growing with a VDE at 1 mm/year.

Acknowledgments Johan Pallud and Emmanuel Mandonnet want to thanks all the members of the French Glioma Network (REG, Réseau d'Etude des Gliomes) and particularly Hugues Duffau.

Johan Pallud wants to thank Bertrand Devaux and François-Xavier Roux of the department of Neurosurgery, Pascale Varlet and Fabrice Chrétien of the department of Neuropathology and Catherine Oppenheim and Jean-François Meder of the department of Neuroradiology of the Sainte-Anne Hospital Center, Paris, France.

References

Bauchet L, Rigau V, Mathieu-Daudé H, Figarella-Branger D, Duffau H, Palusseau L, Bauchet F, Fabbro M, Campello C, Capelle L, Durand A, Trétarre B, Frappaz D, Hénin D, Menei P, Honnorat J, Segnarbieux F (2007) French brain tumor data bank: methodology and first results on 10,000 cases. J Neuro Oncol 84(2):189–199

Bristol RE (2009) Low-grade glial tumors: are they all the same? Semin Pediatr Neurol 16(1):23–26

Davis FG, Kupelian V, Freels S, McCarthy B, Surawicz T (2001) Prevalence estimates for primary brain tumors in the United States by behavior and major histology groups. Neuro Oncol 3(3):152–158

Duffau H (2009) Surgery of low-grade gliomas: towards a 'functional neurooncology'. Curr Opin Oncol 21(6):543–549

Duffau H (2012a) The rationale to perform early resection in incidental diffuse low-grade glioma: towards a 'preventive surgical neurooncology'. World Neurosurg, 2012 Jun 25. doi:pii: S1878-8750(12)

Duffau H (2012b) Awake surgery for incidental WHO grade II gliomas involving eloquent areas. Acta Neurochir 154(4):575–584

Duffau H, Pallud J, Mandonnet E (2011) Evidence for the Genesis of WHO Grade II Glioma in an asymptomatic young adult using repeated MRIs. Acta Neurochir 153(3):473–477

Floeth FW, Sabel M, Stoffels G, Pauleit P, Hamacher K, Steiger HJ, Langen KJ (2008) Prognostic value of 18F-Fluoroethyl-L-Tyrosine PET and MRI in small nonspecific incidental brain lesions. J Nucl Med 49(5):730–737

Gérin C, Pallud J, Grammaticos B, Mandonnet E, Deroulers C, Varlet P, Capelle L, Taillandier L, Bauchet L, Duffau H, Badoual M (2011) Improving the time-machine: estimating date of birth of grade II gliomas. Cell Prolif 45(1):76–90

Kamiguchi H, Shiobara R, Toya S (1996) Accidentally detected brain tumors: clinical analysis of a series of 110 patients. Clin Neurol Neurosurg 98(2):171–175

Katzman GL, Dagher AP, Patronas NJ (1999) Incidental findings on brain magnetic resonance imaging from 1000 asymptomatic volunteers. JAMA 82(1):36–39

Kelly PJ (2010) Gliomas: survival, origin and early detection. Surg Neurol Int 1:96

Klein M, Engelberts N, van der Ploeg HM, Kasteleijn-Nolst Trenité D, Aaronson N, Taphoorn M, Baaijen H, Vandertop WP, Muller M, Postma TJ, Heimans JJ (2003) Epilepsy in low-grade gliomas: the impact on cognitive function and quality of life. Ann Neurol 54(4):514–520

Mandonnet E, Delattre JY, Tanguy ML, Swanson KR, Carpentier AF, Duffau H, Cornu P, Van Effenterre R, Alvord EC, Capelle L (2003) Continuous growth of mean tumor diameter in a subset of grade II gliomas. Ann Neurol 53(4):524–528

Mcgirt MJ, Chaichana KJ, Attenello FJ, Weingart JD, Than K, Burger PC, Olivi A, Brem H, Quinoñes-Hinojosa A (2008) Extent of surgical resection is independently associated with survival in patients with hemispheric infiltrating low-grade gliomas. Neurosurgery 63(4):700–707

Morris Z, Whiteley WN, Longstreth WT, Weber F, Lee YC, Tsushima Y, Alphs H, Ladd SC, Warlow C, Wardlaw JM, Al-Shahi Salman R (2009) Incidental findings on brain magnetic resonance imaging: systematic review and meta-analysis. BMJ 339:b3016

Nobusawa S, Watanabe T, Kleihues P, Ohgaki H (2009) IDH1 mutations as molecular signature and predictive factor of secondary glioblastomas. Clin Cancer Res 15(19):6002–6007

Olson JD, Riedel E, DeAngelis LM (2000) Long-term outcome of low-grade oligodendroglioma and mixed glioma. Neurology 54(7):1442–1448

Onizuka M, Suyama K, Shibayama A, Hiura T, Horie N, Miyazaki H (2001) Asymptomatic brain tumor detected at brain check-up. Neurol Med Chir 41(9):431–434

Pallud J, Mandonnet E (2011) Chapter 18. In: Hayat MA (ed) Quantitative approach of the natural course of diffuse low-grade gliomas. Tumors of the central nervous system, vol 2. Springer, Dordrecht

Pallud J, Mandonnet E, Duffau H, Kujas M, Guillevin R, Galanaud D, Taillandier L, Capelle L (2006) Prognostic value of initial magnetic resonance imaging growth rates for world health organization grade ii gliomas. Ann Neurol 60(3):380–383

Pallud J, Capelle L, Taillandier L, Fontaine D, Mandonnet E, Guillevin R, Bauchet L, Peruzzi P, Laigle-Donadey F, Kujas M, Guyotat J, Baron MH, Mokhtari K, Duffau H (2009) Prognostic significance of imaging contrast enhancement for who grade ii gliomas. Neuro Oncol 11(2):176–182

Pallud J, Varlet P, Devaux B, Geha S, Badoual M, Deroulers C, Page P, Dezamis E, Daumas-Duport C, Roux FX (2010a) Diffuse low-grade oligodendrogliomas extend beyond MRI-defined abnormalities. Neurology 74(21):1724–1731

Pallud J, Fontaine D, Duffau H, Mandonnet E, Sanai N, Taillandier L, Peruzzi P, Guillevin R, Bauchet L, Bernier V, Baron MH, Guyotat J, Capelle L (2010b) Natural history of incidental world health organization grade ii gliomas. Ann Neurol 68(5):727–733

Pallud J, Capelle L, Mandonnet E (2010c) Comment on parameters of low-grade glioma as predictors. Radiology 256(3):1014

Pallud J, Taillandier L, Capelle L, Fontaine D, Peyre M, Ducray F, Duffau H, Mandonnet E (2012) Quantitative morphological magnetic resonance imaging follow-up of low-grade glioma. Neurosurgery 71(3):729–740

Potts MB, Smith JS, Molinaro AM, Berger MS (2012) Natural history and surgical management of incidentally discovered low-grade gliomas. J Neurosurg 116(2):365–372

Sanai N, Berger MS (2008) Glioma extent of resection and its impact on patient outcome. Neurosurgery 62(4):753–764

Sanai N, Mirzadeh Z, Berger MS (2008) Functional outcome after language mapping for glioma resection. N Engl J Med 358(1):18–27

Shah AH, Madhavan K, Sastry A, Komotar RJ (2012) Managing intracranial incidental findings suggestive of low-grade glioma: learning from experience. World Neurosurg, Jun 19. doi:pii: S1878-8750(12)

Smith JS, Chang EF, Lamborn KR, Chang SM, Prados MD, Cha S, Tihan T, Vandenberg S, McDermott MW, Berger MS (2008) Role of extent of resection in the long-term outcome of low-grade hemispheric gliomas. J Clin Oncol 26(8):1338–1345

Soffietti R, Baumert BG, Bello L, Von Deimling A, Duffau H, Frénay M, Grisold W, Grant R, Graus F, Hoang-Xuan K, Klein M, Melin B, Siegal T, Smits A, Stupp R, Wick W (2010) Guidelines on management of low-grade gliomas: report of an EFNS-EANO* task force. Eur J Neurol 7(9):1124–1133

Vernooij M, Ikram MA, Tanghe HL, Vincent AJ, Hofman A, Krestin GP, Niessen WJ, Breteler MM, van der Lugt A (2007) Incidental findings on brain mri in the general population. N Engl J Med 357(18):1821–1828

Weber F, Knopf H (2006) Incidental findings in magnetic resonance imaging of the brains of healthy young men. J Neurol Sci 240(1–2):81–84

Yordanova YN, Moritz-Gasser S, Duffau H (2011) Awake surgery for who grade ii gliomas within "noneloquent" areas in the left dominant hemisphere: toward a 'supratotal' resection. Clinical article. J Neurosurg 115(2):232–239

Zouaoui S, Rigau V, Mathieu-Daudé H, Darlix A, Bessaoud F, Fabbro-Peray P, Bauchet F, Kerr C, Fabbro M, Figarella-Branger D, Taillandier L, Duffau H, Trétarre B, Bauchet L (2012) French brain tumor database: general results on 40,000 cases, main current applications and future prospects. Neurochirurgie 58(1):4–13

Part III

Stereotactic Radiosurgery

Stereotactic Radiosurgery for the Treatment of Brain Metastases

12

Emmanouil Fokas

Contents

Abstract

Stereotactic radiosurgery (SRS) constitutes a highly conformal radiotherapy technique that aims to deliver a single, large radiation dose with high precision to the target volume while sparing adjacent normal tissues. SRS is an important therapeutic modality in the treatment of patients with brain metastases (BM) as it has proven benefits for local control in individuals with both single and multiple lesions. The purpose of the present article is to review the role of SRS in the management of BM. We briefly examine the technical basis and application characteristics, the various prognostic factors that affect treatment outcome and the safety of SRS in patients with BM. The clinical evidence and rationale for the use of SRS, either alone or in combination with other modalities are discussed, based mainly on randomized and prospective clinical studies and some important retrospective analyses. We finally highlight important future perspectives and open questions in regards to this important therapeutic option and discuss how we can improve the efficacy of SRS for the benefit of patients with BM.

Introduction

Brain metastases (BM) occur in a large proportion of patients with malignant tumors (up to 40–50 % in some histological types) (Gavrilovic and

E. Fokas (✉)
Department of Radiation Therapy and Oncology, Johann Wolfgang Goethe University, Frankfurt, Germany
e-mail: Emmanouil.fokas@yahoo.de

M.A. Hayat (ed.), *Tumors of the Central Nervous System, Volume 11*,
DOI 10.1007/978-94-007-7037-9_12,

Posner, 2005). The incidence of BM has been increasing as advances in systemic treatment lead to prolonged patient survival and hence increased risk for developing metastatic tumor spread to the brain (Gavrilovic and Posner, 2005). Even though detailed epidemiological studies are lacking, it has been estimated that 35–45 % of patients with solid tumors present with single cerebral lesions and 50–60 % have multiple BM at initial diagnosis (Cavaliere and Schiff, 2006).

Therapeutic options for patients with BM include surgical resection, whole brain radiotherapy (WBRT) and stereotactic radiotherapy (SRS) (Soffietti et al., 2008). The prognosis of patients with BM is dismal and most individuals treated with WBRT alone have a median survival of 3–4 months (except patients with small cell lung cancer; SCLC). Approximately 50 % of the deaths are related to the BM and their associated neurological side effects (Soffietti et al., 2008). Hence, significant efforts have been made to increase local control (LC) and improve patient outcome but also quality of life. In the present chapter, the role of SRS in the management of BM will be discussed. The efficacy of SRS, either alone or in combination with other modalities, in comparison to alternative therapeutic options will also be examined.

Radiosurgery: Technical Basis, Application and Safety

SRS can be applied using either a conventional linear accelerator or more specialized equipment such as Gammaknife®, Brainlab Novalis™ and Cyberknife® (Chung and Kim, 2012). SRS enables the delivery of high radiation doses with precision to a defined target in a single therapeutic session (Chung and Kim, 2012). Precise patient immobilization and positioning is required for administering SRS in a safe and efficient manner. This is enabled by the use of an invasive stereotactic ring (frame), a non-invasive frame or a frameless system that directs accurate targeting of the radiation beam targeting. The accuracy of positioning in most SRS platforms varies between 1 and 2 mm. Linac-based SRS can be administered using multiple beams with modern tools (micro-multileafs or arcs) that enable a steep dose-gradient at the margins of the radiation field (Chung and Kim, 2012). In consequence, the exposure of the surrounding normal brain tissues to radiation and the subsequent toxicity are low, although this depends on the dose applied and the metastatic lesion size (Cavaliere and Schiff, 2006; Chung and Kim, 2012).

Radiotherapy planning is performed using computed tomography imaging co-registered i.e. fused with magnetic resonance imaging. The planning target volume (PTV) is consisted of gross tumour volume (GTV), based on contrast extension in MRI, plus a safety margin that depends on the accuracy of the equipment used. Usually a safety margin of 2 mm is considered sufficient. The dose distribution to the organs at risk, such as brainstem, basal ganglia, eyes, optic chiasm and optic nerves should be taken into consideration. SRS is often used in patients with small lesions (usually with a diameter $\leq$3 cm i.e. less than 10 cc in volume) (Sanghavi et al., 2001; Shaw et al., 2000). While some radiation oncologists advocate SRS for up to three BM, others chose to apply SRS for more than three lesions.

SRS is characterized by several advantages over conventional radiotherapy for brain metastases. Treatment with a single fraction of large radiation dose is expected to result in extensive vascular damage and increased direct tumor cell killing and hence better tumor control (Jagannathan et al., 2007; Park et al., 2012; Soffietti et al., 2008). This is highly relevant in the treatment of BM induced from radioresistant tumors such as melanoma, renal cell carcinoma or sarcoma, where WBRT often fails to control metastatic tumors efficiently (Jagannathan et al., 2007; Powell et al., 2008).

SRS is a safe therapeutic option that can offer similar control rates to surgery, both for single and multiple lesions (Hillard et al., 2003; Muller-Riemenschneider et al., 2009). The majority of series report LC rates over 75 % (Muller-Riemenschneider et al., 2009). In contrast to surgery, SRS is non-invasive and requires minimal hospitalization. Moreover, lesions that are surgically inaccessible or are located very close to organs at risk such as in the deep white and gray

matter and brainstem can be treated with SRS (Koyfman et al., 2010).

A large amount of data has indicated that SRS is well-tolerated (Hatiboglu et al., 2011; Kondziolka et al., 2012). Acute side effects are induced by edema that results in headache and less frequently seizures. Edema usually occurs in a small proportion of patients (usually 4–5 %) shortly after SRS and it is well-manageable by corticosteroids (Monaco et al., 2012). Chronic side effects vary according to the size and location of the metastatic lesion and the dose applied (Kondziolka et al., 2012). Radionecrosis can occur several months post-radiotherapy but it is often challenging to distinguish from tumor progression (Blonigen et al., 2010; Monaco et al., 2012). Especially in the case of large lesions and/or BM located close to organs at risk, hypofractionated stereotactic radiotherapy i.e. delivery of relatively large doses in more than multiple fractions might be a better alternative option to avoid excessive toxicity (Fokas et al., 2012).

Several factors such as performance status, recursive partitioning analysis (RPA) class, tumor location, treatment volume, presence of extracranial disease and number of BM can affect the outcome of patients subjected to SRS (Andrews et al., 2004; Aoyama et al., 2006; Caballero et al., 2012; DiLuna et al., 2007; Likhacheva et al., 2012; Maranzano et al., 2012).

Although the dose-effect and tolerance of normal brain tissues to SRS had been examined by numerous retrospective studies (Shehata et al., 2004), the decision in regards to the optimal SRS dose for BM was until recently empirical and largely dependent on the clinical experience of the radiosurgery centre. The Radiation Therapy Oncology Group (RTOG) 90–05 clinical trial studied the dose-dependent tolerance of organs at risk, such as brainstem, in patients with BM or gliomas treated with SRS (Shaw et al., 2000). In total, 156 patients with tumor progression or recurrence upon conventional radiotherapy were treated with a dose-escalation schedule. The protocol allocated patients to initial doses of 18, 15, and 12 Gy for BM (or gliomas) with diameters <20, 21–30, and 31–40 mm, respectively. Prescription doses were escalated in 3 Gy intervals until more than 20 % of the patients encountered irreversible toxicity within 3 months. Notably, patients with tumors smaller than 20 mm in diameter never reached dose-limiting toxicity but doses were never escalated above 24–27 Gy. Based on that study, the investigators proposed administration of SRS using doses of 24, 18, and 15 Gy for BM with diameters of <20, 21–30, and 31–40 mm (Shaw et al., 2000). This important report constituted a keystone in the therapeutic management of BM as it was the first comprehensive study to provide dose guidance for application of SRS by radiation oncologists and neurosurgeons.

SRS also has limitations as large lesions (>3 cm in diameter) can only be treated safely with lower doses of SRS that compromises the therapeutic benefit (Shaw et al., 2000). In addition, BM that lead to midline shift and acute neurological deficits are not suitable for treatment with SRS and need surgical resection (Claus, 2012; Kondziolka et al., 2012).

SRS and Clinical Evidence in Patients with Brain Metastases

SRS Alone vs. SRS + WBRT

In a randomized clinical study, Aoyama et al. recruited patients with 1–4 BM and a maximum diameter of 3 cm to either SRS alone (n = 67; 16 % did not receive SRS; 16 % received salvage WBRT) or SRS + WBRT (n = 65; 9 % did not receive SRS; 3 % did not receive WBRT; 15 % received salvage SRS) (Aoyama et al., 2006). A third group of patients were treated with WBRT alone. Patient stratification was performed according to age, sex, histological subtype, number of BM, presence of extracranial metastases, Karnofsky performance scale (KPS) and mini mental status examination (MMSE) score and was comparable among the three treatment groups. Overall survival (OS) constituted the primary endpoint while secondary endpoints included LC, intracerebral control (IC), locoregional recurrence (LRR), KPS and MMSE score at 1-year together with neurologic death cause.

The median OS between SRS and SRS + WBRT was comparable (8 vs. 7.5 months, respectively) (Aoyama et al., 2006). Similarly, no significant differences were observed in 1-year LC rate, KPS score, MMSE score or neurologic death rates. In contrast, addition of WBRT to SRS resulted in significantly lower local failure (11.3 vs. 27.5 %), distant failure (41.5 vs. 63.7 %) or failure anywhere in the brain (46.8 vs. 76.4 %), indicating an important role of WBRT in improving LC and IC in this patient cohort (Aoyama et al., 2006). The same group investigated the impact of WBRT addition to SRS on the neurologic status of a patient subgroup (70 %) that had received pre-treatment and also follow-up MMSE examinations (Aoyama et al., 2007). The time to neurologic deterioration was significantly longer in the SRS + WBRT group compared to SRS alone (Aoyama et al., 2007). In a prospective clinical study conducted in patients with SCLC or non-small cell lung cancer (NSCLC) and single brain metastasis (diameter ≤4.5 cm), Li et al. compared the efficacy of SRS (n = 23) with SRS + WBRT (n = 18) in a three-arm study that also included WBRT alone (n = 19) (Li et al., 2000). Patient accrual was homogenous in terms of prognostic parameters. Similarly to the previous study, OS (9.3 vs. 10.6 months, respectively) and LRR were similar between SRS and SRS + WBRT while IC was not evaluated (Li et al., 2000). In a different retrospective study in 88 patients with renal cell carcinoma and BM, addition of WBRT to SRS resulted in better IC in RPA class I patients, indicating an important role of WBRT for the prevention of distal intracranial failure (Fokas et al., 2010).

WBRT Alone vs. SRS + WBRT

In an important randomised control trial conducted by the Radiation Therapy Oncology Group (RTOG), Andrews et al. randomized patients with 1–3 BM and a KPS ≥70 to either WBRT (n = 167; 17 % of patients were treated with salvage SRS) or WBRT + SRS (n = 164; SRS was not performed in 19 % of patients) (Andrews et al., 2004). Different parameters including age, sex, KPS, histological subtype and mental status were well-matched among the two groups. OS was the primary endpoint while secondary endpoints included KPS, MMSE at 6 months, local control at 12 months and cause of death. WBRT + SRS resulted in better OS in patients single metastatic lesions compared to WBRT alone (Andrews et al., 2004). Additionally, incorporation of SRS to WBRT led to better LC in patients with 1–3 BM, and improved KPS. OS was comparable in patients with more than one metastatic lesions and was not affected by MMSE or neurologic death incidence. The trial was characterised by lack of consistent follow-up imaging in a large proportion of patients (43 %) and a large crossover rate (Andrews et al., 2004). In a different clinical trial, Kondziolka et al. randomized patients with 2–4 BM, a mean diameter of 2.5 cm and a KPS ≥70 into either WBRT (n = 14) or WBRT + SRS (n = 13) (Kondziolka et al., 1999). Group matching was well performed for the different parameters (age, sex, number of lesions, histological types, KPS and presence of extracranial metastases). LC was the primary endpoint while OS and time to recurrence constituted the secondary endpoints. WBRT + SRS significantly improved LC compared to WBRT alone (LC at 1 year: 8 vs. 100 %, respectively) and time to local progression (36 vs. 6 months) (Kondziolka et al., 1999). Notably, this randomized trial did not reach its accrual target as the significantly better results in the combination group forced the investigators to stop the study at 60 % accrual. Even though addition of SRS to WBRT resulted in better median OS compared to WBRT alone (11 vs. 7.5 months, respectively), this difference was not significant, possibly due to the low number of patients recruited in this study (Kondziolka et al., 1999). Shangavi et al. retrospectively analysed the treatment outcome, based on RPA class in 502 patients with BM caused by tumors of variable histological type (Sanghavi et al., 2001). A statistically significant improvement in OS was observed in all three RPA classes in the SRS + WBRT group compared to WBRT, including patients with more than one cerebral metastasis, low KPS score and the presence of extracranial metastases. Interestingly, the

proportion of patients with radioresistant BM, such as melanoma was higher in the combination group (Sanghavi et al., 2001).

SRS + WBRT Versus Resection + WBRT

To the author's best knowledge, no randomized control studies have compared the efficacy of SRS + WBRT vs. resection + WBRT in the treatment of BM. In a retrospective study, Bindal et al. compared the two treatments in 62 patients with single brain metastasis and a diameter up to 3 cm (Bindal et al., 1996). Both groups were well-matched for prognostic factors. Resection + WBRT resulted in significantly better OS (16.4 vs. 7.5 months), time to recurrence and incidence of neurologic death (19 % vs. 50 %) than SRS + WBRT. Notably, this work only investigated one dose of SRS i.e. no BM size-dependent dose application was performed, and revealed a necrosis rate of 12.9 % (Bindal et al., 1996), which is much higher than the 4–5 % reported in the majority of the studies. Schoggl et al. (2000) also compared SRS + WBRT vs. resection + WBRT and revealed a median OS of 12 vs. 9 months, respectively. In that retrospective analysis, the time to LRR was shorter for the surgery-incorporating arm (3.9 vs. 4.9 months) while the incidence of neurologic deaths was higher (21.8 vs. 12.5 %). No differences in toxicity were observed between the two treatment arms (Schoggl et al., 2000).

SRS Alone vs. Resection + WBRT

In a randomized control study, Muacevic et al. compared SRS alone (n = 31) with resection + WBRT (n = 33) for the treatment of single brain metastasis with a diameter up to 3 cm (Muacevic et al., 2008). Both groups were well-matched for prognostic factors. No significant differences in OS (10.3 vs. 9.5 months, respectively), neurologic death or performance status were observed between the two arms (Muacevic et al., 2008). The incidence of intracranial recurrence was higher in the SRS arm (25.8 vs. 3 %, respectively) while resection + WBRT were was characterized by a higher incidence of grade 1–2 side effects. Notably, this study was stopped prematurely due to low accrual (25 %) (Muacevic et al., 2008). Furthermore, Rades et al. (2007a) retrospectively evaluated the outcome of patients with BM up to 4 cm in diameter after treatment with either SRS alone (n = 94) or resection + WBRT (n = 112). Patients included in the study had an RPA class I-II and both groups were well-matched for prognostic factors. A trend towards better 1-year survival was observed in the SRS alone group, compared to resection + WBRT (54 % vs. 38 %) but this was not significant. Similarly, no significant difference in 1-year LR rate (36 % vs. 44 %) or toxicity was noted (Rades et al., 2007a).

SRS or Resection Followed by WBRT or Observation

In a recent phase III randomized clinical study initiated by the European Organisation for Research and Treatment of Cancer, Kocher et al. (2011) investigated the impact of WBRT (10 × 3 Gy) on the outcome of 359 patients with 1–3 BM following treatment with either SRS (n = 199) or surgical resection (n = 160). The study included patients with stable extracranial disease or asymptomatic primary tumors and WHO performance status (PS) of 0–2. The primary endpoint was time to PS deterioration more than 2. In the SRS cohort, 99 patients were allocated to WBRT and 100 patients to observation. In the resection cohort, 81 patients received WBRT and 79 patients were randomized to the observation group. The median time to WHO PS more than 2 was similar (9.5 vs. 10 months for WBRT and observation, respectively) (Kocher et al., 2011). WBRT resulted in significantly reduced 2-year local and distal intracranial relapse rates after surgery and radiosurgery. This effect was most pronounced at the site of resection bed, where the frequency of recurrence was reduced from 60 % to less than 30 %. There was no difference in OS between any of the groups studied. Patients allocated to observation needed more salvage therapies than after WBRT. Similarly,

intracranial progression that resulted in death was commoner in the observation arm (44 %) than in the WBRT arm (28 %) (Kocher et al., 2011). Hence, after radiosurgery and surgery, incorporation of WBRT appears to improve IC and decrease the incidence of neurologic deaths without improving OS or patient performance.

SRS Alone vs. WBRT Alone

The impact of SRS alone versus WBRT alone on the outcome of patients with BM has only been studied in prospective and retrospective studies but not in a randomized clinical trial. In the three-arm study of Li et al. (2000), SRS alone resulted in better OS (9.3 vs. 5.7 months) and complete or partial tumor response, as assessed by neuroradiological follow-up (87 % vs. 38 %), compared to WBRT alone. Similarly, SRS resulted in longer time to progression (6.9 vs. 4 months) while IC was not measured (Li et al., 2000). Rades et al. (2007b) retrospectively studied the outcome of 183 patients with 1–3 BM and a diameter of up to 4 cm induced by tumors of different histological subtypes, after treatment with either SRS alone (n = 95) or WBRT alone (n = 91). The two study arms were well matched for different prognostic factors such as age, sex, RPA class, presence of extracranial secondaries and number of BM. Similarly to the previous work, SRS was superior to WBRT and resulted in better OS (13 vs. 7 months, respectively) and 1-year LC (64 vs. 26 %, respectively). Notably, IC (61 % vs. 66 %, respectively) and the incidence of adverse effects were similar in both study arms (Rades et al., 2007b).

SRS + Resection vs. WBRT + Resection

A retrospective report compared the efficacy of resection + WBRT (n = 34) vs. resection + SRS (n = 62) in patients with NSCLC and multiple BM up to 3 cm in diameter (Serizawa et al., 2000). A significantly longer OS survival was observed in the resection + SRS group (12.5 vs. 6.6 months). However, information in regards to the precise number of BM resected in the resection + WBRT groups was lacking and thus interpretation of the results is difficult. In addition, LC were not presented by the authors (Serizawa et al., 2000). No prospective studies have been reported to date regarding c comparison of these therapeutic schedules.

Future Perspectives and Open Questions

The progress in our understanding of the biological background of BM and the advent of novel targeted therapies have inevitably raised new questions. Do the genetic and molecular pathways activated in BM differ among the various histological types? If the answer to this question is “yes”, then the response of BM to SRS might vary accordingly, similarly to the response in primary tumors. It will be interesting to investigate in future studies the radiobiological impact of SRS in patients with BM induced from the same histological type and not in a cohort of patients with cerebral lesions from various tumor histologies. Such studies are highly relevant, especially in patients with radioresistant tumors and will better elucidate the optimal histology-specific SRS dose. Furthermore, results from studies combining SRS with novel biological therapies are desperately missing and it will be interesting to test the feasibility and efficacy of such therapeutic regimens in patients with BM.

Additionally, the role of SRS in patients with multiple metastases (more than 3–4) remains unclear. Some radiation oncologists advocate use of SRS for up to three cerebral lesions while others chose to treat patients even with multiple lesions. The studies of Aoyama and Kocher and colleagues (Aoyama et al., 2006; Kocher et al., 2011) have demonstrated the benefit of WBRT in preventing intracerebral recurrence but this might come to the cost of cognitive effects. Although there is evidence that SRS could provide adequate LC without cognitive deficits, more randomized trials are needed.

Even though several groups have demonstrated the efficacy of SRS in enhancing LC of

BM, local tumor progression still occurs and hence improved LC is warranted. Surprisingly, detailed studies to investigate the combination effect of SRS with chemotherapy drugs and, even more, with novel targeted therapies are lacking and it will be interesting to see whether these regimens are feasible and effective in patients with BM. Furthermore, although the RTOG 90–05 trial demonstrated the maximum tolerated dose of SRS in patients with BM, no further reports have confirmed the findings of this study. Thus, it is important that a new randomized study will confirm the size-dependent dose guidelines.

Another open question regards the efficacy and the precise indications for re-irradiation using SRS in patients with recurrent BM. Currently, it remains unclear which patients with recurrent BM could benefit from a potential re-irradiation using SRS. Conflicting findings have been reported in regards to the histological type, the maximum number and the location of lesions that could be irradiated. Especially for lesions previously treated with SRS, there is high controversy as to whether a repeated SRS can be safely administered due to the risk of radionecrosis.

In summary, the advent of SRS has enabled a rapid, safe, non-invasive management of patients with BM and can offer high LC for single or multiple lesions caused by a wide range of histological tumor types. Although highly efficient, recurrence of BM is not uncommon. Hence, future randomized studies are needed to assess the value of repeated SRS and also examine the potential of combining SRS with new biological agents to further improve the control of intracranial lesions, for the best benefit of patients with BM.

References

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

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 295:2483–2491

Aoyama H, Tago M, Kato N, Toyoda T, Kenjyo M, Hirota S, Shioura H, Inomata T, Kunieda E, Hayakawa K, Nakagawa K, Kobashi G, Shirato H (2007) Neurocognitive function of patients with brain metastasis who received either whole brain radiotherapy plus stereotactic radiosurgery or radiosurgery alone. Int J Radiat Oncol Biol Phys 68:1388–1395

Bindal AK, Bindal RK, Hess KR, Shiu A, Hassenbusch SJ, Shi WM, Sawaya R (1996) Surgery versus radiosurgery in the treatment of brain metastasis. J Neurosurg 84:748–754

Blonigen BJ, Steinmetz RD, Levin L, Lamba MA, Warnick RE, Breneman JC (2010) Irradiated volume as a predictor of brain radionecrosis after linear accelerator stereotactic radiosurgery. Int J Radiat Oncol Biol Phys 77:996–1001

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

Cavaliere R, Schiff D (2006) Cerebral metastases–a therapeutic update. Nat Clin Pract Neurol 2:426–436

Chung HT, Kim DG (2012) Modern radiosurgery equipment for treating brain metastases. Prog Neurol Surg 25:236–247

Claus EB (2012) Neurosurgical management of metastases in the central nervous system. Nat Rev Clin Oncol 9:79–86

DiLuna ML, King JT Jr, Knisely JP, Chiang VL (2007) Prognostic factors for survival after stereotactic radiosurgery vary with the number of cerebral metastases. Cancer 109:135–145

Fokas E, Henzel M, Hamm K, Surber G, Kleinert G, Engenhart-Cabillic R (2010) Radiotherapy for brain metastases from renal cell cancer: should whole-brain radiotherapy be added to stereotactic radiosurgery?: analysis of 88 patients. Strahlenther Onkol 186:210–217

Fokas E, Henzel M, Surber G, Kleinert G, Hamm K, Engenhart-Cabillic R (2012) Stereotactic radiosurgery and fractionated stereotactic radiotherapy: comparison of efficacy and toxicity in 260 patients with brain metastases. J Neurooncol 109:91–98

Gavrilovic IT, Posner JB (2005) Brain metastases: epidemiology and pathophysiology. J Neurooncol 75:5–14

Hatiboglu MA, Chang EL, Suki D, Sawaya R, Wildrick DM, Weinberg JS (2011) Outcomes and prognostic factors for patients with brainstem metastases undergoing stereotactic radiosurgery. Neurosurgery 69:796–806

Hillard VH, Shih LL, Chin S, Moorthy CR, Benzil DL (2003) Safety of multiple stereotactic radiosurgery treatments for multiple brain lesions. J Neurooncol 63:271–278

Jagannathan J, Sherman JH, Mehta GU, Chin LS (2007) Radiobiology of brain metastasis: applications in stereotactic radiosurgery. Neurosurg Focus 22:E4

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

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

Kondziolka D, Flickinger JC, Lunsford LD (2012) Radiosurgery for brain metastases. Prog Neurol Surg 25:115–122

Koyfman SA, Tendulkar RD, Chao ST, Vogelbaum MA, Barnett GH, Angelov L, Weil RJ, Neyman G, Reddy CA, Suh JH (2010) Stereotactic radiosurgery for single brainstem metastases: the cleveland clinic experience. Int J Radiat Oncol Biol Phys 78:409–414

Li B, Yu J, Suntharalingam M, Kennedy AS, Amin PP, Chen Z, Yin R, Guo S, Han T, Wang Y, Yu N, Song G, Wang L (2000) Comparison of three treatment options for single brain metastasis from lung cancer. Int J Cancer 90:37–45

Likhacheva A, Pinnix CC, Parikh NR, Allen PK, McAleer MF, Chiu MS, Sulman EP, Mahajan A, Guha-Thakurta N, Prabhu SS, Cahill DP, Luo D, Shiu AS, Brown PD, Chang EL (2012) Predictors of survival in contemporary practice after initial radiosurgery for brain metastases. Int J Radiat Oncol Biol Phys 85:656–661

Maranzano E, Trippa F, Casale M, Costantini S, Anselmo P, Carletti S, Principi M, Caserta C, Loreti F, Giorgi C (2012) Reirradiation of brain metastases with radiosurgery. Radiother Oncol 102:192–197

Monaco EA 3rd, Niranjan A, Kano H, Flickinger JC, Kondziolka D, Lunsford LD (2012) Management of adverse radiation effects after radiosurgery. Prog Neurol Surg 25:210–220

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

Muller-Riemenschneider F, Bockelbrink A, Ernst I, Schwarzbach C, Vauth C, von der Schulenburg JM, Willich SN (2009) Stereotactic radiosurgery for the treatment of brain metastases. Radiother Oncol 91:67–74

Park HJ, Griffin RJ, Hui S, Levitt SH, Song CW (2012) Radiation-induced vascular damage in tumors: implications of vascular damage in ablative hypofractionated radiotherapy (SBRT and SRS). Radiat Res 177:311–327

Powell JW, Chung CT, Shah HR, Canute GW, Hodge CJ, Bassano DA, Liu L, Mitchell L, Hahn SS (2008) Gamma Knife surgery in the management of radioresistant brain metastases in high-risk patients with melanoma, renal cell carcinoma, and sarcoma. J Neurosurg 109(Suppl):122–128

Rades D, Bohlen G, Pluemer A, Veninga T, Hanssens P, Dunst J, Schild SE (2007a) Stereotactic radiosurgery alone versus resection plus whole-brain radiotherapy for 1 or 2 brain metastases in recursive partitioning analysis class 1 and 2 patients. Cancer 109:2515–2521

Rades D, Pluemer A, Veninga T, Hanssens P, Dunst J, Schild SE (2007b) Whole-brain radiotherapy versus stereotactic radiosurgery for patients in recursive partitioning analysis classes 1 and 2 with 1 to 3 brain metastases. Cancer 110:2285–2292

Sanghavi SN, Miranpuri SS, Chappell R, Buatti JM, Sneed PK, Suh JH, Regine WF, Weltman E, King VJ, Goetsch SJ, Breneman JC, Sperduto PW, Scott C, Mabanta S, Mehta MP (2001) Radiosurgery for patients with brain metastases: a multi-institutional analysis, stratified by the RTOG recursive partitioning analysis method. Int J Radiat Oncol Biol Phys 51:426–434

Schoggl A, Kitz K, Reddy M, Wolfsberger S, Schneider B, Dieckmann K, Ungersbock K (2000) Defining the role of stereotactic radiosurgery versus microsurgery in the treatment of single brain metastases. Acta Neurochir (Wien) 142:621–626

Serizawa T, Iuchi T, Ono J, Saeki N, Osato K, Odaki M, Ushikubo O, Hirai S, Sato M, Matsuda S (2000) Gamma knife treatment for multiple metastatic brain tumors compared with whole-brain radiation therapy. J Neurosurg 93:32–36

Shaw E, Scott C, Souhami L, Dinapoli R, Kline R, Loeffler J, Farnan N (2000) Single dose radiosurgical treatment of recurrent previously irradiated primary brain tumors and brain metastases: final report of RTOG protocol 90–05. Int J Radiat Oncol Biol Phys 47:291–298

Shehata MK, Young B, Reid B, Patchell RA, St Clair W, Sims J, Sanders M, Meigooni A, Mohiuddin M, Regine WF (2004) Stereotatic radiosurgery of 468 brain metastases < or =2 cm: implications for SRS dose and whole brain radiation therapy. Int J Radiat Oncol Biol Phys 59:87–93

Soffietti R, Ruda R, Trevisan E (2008) Brain metastases: current management and new developments. Curr Opin Oncol 20:676–684

Local Control of Low-Volume Brain Metastasis Using Stereotactic Radiosurgery

13

Howard Hsu, Stephen Rush, Christine Min, and John G. Golfinos

Contents

Abstract

Stereotactic radiosurgery (SRS) is a non-invasive means of treating brain metastases with high dose radiation therapy in a single fraction. It is a useful alternative to surgical resection in selected patients with good performance status and low-volume brain metastases. It can complement or replace whole brain radiation therapy (WBRT), which has historically been the mainstay of palliative brain radiation therapy. Randomized clinical trials have demonstrated the survival benefit of adding SRS to WBRT in the case of a single brain metastasis in a patient with good performance status. Conversely, there appears to be no survival detriment to using SRS alone in patients with up to 4 and possibly even more brain metastases. While there is an increase in recurrent lesions either locally or in distant areas of the brain with the use of SRS alone, these are amenable to salvage therapy if found early with stringent follow-up imaging. Such a strategy has been used successfully in our institution and others to delay or forego WBRT in most patients with low-volume brain metastases. This helps to avoid the morbidities that have been documented with WBRT including

H. Hsu • C. Min
Department of Radiation Oncology, NYU Langone Medical Center, 530 First Avenue, New York, NY 10016, USA

S. Rush
The NYU Gamma Knife Center, NYU Langone Medical Center, 530 First Avenue, New York, NY 10016, USA

J.G. Golfinos (✉)
Department of Neurosurgery, NYU Langone Medical Center, 530 First Avenue, Suite 8R, New York, NY 10016, USA
e-mail: john.golfinos@nyumc.org

M.A. Hayat (ed.), *Tumors of the Central Nervous System, Volume 11*,
DOI 10.1007/978-94-007-7037-9_13,

neurocognitive impairment, alopecia, fatigue and associated psychological stress. In addition, SRS alone avoids the delay in systemic therapy that is common with the use of WBRT. In this chapter, we focus on the randomized clinical trials that have examined SRS as a primary treatment modality for low-volume brain metastases.

Introduction

It has been estimated that the incidence of newly diagnosed invasive cancer is approximately 1.3 million per year in the United States (Landis et al., 1998). Between 100,000 and 170,000 of these patients will develop brain metastases. It is speculated that these figures will continue to increase with the improvement of local control of the primary site, systemic treatments, and overall survival of these individuals. Enhanced diagnostic capabilities, routine use of magnetic resonance imaging (MRI) in asymptomatic patients for extent of disease work up, and an overall aging population may also contribute to rises in incidence. The most common primary cancers associated with brain metastases include lung, breast, skin, kidney, and colon cancers (Koay and Sulman, 2012). Brain metastases are caused by hematogenous spread to the white matter of the brain, often at the watershed area at the junction of the gray and white matter. The majority of metastases arise in the supratentorial brain, with relatively fewer arising in the cerebellum and brainstem, because of the greater blood supply to the cerebral hemispheres. On imaging, most metastases appear fairly spherical and well demarcated, and they tend to displace rather than invade adjacent brain tissue. This latter point is true pathologically as well, and it is what makes SRS more suitable for secondary rather than primary brain tumors. The microscopic appearance of brain metastases will resemble that of the primary tumor (Narayana et al., 2010).

Patients with brain metastases previously presented more often with neurologic signs and symptoms, though with the growing use of MRI, more cases are being detected while still asymptomatic. Prior to widespread use of CT and MRI, brain metastases were diagnosed when the patients became symptomatic. More recently, with the increased frequency of screening imaging and improved sensitivity of imaging technology, fewer patients are symptomatic at diagnosis (Larson et al., 2008; Rush et al., 2006). Those patients who present with symptoms commonly report headache, mental problems, focal weakness, ataxia, seizures, and speech problems, with headache being the most frequent and present in approximately half of symptomatic patients. Observed signs include hemiparesis, cognitive deficits, sensory deficits, papilledema, ataxia, and apraxia. Hemiparesis and cognitive deficits are the most common and may be seen in more than half of patients with neurologic signs. Although the differential diagnosis includes infectious and vascular etiologies such as abscess and stroke, respectively, new onset neurologic symptoms and signs in a known cancer patient should be presumed to be from brain metastases until proven otherwise (Kwok et al., 2008). Diagnostic work-up ideally involves gadolinium-enhanced MRI. MRI has been demonstrated to be more sensitive than computed tomography (CT), particularly for small lesions in the infratentorial brain. Metastases will usually appear hyperintense on T_1-weighted images post contrast enhancement. T_2-weighted images will reveal the tumor itself as well as any surrounding edema as areas of hyperintensity. A clinical history of cancer, particularly systemic cancer, combined with MRI results consistent with metastatic disease can establish the diagnosis with reasonable certainty. One prospective, randomized trial demonstrated that 11 % of patients who underwent resection for a single lesion, presumed to be a brain metastasis, actually had primary brain tumor, abscess or other inflammatory process on final pathology (Patchell et al., 1990). This diagnostic error rate is likely much lower for patients with multiple brain lesions and with the use of modern imaging techniques. For equivocal cases in which a definitive diagnosis cannot be made on clinical and radiographic evidence, biopsy with pathologic tissue examination is sometimes performed (Narayana et al., 2010).

Several prognostic indices for patients with brain metastases have been reported in the literature, with the most widely utilized being the Radiation Therapy Oncology Group recursive partitioning analysis (RTOG RPA). This was based on 1,200 patients treated on prospective clinical trials with whole brain radiation therapy (WBRT) (Gaspar et al., 1997, 2000). There are three classes to the RPA which are prognostic for median survival: class I (KPS ≥70, age <65 years, controlled primary, no extracranial metastases; median survival 7.1 months), class II (not in class I or class III; median survival 4.2 months), class III (KPS <70; median survival 2.3 months). It is important to note that the patients treated on these trials primarily represented a different cohort of patients than the modern era. More on this will be discussed below.

The definition of low volume and number of lesions has remained somewhat controversial. A recent systematic review and evidence-based clinical practice guideline defined a low volume tumor as less than 10 cc in volume or less than 3 cm in diameter (Linskey et al., 2010). The RTOG conducted a randomized trial (RTOG, 9508) evaluating the role of stereotactic boost after WBRT and included patients with 1–3 brain metastases, with maximum diameters of 4 cm for the single largest lesion and 3 cm for the other lesions (Andrews et al., 2004). It becomes more debatable when 4 or more lesions are identified. A recent retrospective review from the University of Pittsburgh evaluated SRS in patients with 4 or more intracranial metastases. They found that the number of metastases was not a statistically significant prognostic factor, whereas the total treatment volume was significant. Therefore, they concluded that the number of lesions is less important when selecting appropriate SRS candidates (Bhatnagar et al., 2006). We consider low volume to mean 1–3 lesions, with none greater than 2.5 cm in maximum diameter, based on precedent and our confidence in treating individual lesions with SRS. To date there is no consensus yet on the definition of low volume metastatic disease to the brain based on criteria for SRS (Table 13.1).

Non-radiosurgical Treatment of Brain Metastases

Corticosteroids

Left untreated, patients have a median survival of approximately 1 month. With corticosteroids alone, median survival may be extended to 2 months. Corticosteroids also improve edema and neurologic deficits in approximately two thirds of patients. As a result, they should be initiated at the onset for all symptomatic patients (Kwok et al., 2008). The recommended dosage is 16 mg of oral dexamethasone daily divided into 2–4 doses. Lower doses of 4 or 8 mg have been shown to be effective as well; however, it has been documented that KPS has the greatest improvement when 16 mg is administered (Vecht et al., 1994). It is also reasonable to give an upfront bolus of 10 mg intravenously with methylprednisolone before beginning the oral doses. Corticosteroid use should be tapered cautiously over approximately 4 weeks to minimize the toxicities associated with rapid discontinuation. In asymptomatic patients with minimal edema on MRI, corticosteroids should be reserved until the onset of neurologic symptoms or signs to minimize steroid-induced side effects such as glucose intolerance, weight gain, easy bruisability and anxiety (Kwok et al., 2008). We do not recommend corticosteroids for asymptomatic patients with mild to moderate edema. We generally use prophylactic corticosteroids for radiosurgery of larger lesions or lesions located in eloquent areas.

Whole Brain Radiation Therapy

With different modalities of treatment, including radiation therapy with or without local treatment, median survival may be extended to up to 4–14 months. Some patients, with the highest performance status, may live even longer, forming a tail on survival curves. In one early study of 38 patients with brain metastases treated with WBRT to a wide range of total doses, the median survival of 4–8 months represented a significant improvement

Table 13.1 Randomized, controlled trials evaluating SRS and WBRT, ordered by year of publication

First author (year) Institution/group	Groups	N	MS (month)	Neurologic death	Recurrence: 1 year distant brain	Local control @ 1 year	Salvage type	Functional status measure	Functional status rate
Muacevic (1999) German multi-center	SRS	31	10.3	11 %	25.8 %	96.8 %	WBRT: 1/8 SRS: 5/8	Duration steroid use (wks)	2
	Surgery + WBRT	33	9.5	29 %	3 %*	82.0 %	SRS: 2/6 Surgery: 2/6		5**
Kondziolka (1999) U. Pittsburgh	WBRT	14	7.5	NR	NR	0 %	NR	NR	NR
	WBRT + SRS	13	11			92 %			
Andrews (2004) RTOG 9508	WBRT	167	5.7	31 %	NR	71 %	NR	KPS improved @ 6 month	4.0 %
	WBRT + SRS	164	6.5	28 %		82 %*			12.7 %*
Aoyama (2006) JROSG 99-1	SRS	67	8	19.3 %	63.7 %	72.5 %	WBRT: 11/29 SRS: 19/29	Neurologic preservation @ 12 month	70.3 %
	WBRT + SRS	65	7.5	22.8 %	41.5 %**	88.7 %**	WBRT: 0/10 SRS: 9/10		72.1 %
Chang (2009) MD Anderson	SRS	30	15.2**	NR	55 %	67 %	WBRT: 10/26 SRS: 6/26 Surgery: 10/26	Learning and memory decline @ 4 month	24 %
	WBRT + SRS	28	5.7		27 %*	100 %*	WBRT: 0/5 SRS: 2/5 Surgery: 0/5		52 %
Kocher (2011) EORTC 22952-26001	SRS/Surgery (OBS)	179	10.7	44 %	48 % (@2 years w/ SRS)	69 % (@2 years w/SRS)	WBRT: 56/139 SRS: 21/139 Surgery: 11/139	Time (month) to WHO PS > 2	10.0
	WBRT + SRS/ Surgery (WBRT)	180	10.9	28 %	33 %* (@2 years w/ SRS)	81 %* (@2 years w/SRS)	WBRT: 6/87 SRS: 20/87 Surgery: 3/87		9.5

NR Not reported or unable to determine from manuscript
Statistical significance: *p < 0.05; **p < 0.01; ***p < 0.001

from historical controls who had received only corticosteroids (Chao et al., 1954). This laid the foundation for further studies that eventually established WBRT as the initial standard of care for all patients who presented with brain metastases. From the 1950s to the 1970s, a period when WBRT represented the mainstay of treatment, the diagnosis of brain metastases was made based on signs and symptoms in a patient known to have cancer. Arteriography and pneumoencephalography may or may not have been done. There were no effective systemic therapies. Patients invariably had symptoms at diagnosis, and it can be inferred that many if not most lesions were greater than 2–3 cm since they were all large enough to cause symptoms. It is clear that this is entirely different than the cohort of patients we see now, the majority of whom have asymptomatic disease found on MRI (Rush et al., 2011).

In an effort to define the optimal dose fractionation scheme, the RTOG conducted 2 randomized trials to address this question. The first study randomized 910 patients to receive the equivalent of 30 Gy in 10 fractions, 30 Gy in 15 fractions, 40 Gy in 15 fractions, or 40 Gy in 20 fractions. The second randomized 902 patients to receive the equivalent of 20 Gy in 5 fractions, 30 Gy in 10 fractions, or 40 Gy in 15 fractions. No differences were observed in neurologic function, neurologic symptoms, general performance status, survival, or palliative indices. Prior to these studies, most RTOG participating institutions were routinely utilizing a regimen of 40 Gy in 20 fractions. The authors concluded that 20 or 30 Gy in fewer fractions could be implemented with equal efficacy. However, they hypothesized that patients with a controlled primary and the brain as the only site of metastasis may represent a prognostically favorable group and may benefit from higher doses (Borgelt et al., 1980). The most commonly used regimen for decades has been 30 Gy in 10 fractions, though 20 Gy in 5 fractions had been shown to be equally effective. This is usually delivered via opposed lateral beams covering the entire cranium with a margin (Kwok et al., 2008). Recently, more patients have been treated with 250 cGy fractions to 30–37.5 Gy due to empiric and documented concerns about adverse cognitive effects in patients who are surviving longer (Andrews et al., 2004; Chang et al., 2009).

We emphasize the importance of the fact that patients treated in the historical WBRT series in the pre-CT era were all symptomatic and had no effective systemic treatments. In contrast, the cohort of patients we see today are predominantly asymptomatic and present with low-volume disease found on screening MRI during a metastatic work-up. The treatment goals for most modern patients are to provide local control in the brain, prevent neurologic symptoms, and maintain functional independence, as opposed to the historical era when the goals were to palliate large metastases manifesting with existing neurologic symptoms. Thus, we challenge the concept that WBRT is the standard of care for low-volume brain metastases diagnosed in the modern era.

Surgery

Randomized trials have demonstrated a benefit of combined modality therapy in the setting of a single brain metastasis. In a randomized trial evaluating the role of surgery in patients with a single brain metastasis, 25 patients who underwent surgical extirpation of their brain metastasis followed by WBRT were compared to 23 patients who underwent biopsy only followed by WBRT (Patchell et al., 1990). This study found that patients who received surgical resection had less frequent local recurrence (20 % in the surgical group versus 52 % in the biopsy only group). Overall survival was also improved, with a median of 40 weeks in the surgical group versus 15 weeks in the biopsy only group. Finally, patients treated with surgical extirpation remained functionally independent longer, with a median of 38 weeks versus 8 weeks when only a biopsy was performed. All of these differences were highly statistically significant. The authors concluded that patients who first undergo full surgical resection followed by WBRT live longer, have fewer local recurrences, and have a better quality of life than those who undergo WBRT alone.

Patchell et al. (1998) conducted a second randomized trial evaluating the role of WBRT in 95 patients. All patients underwent surgical resection, and 49 patients were thereafter randomized to receive post-operative WBRT, while 46 patients were randomized to receive no further treatment. They found that recurrences in the brain, both local and elsewhere, were less frequent in the radiotherapy group than in the observation group (18 % versus 70 %). Death due to neurologic causes was also less frequent, with a rate of 14 % in the radiotherapy group and 44 % in the observation group. Both of these endpoints were highly statistically significant. In contrast to their previous study, the authors did not find differences in overall survival or length of functional independence. They concluded that WBRT reduces intracranial recurrence and neurologic death, which they describe as the most difficult type of death for patients and their families due to the loss of mental and physical abilities that accompany it. They felt that this alone justified the use of WBRT in patients with a single metastasis (Patchell et al., 1998). It is important to note that a follow-up salvage strategy for recurrent disease was not explicitly stated. We and others believe that routine surveillance after focal treatment and early institution of effective salvage therapy (focal when possible) is central to the concept of limited treatment upfront, thereby reducing the need for WBRT in a patient's lifetime while also keeping the risk of neurologic death below 20 % (Rush et al., 2011). However, the historic importance of these trials is that they were the first prospective trials, outside of prophylactic cranial irradiation for small cell lung cancer, to suggest a role for WBRT as a non-palliative tool in the management of metastatic epithelial carcinoma.

Stereotactic Radiosurgery for Brain Metastases

Background

Stereotactic radiosurgery (SRS) refers to the delivery of high dose, highly conformal radiation for the treatment of intracranial lesions using a single fraction. Stereotactic radiotherapy (SRT) is an alternative schedule for hypofractionated intracranial radiation therapy given in 2–5 fractions. The preponderance of literature deals with single fraction SRS, and it is the focus of this chapter. The treatment is performed with three dimensional image guidance and generally requires some form of immobilization to ensure accurate patient setup and spatial registration for treatment planning. Several different types of radiation delivery systems are used for SRS including multiple fixed cobalt-60 sources (Gamma Knife, Elekta AB, Sweden), proton radiosurgery, and linear accelerator (LINAC) based radiosurgery. Our institution utilizes Gamma Knife (GK) radiosurgery. Lars Leksell and Borje Larsson developed the idea for stereotactic radiosurgery in 1951 and later created the first prototype Gamma Knife delivery system in 1968. The most current model of Gamma Knife utilizes 192 fixed cobalt-60 sources focused to a single point (isocenter) and housed within a self-shielded system. Patients have a rigid, stereotactic head frame secured into the outer table of the skull in four positions using local anesthetic. This head frame allows for both rigid immobilization onto the treatment table and defines the x, y, and z coordinates for treatment planning and delivery. Gadolinium-enhanced magnetic resonance imaging is taken of the patient with the head frame secured, and these images are used for treatment planning. Typically, no margin is placed on the MRI visualized gross tumor for GK, as the setup errors are in the sub-millimeter range. However, margins are routinely used on LINACs and other devices (Shrieve et al., 2010).

Dose for Stereotactic Radiosurgery

The Radiation Therapy Oncology Group (RTOG) 9005 trial investigated the maximum tolerated dose (MTD) for single fraction SRS (Shaw et al., 2000). Eligibility requirements included age ≥18 years old, Karnofsky Performance Status (KPS) of ≥60 %, life expectancy of ≥3 months, and a history of having received prior partial or whole brain fractionated external beam radio-

therapy for either a primary brain tumor or brain metastases. While patients with multiple lesions were allowed on study, only the dominant lesion was treated with SRS. Initial dose was varied depending on the greatest tumor diameter in any plane, and doses were prescribed to the 50–90 % isodose line. Dose escalation in 3 Gy increments was performed as long as there was <20 % unacceptable toxicity within 3 months of SRS. Unacceptable toxicity included irreversible grade 3 (severe), any grade 4 (life threatening) or grade 5 (fatal) acute toxicity as defined using the RTOG central nervous system (CNS) scale. With 156 analyzable patients, the maximum tolerated doses were 24, 18, and 15 Gy for tumor diameters of ≤20, 21–30, and 31–40 mm, respectively. Of note, the MTD of 24 Gy for tumors ≤20 mm was determined due to the investigators' reluctance to escalate to 27 Gy, rather than due to excessive toxicity. However, the acceptance of up to 20 % Grade 3–5 toxicity is much higher than the tolerance for such toxicity in routine clinical practice, especially in patients not treated for curative intent. Traditionally in radiation oncology, the tolerance for severe toxicity has arbitrarily been set at less than 5 % at 5 years. Other criticisms of this study include the heterogeneity of the patients, with both primary and secondary brain tumors eligible, and varying doses of prior partial or whole brain radiation (median 30 Gy for metastases and 60 Gy for primary brain tumors). This benchmark dose-escalation study needs to be followed up with further prospective data to establish the relevant tolerance doses for SRS without prior WBRT, and based on the more clinically relevant endpoints of neurocognitive function and patient quality of life.

New York University performed a retrospective analysis on 109 patients with low-volume brain metastases (1–3 lesions, diameter ≤2 cm each) treated with GK SRS alone to a uniform dose of 20 Gy prescribed to the 50 % isodose line (Elliott et al., 2011). Patients were followed with routine MRI every 3 months. Primary GK resulted in a crude local control rate of 91.3 % and a 24 month actuarial local control rate of 85 %. Fifty-two patients (49.1 %) developed distant brain failures, and 33 of those patients received secondary GK. Only 16 patients (14.7 %) received salvage WBRT. In total, 255 metastatic lesions were treated and evaluated with post-treatment imaging. The overall crude local control rate for primary and secondary GK combined was 93.3 %, with a 24 month actuarial local control rate of 89 %. Neurologic symptom-free survival at 24 months was 86 %. Transient neurological deficits occurred in five patients (4.6 %), and permanent neurological complications occurred in three patients (2.8 %). These results suggest that for low-volume brain metastases, a dose of 20 Gy (which is lower than the RTOG 9005 MTD and was delivered in patients with no history of prior brain irradiation) can result in durable local control with a lower risk of permanent neurologic toxicity.

Whole Brain Radiation Therapy Versus Whole Brain Radiation Therapy + Stereotactic Radiosurgery

The University of Pittsburgh performed a single institution randomized controlled trial in patients with 2–4 brain metastases (each ≤25 mm diameter) comparing WBRT alone (30 Gy in 12 fractions) versus the same WBRT dose with SRS (16 Gy to the 50 % isodose line) (Kondziolka et al., 1999). The primary outcome was image-defined local control. The trial was stopped early at a pre-specified interim analysis with 60 % accrual (total of 27 patients randomized: 14 to WBRT only, 13 WBRT + SRS). At the interim analysis, local control was significantly better in the WBRT + SRS arm ($p = 0.0016$) which exceeded the nominal significance value required to stop the trial. Median time to local failure after WBRT alone was 6 months, compared to 36 months after WBRT + SRS ($p = 0.0005$). Median survival was 7.5 months with WBRT alone and 11 months with WBRT + SRS, but this was not significantly different. No complications were seen related to SRS, and only mild scalp erythema and hair loss was seen with WBRT. This trial demonstrated significantly improved local control with the addition of SRS to WBRT with no additional neurologic complications.

The RTOG 9508 multicenter randomized clinical trial compared WBRT (37.5 Gy in 15 fractions) versus the same dose WBRT with SRS (15–24 Gy according to maximum tumor diameter as per RTOG 9005) (Andrews et al., 2004). Eligibility criteria included age ≥18 years old, 1–3 brain metastases, maximum tumor diameter ≤4 cm with any additional lesions ≤3 cm, and KPS ≥70. The study was powered to detect a 50 % improvement in median survival for all patients with the addition of SRS, as well as to detect a 75 % improvement in median survival for the subgroup of patients with single brain metastasis with the addition of SRS. From 1996 to 2001, a total of 333 patients were randomized. Of the 164 patients in the WBRT + SRS arm, 31 patients (19 %) did not receive the planned SRS. Of the 167 patients assigned to the WBRT alone arm, 28 patients (17 %) received salvage SRS. This bilateral crossover rate has been a point of criticism for this trial (Linskey et al., 2010). Median survival was not significantly different for the primary analysis including all patients (5.6 months for WBRT alone vs. 6.5 months for WBRT + SRS, p = 0.1356). However, the planned subset analysis did show a significant median survival advantage with the addition of SRS in patients with a single metastasis (4.9 months for WBRT alone vs. 6.5 months for WBRT + SRS, p = 0.0393). Post-hoc analyses demonstrated no significant differences in median survival in patients with multiple metastases or when analyzed according to tumor size, SRS dose, or LINAC vs. GK treatment unit. Local control of treated lesions at 1 year was improved with WBRT + SRS (82 %) compared to WBRT alone (71 %) (p = 0.01). Despite the improved local control, there was no difference seen in terms of neurologic death between the two arms. However, there was a significant decrease in steroid use at 6 months' follow-up in the WBRT + SRS group (41 patients) compared to those in the WBRT group (25 patients), p < 0.0158. This decrease in steroid usage likely improved patient quality of life in the WBRT + SRS arm, but the trial was not designed to assess this endpoint. Patients in the WBRT + SRS group were more likely to have stable or improved KPS at 6 months than patients in the WBRT group. On multivariate analysis, improved survival was associated with RPA class 1 and lung primary histology. The authors tabulated treatment toxicities, but no formal comparisons were reported.

Stereotactic Radiosurgery Versus Whole Brain Radiation Therapy + Stereotactic Radiosurgery

The Japanese Radiation Oncology Study Group (JROSG) conducted the first multi-institutional, randomized controlled trial of WBRT + SRS versus SRS alone (Aoyama et al., 2006). Eligibility criteria included adult patients with KPS ≥70 who had 1–4 brain metastases, each with maximum diameter ≤3 cm. Patients in the SRS alone arm received prescribed doses to the tumor margin of 22–25 Gy for metastases up to 2 cm, and 18–20 Gy for metastases >2 cm. Patients in the WBRT + SRS arm received 30Gy in 10 fractions WBRT first, followed by SRS to a margin dose 30 % less than in the SRS only arm. The primary endpoint was overall survival, with secondary endpoints of cause of death, functional preservation (KPS ≥70), brain tumor recurrence, salvage treatment and toxicity. The sample size was calculated as 178 patients in order to have 80 % power to detect a 30 % difference in median survival. However, at a planned interim analysis after accruing 100 patients, it was determined that at least 805 patients would be necessary to detect a significant difference in median survival, so the study was terminated early at 132 randomized patients. Median survival and 1 year actuarial survival were not statistically different between the WBRT + SRS group versus the SRS alone group (7.5 months and 38.5 % vs. 8 months and 28.4 %, respectively, p = 0.42 for 1 year actuarial survival). Neurologic death was also comparable with 22.8 % in the WBRT + SRS group versus 19.3 % in the SRS alone group (p = 0.64). Overall brain tumor recurrence at either distant or local sites was improved in the WBRT + SRS group (23 patients) versus the SRS alone group (40 patients), with 1 year actuarial brain tumor recurrence rates of 46.8 versus 76.4 %, respectively

($p < 0.001$). Local brain tumor control was significantly improved in the WBRT + SRS group as compared to the SRS alone group, with 1 year actuarial local control rates of 88.7 % vs. 72.5 % ($p = 0.002$). Salvage treatments were accordingly used more often in the SRS alone group (29 patients) than in the WBRT + SRS group (10 patients), $p < 0.001$. Salvage SRS was used in 19 patients and salvage WBRT was used in 11 patients in the SRS alone group. Salvage SRS was used in 9 patients in the WBRT + SRS group, and no patient in that group received salvage WBRT. There were no significant differences seen between the WBRT + SRS or SRS alone groups for the endpoints of systemic functional preservation ($p = 0.53$), or neurologic preservation ($p = 0.99$). In a follow-up paper reporting neurocognitive function as assessed by the Mini-Mental State Examination (MMSE), there was no significant difference in the actuarial rate of decrease in MMSE scores between WBRT + SRS and SRS alone groups (Aoyama et al., 2007). However, other investigators have criticized the use of the MMSE in this setting because it is an insensitive test for neurocognitive changes in patients receiving radiation therapy for brain tumors (Meyers and Wefel, 2003).

Investigators at MD Anderson Cancer Center performed a landmark single-institution randomized controlled trial comparing SRS alone to SRS + WBRT (Chang et al., 2009). Eligible patients were age 18 years or older with RPA class 1 or 2, KPS ≥70, and had 1–3 brain metastases (median total tumor volume 1.4 cc SRS alone and 2.3 cc SRS + WBRT). The median SRS tumor margin doses for the SRS alone versus the SRS + WBRT arms were 19 Gy (range 15–20 Gy) and 20 Gy (range 15–20 Gy), respectively. Patients in the WBRT arm received 30 Gy in 12 fractions given within 3 weeks after SRS. The primary endpoint was neurocognitive function at 4 months measured by the Hopkins Verbal Learning Test-Revised (HVLT-R) total recall. Fifty-eight patients were randomized (30 patients in the SRS alone arm and 28 patients in the SRS + WBRT arm) prior to the trial being stopped by the data monitoring committee on the basis of a high probability (96 %) that patients in the SRS + WBRT arm were more likely to show a decline on the HVLT-R total recall at 4 months. Median survival was higher in the SRS alone group compared to the SRS + WBRT group (15.2 vs. 5.7 months, $p = 0.003$). One year local tumor control rate was 67 % for the SRS group and 100 % for the SRS + WBRT group ($p = 0.012$). Similarly, 1-year distant brain tumor control (SRS 45 % vs. SRS + WBRT 73 %, $p = 0.02$) and 1-year freedom from CNS recurrence (SRS 27 % vs. SRS + WBRT 73 %, $p = 0.0003$) were better in the SRS + WBRT group. Ten patients in the SRS alone group underwent surgical resection for 12 local brain failures, with histologic confirmation of 10 carcinomas and 2 specimens attributed to necrosis and astrogliosis. Radiation salvage utilized in the SRS alone group included six patients who underwent salvage SRS treatments for distant brain failures and ten patients who received salvage WBRT. Two patients in the SRS + WBRT group underwent salvage SRS, and no patients in that group underwent surgical salvage or repeat WBRT.

The European Organisation for Research and Treatment of Cancer (EORTC) conducted a phase III trial in patients with 1–3 brain metastases who had received definitive local therapy with either surgical resection or SRS and randomized these patients to adjuvant WBRT (30 Gy in 10 fractions) versus observation (OBS) (Kocher et al., 2011). Eligibility criteria included age ≥18, number of brain metastases ≤3, World Health Organization performance status (WHO PS) of 0–2, and stable systemic disease. Patients who received SRS had size limitations of ≤3.5 cm diameter for a single metastasis or ≤2.5 cm for 2–3 metastases. The planning target volumes (PTV) included gross tumor volumes for up to 3 metastases expanded by 1–2 mm margin. Dose was a minimum of 20 Gy to any point in the PTV given by either LINAC or GK SRS. Patients undergoing surgical resection had no size limitations but were required to have gross total resections. 359 patients were deemed eligible for the trial, with 199 patients randomized before radiosurgery (100 patients OBS, 99 patients WBRT) and 160 patients randomized after surgery (79 patients OBS, 81 WBRT). The trial was powered

to detect an 11 % difference in the primary endpoint of functional independence (WHO PS ≤2) at 6 months from 50 % with OBS to 61 % with WBRT. Secondary endpoints included progression-free survival (PFS), OS, late toxicities, and quality of life. Survival with functional independence, defined as median time to WHO PS >2, was not statistically different (10 months for OBS vs. 9.5 months for WBRT, p = 0.71). Similarly, there was no difference in median survival. However, neurologic death, defined as intracranial failure as a component of the cause of death, was more frequent in the OBS arm compared to the WBRT arm (44 % vs. 28 %, p < 0.002). This is different from our definition of neurologic death which is death due to the neurologic complications from brain metastases. Extracranial progression did not differ between arms, but intracranial progression differed significantly (78 % for OBS vs. 48 % for WBRT, p < 0.001). As in other studies, addition of WBRT reduced the rates of intracranial progression and the need for salvage therapy for both initially treated sites and new sites. Salvage WBRT was used in 31 % of all patients in the OBS arm, similar to the MD Anderson study. Late toxicities were not statistically different between the OBS and WBRT arms. The study was not designed to directly compare outcomes based on type of initial local therapy (SRS versus surgery). As compared to patients randomized before SRS, the patients who were randomized after surgery more frequently had a single metastasis, lesions with larger diameters (up to 70 mm), and lesions located in the posterior fossa.

Whole Brain Radiation Therapy Versus Stereotactic Radiosurgery

No randomized controlled trials have compared WBRT alone versus SRS alone for brain metastases. This question was addressed in a retrospective cohort study of 186 patients in RPA classes 1 and 2 who had 1–3 brain metastases (Rades et al., 2007). The WBRT cohort included 91 patients who received 30–40 Gy in conventional fractionation. The SRS cohort received 18–25 Gy tumor margin dose using either LINAC based or GK SRS. Cohorts were well-matched with respect to prognostic factors including age, sex, KPS, primary tumor, RPA class and status of extracranial metastases. Median survival was 7 months for the WBRT cohort versus 13 months for the SRS cohort, though radiation regimen was not significant in the multivariate analysis (RR = 1.04, p = 0.89). SRS alone was associated with improved overall brain control at 1 year when compared to WBRT alone (49 % versus 23 %, respectively), and this was significant on multivariate analysis (RR 1.33, p = 0.003). Similarly, SRS was associated with improved 1 year local control of treated brain metastases over WBRT (64 % versus 26 %, respectively), with significance demonstrated in multivariate analysis (RR 1.64, p < 0.001).

In a three arm prospective cohort study, WBRT alone (n = 29), SRS alone (n = 23) and WBRT + SRS (n = 18) were compared in the treatment of single brain metastases (Li et al., 2000). This study included patients with both small cell lung cancer and non-small cell lung cancer. Radiation doses were 35–45 Gy in conventional fractions for the WBRT only cohort, 15–35 Gy to the tumor margin for the SRS cohort, and 30–45 Gy conventional fractions followed by 15–35 Gy SRS for the WBRT + SRS cohort. Median survival was 5.7 months with WBRT alone, 9.3 months with SRS alone, and 10.6 months with WBRT + SRS. This difference was significant by Chi-square test across all three groups (p = 0.040), but treatment cohort was not significant in the Cox regression model (p = 0.08). Freedom from local progression was 4, 6.9, and 8.6 months for WBRT alone, SRS alone, and WBRT + SRS cohorts, respectively. This study suggested that there are median survival and local control benefits to SRS alone as compared to WBRT alone, though these pair-wise comparisons were not explicitly reported.

Stereotactic Radiosurgery Versus Resection

While there has not been a large, prospective randomized trial comparing SRS versus surgery

alone, there are theoretical advantages for local control with SRS due to the "penumbra effect." This effect occurs because the dose prescribed to the tumor margin decreases over a few millimeters into the surrounding tissue, giving a rim of non-tumor brain tissue treated to less than full dose. This is in contrast to the sharp margins in surgery that may allow untreated cells to persist in the resection cavity. One prospective randomized controlled trial compared SRS alone versus surgical resection plus WBRT in patients with single brain metastases (Muacevic et al., 2008). Eligibility criteria included age 18–80 years, a single brain metastasis with diameter ≤3 cm in an operable site, KPS ≥70, stable systemic disease, and life expectancy of 4 months or greater. For the resection + WBRT group, the WBRT was started within 14 days of resection to a dose of 40 Gy in 20 fractions. The SRS group received a mean dose of 21 Gy to the tumor margin (range 14–27 Gy). The study sample size of 242 patients was calculated to detect a difference of 15 % in 1 year overall survival with 80 % power. Due to poor accrual, the trial was closed with only 64 evaluable patients (33 patients in the surgery + WBRT group and 31 patients in the SRS group). There were no statistically significant differences seen in median survival (9.5 months with resection + WBRT vs. 10.3 months with SRS, $p = 0.8$), 1 year neurologic death rate (29 % resection + WBRT vs. 11 % SRS, $p = 0.3$) or 1 year local tumor control (82 % resection + WBRT vs. 96.8 % SRS, $p = 0.06$). Freedom from distant recurrence at 1 year was significantly better with resection + WBRT compared to SRS alone (3 % vs. 25.8 %, $p < 0.05$), but this was no longer significant if salvage SRS was factored into the analysis ($p = 0.4$). Of the eight patients in the SRS group with distant recurrence, five received repeat SRS, one received WBRT for miliary seeding, and two received no additional treatment due to progressive systemic disease. While it is difficult to draw firm conclusions from this randomized trial regarding survival outcomes as it is underpowered, it adds to the evidence that SRS in selected patients is an alternative to surgery and WBRT.

Stereotactic Radiosurgery for More than 4 Metastases

All of the randomized trials discussed so far have limited the number of metastases to 4 or less. The University of Pittsburgh performed a retrospective study of patients with 4 or more intracranial metastases treated with Gamma Knife SRS and compared these patients by RPA class to historical controls (Bhatnagar et al., 2006). There were 205 patients identified who had undergone SRS for 4 or more intracranial metastases in a single session. Radiosurgery was used alone in 17 % of patients, in combination with WBRT in 46 % of patients, and as salvage after WBRT failure in 38 % of patients. The median number of brain metastases was 5 (range 4–18), and the median total treatment volume was 6.8 cc (range 0.6–51 cc). Median marginal dose for SRS was 16 Gy (range 12–20 Gy). The median survival for all patients after SRS was 8 months, and the median time to progression was 9 months. One year local control was 71 %. When broken down by RPA class, the median survivals were 18, 9 and 3 months for RPA class I, II, and III, respectively. This compared favorably with historic controls for WBRT alone (median survivals 7, 4, and 2 months for RPA class I, II, and III, respectively). Multivariate analysis showed that total treatment volume ($p = 0.002$), age ($p = 0.005$), RPA classification ($p = 0.009$), and marginal dose ($p = 0.019$) were significant prognostic factors for median survival. However, the number of metastases was not a statistically significant prognostic factor ($p = 0.333$). Total treatment volume was also shown in multivariate analysis to be a statistically significant prognostic factor for local control ($p = 0.002$), but number of intracranial metastases was not significant ($p = 0.091$). These results suggest that it is the volume of intracranial metastases, rather than the total number of lesions, that determines the efficacy of SRS. This has yet to be validated in a prospective clinical trial setting.

A retrospective analysis of outcomes from Yonsei University in Seoul, Republic of Korea, grouped according to the number of lesions treated showed that local control and median

survival were not affected by the number of lesions treated with SRS, even in a cohort with more than 15 metastases (Chang et al., 2010). The report included 323 patients who received SRS to 1–5 lesions (215 patients), 6–10 lesions (58 patients), 11–15 lesions (17 patients), and >15 lesions (33 patients). The overall median survival after SRS was 10 months, and there was no statistical difference between groups ($p = 0.554$). Similarly, local control was not statistically different between groups ($p = 0.989$). In patients treated with SRS to >15 lesions, the systemic disease progression rate was higher ($p = 0.014$), reflecting the higher probability of systemic metastases when there are multiple intracranial metastases. Investigators from Katsuta Hospital, Japan calculated the cumulative irradiation doses to the whole brain for 80 patients treated with SRS for 10 or more metastases (Yamamoto et al., 2002). The median cumulative dose to the whole brain was calculated as 4.71 Gy (range 2.16–8.51 Gy), corresponding to the conventional fractionation equivalent dose of 11.78 Gy. They concluded that dosimetrically, the integral dose given by SRS to the whole brain during treatment of 10 or more metastases was safely below whole brain tolerance and should not pose an unacceptably high risk for radiation necrosis.

Salvage Stereotactic Radiosurgery

From the randomized trials, it is evident that new brain metastases occur more frequently when WBRT is omitted. However, patients do not show consistently worse neurologic survival or functional outcomes. This could be explained by the success of salvage therapies when new brain metastases are discovered early on follow-up imaging. While WBRT could be administered for new or progressive brain metastases after SRS, repeat SRS is also a viable option. This strategy was reported in a retrospective analysis of 114 consecutive adults who had previously been treated with GK SRS (margin dose 20 Gy) for 1–3 brain metastases ≤2 cm (Rush et al., 2011). Patients underwent follow-up imaging at 6 weeks and every 3 months thereafter. New metastases were preferentially treated with repeat GK SRS. Of the 109 patients with adequate follow-up, 53 patients had distant brain failures at a median of 5 months after initial SRS. The 1 year actuarial distant progression free survival was 44 %. Only six instances (7 %) of distant progression were associated with neurologic symptoms, with the remaining instances discovered radiographically. Sixty-seven percent of patients with new lesions were successfully treated with salvage GK SRS alone. Whole brain RT was used in 18.3 % of patients, and 11.9 % of patients suffered neurologic deaths. The median overall survival from GK SRS was 13.8 months. Transient neurological worsening occurred in five patients (4.6 %), with permanent neurological worsening occurring in three patients (2.8 %). Conversely, out of 17 patients with deficits attributable to metastases, 5 patients (29.4 %) had complete resolution of deficits, and seven patients (41.2 %) had improved deficits after salvage GK SRS. The study authors made the point that less than 10 % of patients develop symptoms from new metastases when treated with this strategy of initial GK SRS, close interval follow-up, and timely salvage SRS. Furthermore, only 18.3 % of patients treated in this manner were exposed to the morbidity of WBRT, as opposed to every patient in this cohort had they been treated with upfront WBRT. It is the development of symptomatic disease and the loss of functional independence from progressive CNS disease that is relevant as a quality of life issue in patients with metastatic cancer, as opposed to individual tumor control. To reduce alopecia and its associated psychological impact, delays in systemic therapy, and especially the potential adverse cognitive effects, strategies that safely reduce the use of WBRT in appropriately selected patients appear justified.

Conclusion

Brain metastases are common occurrences that historically were treated with corticosteroid therapy and whole brain radiation therapy. Since the 1990s the evidence-based standard of care for patients with solitary brain lesions and good

performance status became surgical resection with or without WBRT. While there is a survival benefit with the addition of surgery to WBRT, the converse is not true. Overall survival and duration of functional independence were not shown to be different in patients who have undergone surgical resection versus patients who had surgery and WBRT. However, WBRT has been shown to reduce recurrence both at the surgical site and elsewhere in the brain. It is unclear what the ultimate clinical significance of recurrence is given that neurologic death and functional independence are similar when effective surveillance and focal salvage strategies are employed. In fact, the therapeutic index likely favors the withholding of WBRT in the cohorts of patients described.

Stereotactic radiosurgery is a non-invasive alternative to surgical resection as local therapy for brain metastases. Surgical resection and SRS have never been compared in a large prospective, randomized trial. They are considered equivalently effective for local tumor control, though there is a theoretical difference due to the penumbra effect of SRS that should be evaluated. Gamma Knife and LINAC based SRS are the two most widely available forms of radiosurgery with similar efficacy in large trials. Analogous to surgery and WBRT, the RTOG 9508 randomized trial demonstrated a survival advantage for the addition of SRS boost to WBRT for patients with a single brain metastasis and good performance status. This trial also showed that with up to 3 metastatic lesions, WBRT + SRS resulted in improved KPS at 6 months and improved local control compared to WBRT alone. The improved local control did not translate into a difference in neurologic death.

Several randomized trials have investigated how SRS alone compares to WBRT + SRS. Overall, there were no differences in median survival or functional independence between SRS alone and WBRT + SRS. The median survival difference seen favoring SRS in the MD Anderson trial may be a result of imbalance in the arms rather than actual treatment effect (Chang et al., 2009). One trial showed an increase in neurologic death with SRS alone (Kocher et al., 2011), but a larger trial showed no difference in neurologic death (Aoyama et al., 2006). Recurrence at both local and distant brain sites was increased when WBRT was withheld. Because of this increased recurrence rate, salvage treatment was utilized more often when SRS alone was used as the initial strategy. However, this strategy allows for avoidance or delay of WBRT in approximately 70–80 % of patients, which in turn may decrease the adverse effects of neurocognitive dysfunction, fatigue, alopecia and delays in systemic therapy. All of the randomized trials to date have evaluated SRS in patients with up to 4 brain metastases. There are retrospective series that have shown safety and efficacy of SRS in patients with more than 4 brain metastases. Similarly, salvage SRS has been shown to be safe and effective in patients who have had prior treatment with either WBRT or SRS. One key advantage to using SRS over WBRT is the avoidance of the neurocognitive decline and decreased quality of life related to WBRT. This needs to be further explored through the use of standardized and well-validated neurocognitive batteries and quality of life assessments in randomized trials. In appropriately selected patients with brain metastases, upfront SRS with close follow-up and early salvage SRS can be a successful strategy to maximize freedom from neurologic death, while avoiding the morbidity of WBRT (Rush et al., 2011).

References

Andrews DW, Scott CB, Sperduto PW, Flanders AE, Gaspar LE, Schell MC, Werner-Wasik M, Demas W, Ryu J, Bahary J-P, Souhami L, Rotman M, Mehta MP, Curran WJ (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

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 295:2483–2491

Aoyama H, Tago M, Kato N, Toyoda T, Kenjyo M, Hirota S, Shioura H, Inomata T, Kunieda E, Hayakawa K, Nakagawa K, Kobashi G, Shirato H (2007)

Neurocognitive function of patients with brain metastasis who received either whole brain radiotherapy plus stereotactic radiosurgery or radiosurgery alone. Int J Radiat Oncol Biol Phys 68:1388–1395

Bhatnagar AK, Flickinger JC, Kondziolka D, Lunsford LD (2006) Stereotactic radiosurgery for four or more intracranial metastases. Int J Radiat Oncol Biol Phys 64:898–903

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

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 10:1037–1044

Chang WS, Kim HY, Chang JW, Park YG, Chang JH (2010) Analysis of radiosurgical results in patients with brain metastases according to the number of brain lesions: is stereotactic radiosurgery effective for multiple brain metastases? J Neurosurg 113 (Suppl):73–78

Chao JH, Phillips R, Nickson JJ (1954) Roentgen-ray therapy of cerebral metastases. Cancer 7:682–689

Elliott RE, Rush SC, Morsi A, Mehta N, Spriet J, Narayana A, Donahue B, Parker EC, Golfinos JG (2011) Local control of newly diagnosed and distally recurrent, low-volume brain metastases with fixed-dose (20 gy) gamma knife radiosurgery. Neurosurgery 68:921–931; discussion 931

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

Gaspar LE, Scott C, Murray K, Curran W (2000) Validation of the RTOG recursive partitioning analysis (RPA) classification for brain metastases. Int J Radiat Oncol Biol Phys 47:1001–1006

Koay E, Sulman EP (2012) Management of brain metastasis: past lessons, modern management, and future considerations. Curr Oncol Rep 14:70–78

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

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

Kwok Y, Patchell RA, Regine WF (2008) Chapter 91 – Palliation of brain and spinal cord metastases. In: Halperin E, Perez C, Brady L (eds) Perez and Brady's principles and practice of radiation oncology. Lippincott Williams & Wilkins, Philadelphia

Landis SH, Murray T, Bolden S, Wingo PA (1998) Cancer statistics, 1998. CA Cancer J Clin 48:6–29

Larson DA, Rubenstein JL, McDermott MW (2008) Chapter 60.1 – Metastatic cancer to the brain. In: DeVita V, Lawrence T, Rosenberg S (eds) DeVita, Hellman, and Rosenberg's cancer: principles & practice of oncology. Wolters Kluwer/Lippincott Williams & Wilkins, Philadelphia

Li B, Yu J, Suntharalingam M, Kennedy AS, Amin PP, Chen Z, Yin R, Guo S, Han T, Wang Y, Yu N, Song G, Wang L (2000) Comparison of three treatment options for single brain metastasis from lung cancer. Int J Cancer 90:37–45

Linskey ME, Andrews DW, Asher AL, Burri SH, Kondziolka D, Robinson PD, Ammirati M, Cobbs CS, Gaspar LE, Loeffler JS, McDermott M, Mehta MP, Mikkelsen T, Olson JJ, Paleologos NA, Patchell RA, Ryken TC, Kalkanis SN (2010) The role of stereotactic radiosurgery in the management of patients with newly diagnosed brain metastases: a systematic review and evidence-based clinical practice guideline. J Neurooncol 96:45–68

Meyers CA, Wefel JS (2003) The use of the mini-mental state examination to assess cognitive functioning in cancer trials: no ifs, ands, buts, or sensitivity. J Clin Oncol 21:3557–3558

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

Narayana A, Recht L, Gutin PH (2010) Chapter 21 – Central nervous system tumors. In: Hoppe R, Phillips T, Roach M (eds) Leibel and Phillips textbook of radiation oncology. Elsevier Saunders, Philadelphia

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. N Engl J Med 322:494–500

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

Rades D, Pluemer A, Veninga T, Hanssens P, Dunst J, Schild SE (2007) Whole-brain radiotherapy versus stereotactic radiosurgery for patients in recursive partitioning analysis classes 1 and 2 with 1 to 3 brain metastases. Cancer 110:2285–2292

Rush S, Savetsky M, Vinokur A, Mehta N (2006) Palliative whole brain radiation therapy (WBRT) for brain metastases (BM) revisited: the patient population in the modern era is different from the original patient cohort of

the RTOG WBRT clinical trials. 2006 ASCO annual meeting proceedings. J Clin Oncol 24(Suppl):1544

Rush S, Elliott RE, Morsi A, Mehta N, Spriet J, Narayana A, Donahue B, Parker EC, Golfinos JG (2011) Incidence, timing, and treatment of new brain metastases after Gamma Knife surgery for limited brain disease: the case for reducing the use of whole-brain radiation therapy. J Neurosurg 115:37–48

Shaw E, Scott C, Souhami L, Dinapoli R, Kline R, Loeffler J, Farnan N (2000) Single dose radiosurgical treatment of recurrent previously irradiated primary brain tumors and brain metastases: final report of RTOG protocol 90–05. Int J Radiat Oncol Biol Phys 47:291–298

Shrieve DC, Loeffler JS, McDermott MW, Larson DA (2010) Chapter 25 – Radiosurgery. In: Hoppe R, Phillips T, Roach M (eds) Leibel and Phillips textbook of radiation oncology. Elsevier Saunders, Philadelphia

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

Yamamoto M, Ide M, Nishio S, Urakawa Y (2002) Gamma Knife radiosurgery for numerous brain metastases: is this a safe treatment? Int J Radiat Oncol Biol Phys 53:1279–1283

Tumor Seeding After Stereotactic Brain Biopsy

14

Gordan Grahovac

Contents

Abstract

Stereotactic biopsy of the brain lesions is safe procedure with a low complication rate. Seeding of tumor along the trajectory of the stereotactic biopsy is a rare complication. Only case reports of tumor seeding after stereotactic brain biopsy have been reported in the literature, and two cases of seeding after neurosurgical endoscopic procedures have been reported. Although these complications are rare after common neurosurgical procedures, they pose great challenge for treatment of these patients. We give overview of these reports together with presentation of our case.

Introduction

The primary parenchymal sarcomas of the central nervous system (CNS) are extremely rare tumors with the incidence of 0.08–0.7 % (Oliveira et al., 2002; Paulus et al., 1991). Imaging studies of CNS and other system should proceed before the final diagnosis of primary parenchymal sarcoma has been made. Due to the rarity of these tumors they can be easily misdiagnosed. It can be very difficult to diagnose such tumors from specimens obtained with the stereotactic biopsy needle.

Stereotactic biopsy of the brain lesions is a common neurosurgical procedure. This technique is simple, effective and caries low risk for serious complications, with diagnostic yield from 70 to 98 % (Chandrasoma et al., 1989;

G. Grahovac (✉)
Department of Neurosurgery, University Hospital "Dubrava", Av. G. Suska 6, 10000 Zagreb, Croatia
e-mail: ggrahov@mef.hr

M.A. Hayat (ed.), *Tumors of the Central Nervous System, Volume 11*,
DOI 10.1007/978-94-007-7037-9_14,

Feiden et al., 1991). Implantation metastasis along the needle tract after the stereotactic brain biopsy is an extremely rare complication. This type of complication has been published 15 articles (Aichholzer et al., 2001; Ashraf et al., 1997; Barloon et al., 1988; Bouillot-Eimer et al., 2005; Grahovac et al., 2013; Karlsson et al., 1997; Kim et al., 2003; Marx et al., 2001; Ogilvy et al., 1993; Perrin and Bernstein, 1998; Pierallini et al., 1999; Regis et al., 1996; Roa et al., 1999; Rosenfeld et al., 1990; Steinmetz et al., 2001).

Case Presentation

In our case, a 47-year-old man presented with 1-month history of memory disturbance and speech problem. The patient developed right hemiparesis with discrete right facial paresis. The magnetic resonance imaging (MRI) revealed a brain tumor in his left temporal lobe with significant peritumoral edema. Diagnostic work-up did not reveal any other primary tumors. The patient was subjected to stereotactic brain biopsy because he refused tumor resection. A computed tomography (CT) guided stereotactic biopsy was done with Leksell frame (Elekta, Stockholm). The brain biopsy was performed with the sedan needle. During the stereotactic procedure several specimen samples where taken. Postoperative CT showed minimal bleeding in the tumor at the site of the biopsy. A histological analysis of the specimen revealed metastatic carcinoma of unknown origin. Two weeks later the patient demanded craniotomy and resection of the brain lesion. The patient underwent left temporal craniotomy, and tumor was removed. Histological diagnosis of resected tumor was the same as stereotactic biopsy histology. The patient underwent fractionated external beam radiation therapy of the whole brain of 30 Gy.

Follow-up MR of the brain 2 months after surgery revealed small recurrence of the tumor at the previous tumor site with tumor in the stereotactic trajectory channel (Fig. 14.1). The patient was retreated with gamma knife surgery, and received prescription dose of 18 Gy as 50 % isodose on the stereotactic biopsy tract.

Patient died 1 month after gamma knife surgery. The additional pathologic evaluation of the tumor specimen, performed by a more experienced pathologist, established new diagnosis of malignant fibrous histiocytoma of the brain.

Seeding After Stereotactic Brain Biopsy

Seeding of tumor cells along the tract of the needle biopsy is a well known complication of the procedure. Seeding can occur during biopsy of the tumors of the liver, pancreas, thyroid, prostate, ocular melanoma and other parenchymal tumors (Engzell et al., 1971; Ferrucci et al., 1979; Glasgow et al., 1988; Haddad and Somsin, 1987; Onodera et al., 1987; Sinner and Zajicek, 1976). The actual risk of seeding can be substantial. It may be as high as 11 % in patients with hepatocellular carcinoma (Stigliano et al., 2007) Fortunately, seeding after stereotactic biopsy of the primary brain tumors or metastatic lesions of the brain has been reported only in 15 articles and twice after ventriculoscope biopsy of germinoma of the pineal gland (Table 14.1). Seeding of the tumor cells occurs during withdrawal of needle from the tumor from the tumor cells which are adherent to the needle. Tumor cells are shedded into bioptic path (Glasgow et al., 1988; Rosenfeld et al., 1990). We can presume that shedding of tumor cells occurs every time during withdrawal of the bioptic needle, but we can only speculate as to how much tumor cells are shedded each time. In addition to the number of cells that are shedded, other factors, such as degree of cell malignancy, cell adhesiveness, growth potential of malignant cells, characteristic of host tissue and adjuvant therapy, contribute to the increased risk of tumor seeding (Haddad and Somsin, 1987; Stigliano et al., 2007). In our case the aggressive type of the tumor cells caused seeding despite the whole brain irradiation therapy. Majority of published cases of seeding occurred after stereotactic biopsy of the primary tumor of the CNS such as glioblastoma multiforme and anaplastic astrocytoma. This

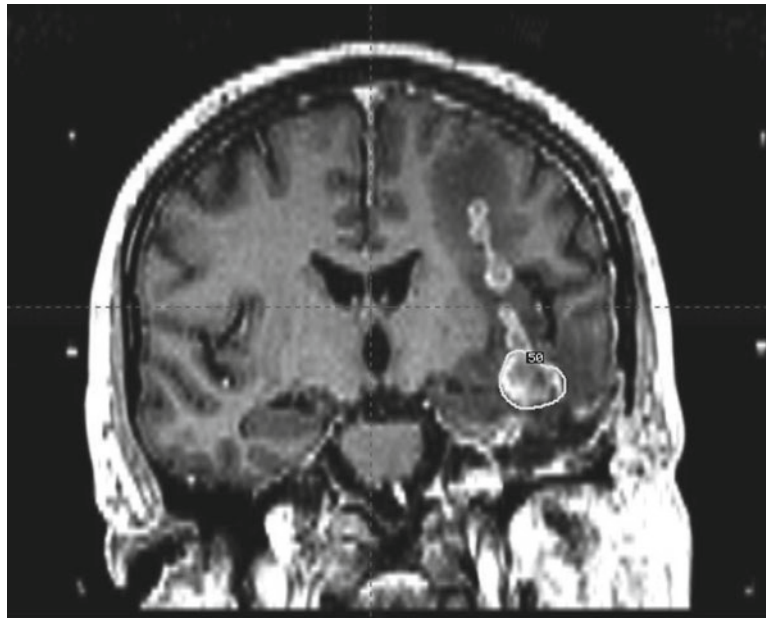

Fig. 14.1 Coronal, gadolinium enhanced T1-weighted MR scans demonstrates an enhancing tumor in the middle of the stereotactic tract

complication has also occurred after biopsy of the brain metastasis, which we initially thought, happened in our case. Because occurrence of metastatic disease was within 2 months after the surgery and whole brain irradiation, we requested additional pathological evaluation. After thorough review and additionally immunohistochemical analysis, the diagnosis of the primary sarcoma of the brain was obtained.

Although the seeding of the tumor cells must occur during every stereotactic brain biopsy, luckily implanted cells do not grow into clinically and radiological significant mass. There are several ways to suggest how to reduce seeding after biopsy, including using a narrow-gauge needle, needle sheet, and applying suction while withdrawing needle (Glasgow et al., 1988; Perrin and Bernstein, 1998; Rosenfeld et al., 1990). Because of the rarity of seeding after stereotactic brain biopsy, it is impossible to calculate real risk of seeding, but we should be aware that this complication might occur.

Seeding After Neuro-Endoscopic Biopsy

Biopsy and surgery of ventricular tumors are becoming more popular in recent decade, and there should also be increased awareness of tumor seeding after such procedures. There are two cases of recurrent germinoma cell tumors of pineal gland that occurred (Table 14.1.). In one case the recurrent tumor occurred at the trajectory of ventriculoscope and in the other case the tumor occurred under burr hole of ETV (Choi et al., 2007; Haw and Steinbok, 2001) In both cases, tumor occurrence complicated initially minimal invasive surgical treatment.

In conclusion, our case of metastatic primary central nervous sarcoma is unusual because these types of tumors are very rare, and they are difficult to diagnose preoperatively. Tumor seeding after stereotactic biopsy and endoscopy biopsy can happen sometimes and this should increase the awareness of neurosurgeons that are performing

Table 14.1 Patient demographic and clinical data

Authors & year	Age (years), sex	Type of tumor	Location of tumor	Radiation therapy	Seeding occurrence after	Implantation pattern	Outcome
Aichholzer et al. (2001)	42, M	Glioblastoma –Anaplastic astrocytoma	Right basal ganglia	Yes	3 months	Epidural	Died
Ashraf et al. (1997)	34, M	Primary malignant rhabdoid tumor	Left basal ganglia	Yes	?	Biopsy channel	Died
Barloon et al. (1988)	10, M	craniopharyngioma	Suprasellar	Yes	5 years	Biopsy channel	?
Bouillot-Eimer et al. (2005)	60, F	Glioblastoma multiforme	Left parietal	Yes	8 months	Subcutaneous and biopsy tract	Died
Grahovac et al. (2013)	47, M	malignant fibrous histiocytoma	Left temporal	Yes	2 months	Biopsy channel	Died
Karlsson et al. (1997)	47, F	Adenocarcinoma	Left cerebellum	Yes	26 weeks	Biopsy channel	Died
	69, M	Renal cell carcinoma	Right parietal	Yes	18 weeks	Biopsy channel	Died
Kim et al. (2003)	64, M	Anaplastic astrocytoma	Left basal ganglia	Yes	3 months after radiation	Biopsy channel	?
Marx et al. (2001)	46, F	Epithelial lung cancer metastasis	Left parietal	Yes	1 month after irradiation	Biopsy channel	?
Ogilvy et al. (1993)	39, M	Cavernous hemangioma	Right occipital lobe	No	5 years	Beneath burr hole	?
Perrin and Bernstein (1998)	23, M	Anaplastic astrocytoma	Left temporal	Yes	6 months	Biopsy channel	Died
Pierallini et al. (1999)	60, M	Glioblastoma multiforme	Right frontal	Yes	3 months after radiation	Biopsy channel	?
Regis et al. (1996)	?,?	?	Pineal region	?	?	?	?
Roa et al. (1999)	31, F	Large cell lymphoma of b cell	Right frontal	Yes	1 month after radiotherapy	The scalp at the biopsy site	?
Steinmetz et al. (2001)	56, M	Glioblastoma multiforme	Right cingulate gyrus	Yes	?	Biopsy channel	?
Rosenfeld et al. (1990)	1.5, M	Pinealoblastoma	Pineal region	No	103 days	Biopsy channel	Died
VENTRICULOSCOPE SEEDING							
Choi et al. (2007)	13, F	Germinoma	Pineal gland	Yes	12 months	At burr hole	?
Haw and Steinbok (2001)	14, M	Germinoma	Pineal gland	Yes	17 months	Ventriculoscope tract	?

Legend: *M* male, *F* female, *?* unknown

stereotactic brain biopsies in everyday clinical practice. This rare complication can complicate clinical management. Multicenter study might give us answer how common is seeding after stereotactic brain biopsy and endoscope surgery and what can be done to prevent this complication.

References

Aichholzer M, Mazal PR, Haberler C, Dietrich W, Bertalanffy A, Roessler K, Ungersboeck K (2001) Epidural metastasis of a glioblastoma after stereotactic biopsy: case report. Minim Invasive Neurosurg 44(3):175–177

Ashraf R, Bentley RC, Awan AN, McLendon RE, Ragozzino MW (1997) Implantation metastasis of primary malignant rhabdoid tumor of the brain in an adult (one case report). Med Pediatr Oncol 28(3):223–227

Barloon TJ, Yuh WT, Sato Y, Sickels WJ (1988) Frontal lobe implantation of craniopharyngioma by repeated needle aspirations. AJNR Am J Neuroradiol 9(2):406–407

Bouillot-Eimer S, Loiseau H, Vital A (2005) Subcutaneous tumoral seeding from a glioblastoma following stereotactic biopsy: case report and review of the literature. Clin Neuropathol 24(6):247–251

Chandrasoma PT, Smith MM, Apuzzo ML (1989) Stereotactic biopsy in the diagnosis of brain masses: comparison of results of biopsy and resected surgical specimen. Neurosurgery 24(2):160–165

Choi UK, Cha SH, Song GS, Choi CH, Lee SW, Lim YT, Kim WT (2007) Recurrent intracranial germinoma along the endoscopic ventriculostomy tract. Case report. J Neurosurg 107(1 Suppl):62–65

Engzell U, Esposti PL, Rubio C, Sigurdson A, Zajicek J (1971) Investigation on tumour spread in connection with aspiration biopsy. Acta Radiol Ther Phys Biol 10(4):385–398

Feiden W, Steude U, Bise K, Gündisch O (1991) Accuracy of stereotactic brain tumor biopsy: comparison of the histologic findings in biopsy cylinders and resected tumor tissue. Neurosurg Rev 14(1):51–56

Ferrucci JT, Wittenberg J, Margolies MN, Carey RW (1979) Malignant seeding of the tract after thin-needle aspiration biopsy. Radiology 130(2):345–346

Glasgow BJ, Brown HH, Zargoza AM, Foos RY (1988) Quantitation of tumor seeding from fine needle aspiration of ocular melanomas. Am J Ophthalmol 105(5):538–546

Grahovac G, Chudy D, Heinrich Z, Zarkovic K (2013) Implantation metastasis of malignant fibrous histiocytoma along the stereotactic biopsy tract. Clin Neurol Neurosurg 115(7):1160–1161

Haddad FS, Somsin AA (1987) Seeding and perineal implantation of prostatic cancer in the track of the biopsy needle: three case reports and a review of the literature. J Surg Oncol 35(3):184–191

Haw C, Steinbok P (2001) Ventriculoscope tract recurrence after endoscopic biopsy of pineal germinoma. Pediatr Neurosurg 34(4):215–217

Karlsson B, Ericson K, Kihlström L, Grane P (1997) Tumor seeding following stereotactic biopsy of brain metastases. Report of two cases. J Neurosurg 87(2):327–330

Kim JE, Kim CY, Kim DG, Jung HW (2003) Implantation metastasis along the stereotactic biopsy tract in anaplastic astrocytoma: a case report. J Neurooncol 61(3):215–218

Marx T, Rainov NG, Heidecke V, Burkert W (2001) Secondary tumor formation after stereotactic biopsy for intracerebral metastatic disease. Surg Neurol 55(1):41–45

Ogilvy CS, Moayeri N, Golden JA (1993) Appearance of a cavernous hemangioma in the cerebral cortex after a biopsy of a deeper lesion. Neurosurgery 33(2):307–309; discussion 309

Oliveira AM, Scheithauer BW, Salomao DR, Parisi JE, Burger PC, Nascimento AG (2002) Primary sarcomas of the brain and spinal cord: a study of 18 cases. Am J Surg Pathol 26(8):1056–1063

Onodera H, Oikawa M, Abe M, Chida N, Kimura S, Satake K, Motojima T, Goto Y (1987) Cutaneous seeding of hepatocellular carcinoma after fine-needle aspiration biopsy. J Ultrasound Med 6(5):273–275

Paulus W, Slowik F, Jellinger K (1991) Primary intracranial sarcomas: histopathological features of 19 cases. Histopathology 18(5):395–402

Perrin RG, Bernstein M (1998) Iatrogenic seeding of anaplastic astrocytoma following stereotactic biopsy. J Neurooncol 36(3):243–246

Pierallini A, Caramia F, Piattella MC, Pantano P, Santoro A, Di Stefano D, Bozzao L (1999) Metastasis along the stereotactic biopsy trajectory in glioblastoma multiforme. Acta Neurochir (Wien) 141(9):1011–1012

Regis J, Bouillot P, Rouby-Volot F, Figarella-Branger D, Dufour H, Peragut JC (1996) Pineal region tumors and the role of stereotactic biopsy: review of the mortality, morbidity, and diagnostic rates in 370 cases. Neurosurgery 39(5):907–912; discussion 912–914

Roa WH, Kim D, Halls SB, Murray B (1999) Implantation metastasis of primary central nervous system lymphoma complicating radiotherapy outcome. Am J Clin Oncol 22(1):29–31

Rosenfeld JV, Murphy MA, Chow CW (1990) Implantation metastasis of pineoblastoma after stereotactic biopsy. Case report. J Neurosurg 73(2):287–290

Sinner WN, Zajicek J (1976) Implantation metastasis after percutaneous transthoracic needle aspiration biopsy. Acta Radiol Diagn (Stock) 17(4):473–480

Steinmetz MP, Barnett GH, Kim BS, Chidel MA, Suh JH (2001) Metastatic seeding of the stereotactic biopsy tract in glioblastoma multiforme: case report and review of the literature. J Neurooncol 55(3):167–171

Stigliano R, Marelli L, Yu D, Davies N, Patch D, Burroughs AK (2007) Seeding following percutaneous diagnostic and therapeutic approaches for hepatocellular carcinoma. What is the risk and the outcome? Seeding risk for percutaneous approach of HCC. Cancer Treat Rev 33(5):437–447

15 Intracranial Stereotactic Radiosurgery in High Risk Patients with Metastases from Radioresistant Primary Tumors

Varun Kumar Chowdhry and Seung Shin Hahn

Contents

Abstract

Traditionally radioresistant brain metastases including melanoma, renal cell carcinoma, and sarcoma have poor outcomes with supportive care and whole brain radiotherapy (WBRT) alone. Although recent advances in biologic and targeted agents have improved systemic disease control in some patients with melanoma and renal cell carcinoma, such agents have poor penetration and are relatively ineffective in controlling brain metastases. Nevertheless, the ability to provide biologically ablative doses of radiotherapy by radiosurgery still can yield excellent local control similar that found in classically non-radioresistant brain tumors. Although conventional radiobiological models suggest that these patients will not respond to conventionally fractionated radiation therapy treatment, stereotactic radiosurgery allows high doses of radiation to be delivered to the target, while minimizing dose to normal tissue. Here we present treatment strategies and clinical outcome data in the management of such patients. Given the excellent local control following radiosurgery in this group of patients we propose that radiosurgery provides a clinical benefit to this group of patients. The use of whole brain radiation therapy should be considered to improve local control, although can be omitted in selected groups of patients.

V.K. Chowdhry (✉) • S.S. Hahn
Department of Radiation Oncology, SUNY Upstate Medical University, 750 East Adams Street, Syracuse, NY 13210, USA
e-mail: ChowdhrV@upstate.edu

M.A. Hayat (ed.), *Tumors of the Central Nervous System, Volume 11*,
DOI 10.1007/978-94-007-7037-9_15,

Introduction

As a whole, brain metastases represent the most common intracranial tumor and continue to be a significant problem in the multidisciplinary management of cancer patients. Particularly challenging are tumors that are thought to be radioresistant including: melanoma, renal cell carcinoma, and sarcoma, as lesions not amenable to surgical resection have historically poor outcomes when treated with whole brain radiation therapy alone. Although non-small cell lung cancer and breast cancer are the most common malignancies to result in brain metastases, melanoma may account from 4 to 16 % of brain metastases, while metastases from renal cell carcinoma range from 0.3 to 7 % (Lassman and DeAngelis, 2003). According to a population-based cohort study, Schouten et al. (2002), found that the cumulative incidence of brain metastases was 7.4 % of patients with melanoma, and 9.8 % in patients with renal cell carcinoma. Although these tumors are thought to be radioresistant to standard radiation fractionation schemes, intracranial stereotactic radiosurgery allows a high dose of radiation therapy in a single fraction to optimize the therapeutic ratio.

The importance of intracranial disease control is not only important in terms of palliation of symptoms, but the use of local therapy has been shown to translate into a survival benefit. Patchell et al. (1990), showed a survival benefit when surgical resection was added to whole brain radiation therapy in patients who had a single metastatic lesion in the brain. While surgical resection provides the benefit of more immediate resolution of symptoms as well as a histological diagnosis, surgical resection may become difficult depending on the number and location of the lesions.

Stereotactic radiosurgery, which provides a biologically ablative radiotherapy dose, has been shown to be effective in providing local intracranial disease control. In general, it is believed that radiosurgery provides equivalent local control compared to open surgery, although a randomized clinical trial looking at this question had to be closed early due to poor patient accrual (Muacevic et al., 2008). The Radiation Therapy Oncology Group (RTOG), performed a randomized clinical trial randomizing patients with one to three brain metastases to either whole brain radiation therapy alone or whole brain radiation therapy in combination with stereotactic radiosurgery. Patients randomized to the radiosurgery arm have a preserved longer functional independence, and patients with a single metastatic lesion were found to have a benefit in overall survival (Andrews et al., 2004). Another randomized clinical trial performed through the University of Pittsburgh randomized patients with 2–4 metastatic lesions to whole brain radiation therapy alone compared to whole brain radiation therapy plus stereotactic radiosurgery showed 100 % local failure with whole brain radiation therapy alone, compared with 8 % in the stereotactic radiosurgery arm. The investigators noted that the histology of the primary lesion did not have an impact on local failure rate (Kondziolka et al., 1999). Although these trials included patients with radioresistant tumors, the overall number of patients in these trials with such tumors was small.

As improvements in systemic therapy lead to improved systemic disease control and overall survival in patients with traditionally radioresistant tumors, it is possible that patients may derive a greater benefit to disease control in the brain than thought previously.

Radiobiology of Radioresistant Tumors

The rationale for use of fractionated radiotherapy is based on the concept that normal tissue can undergo repair of sublethal damage, while tumor cells can undergo reassortment to a more radiosensitive phase of the cell cycle and reoxygenation which results in increased radiosensitivity ultimately yielding a therapeutic window. This is based on early experiences when fractionated courses of radiotherapy could result in a better side effect profile, yet similar tumor control (Fowler, 1989). Melanoma, sarcoma, and renal cell carcinoma are classically thought to be radioresistant based on historical data that

these tumors do not respond well to standard fractionated radiotherapy.

Various models have been proposed to explain cell killing during a particular course of radiotherapy, although a common model that is frequently applied to the clinic is the linear quadratic model. Using this model, it is possible to quantitate how a given tumor may respond to radiation therapy. This model presumes that there are two components of a radiotherapy dose that contribute to cell death, one that is proportional to the dose, and the other that is proportional to the square of the dose. Based on this model, the surviving fraction of cells (S) following a dose (D) is based on the following formula, where alpha represents the magnitude of cell kill proportional to the dose beta represents the magnitude of cell kill proportional to the dose squared (Hall and Giaccia, 2006).

$$S = e^{-\alpha D - \beta D^2}$$

Based on the equation above, if one wanted to determine the dose at which both components of cell killing contribute equally to cell death, the equation above can be reduced to the following equation.

$$\alpha D = \beta D^2$$

$$D = \alpha/\beta$$

A large alpha-beta ratio means that the linear portion dominates in terms of cell killing, while a smaller alpha-beta ratio means that the quadratic portion dominates. Normal cells are believed to have a low alpha beta ratio, and therefore greatest therapeutic benefit to fractionation is achieved when a tumor cell has a large alpha-beta ratio (Fig. 15.1). Therefore, in general it is believed that low doses of radiation per day will selectively kill tumor cells, while sparing normal cells.

However, it is believed that radioresistant tumors have smaller alpha-beta ratios, making the benefit to standard fractionation less pronounced. However, it does not imply that these tumors are radioresistant, and higher doses of radiotherapy may still be able to control the disease.

Radioresistance of tumor cells is governed by a number of factors. In part it is believed that radioresistant cells containing high percentages

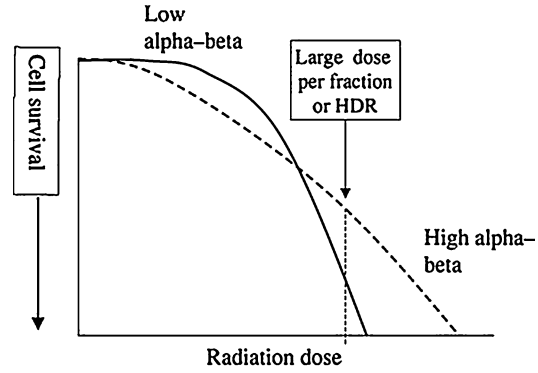

Fig. 15.1 Cell survival curve depicting survival parameters for cell lines with low alpha-beta rations and high alpha beta ratios. In general, it is thought that tumor cells have a high alpha beta ratio compared to normal tissues which have a low alpha-beta ratio. At low radiation doses, there is enhanced cell killing in cells with high-alpha beta ratio (tumor cells), with decreased cell killing in with cells of a low-alpha beta ratio (normal cells). On the other hand, since it is believed that radioresistant tumors have a low alpha beta ratio, it would be expected that cell killing would be enhanced with higher dose per fraction (Figure from Morton, 2005)

of hypoxic cells, which ultimately results in decreased oxygen dependent cell killing. Other factors include variations in gene expression, the presence of cells which are able to divide in an uncontrolled fashion, and distribution of cells in radioresistant phases of the cell cycles (Zhivotovsky et al., 1999). Despite the term radioresistant tumors, even a given histology may show wide variations in cell death patterns. *In vitro* studies attempting to determine the alpha/beta ratios for melanoma cells have been shown to have a wide degree of variation (Rofstad, 1994).

There is a controversy regarding whether or not the linear quadratic model is applicable to the high doses used in stereotactic radiosurgery treatments as outlined by Kirkpatrick et al. (2008) and Brenner (2008). It is believed by some that the biological effect of ablative doses of radiotherapy is underestimated from the linear quadratic model, as the damage may involve alternative mechanisms of cell killing including damage to the vasculature and stroma that is not well explained by the linear quadratic model (Kirkpatrick et al., 2008). Nevertheless, even if one accepts the linear quadratic model, hypofractionation using high

dose per fraction either with stereotactic radiosurgery or stereotactic radiation therapy is expected to result in enhanced cell killing compared to standard fractionation alone making it at least feasible theoretically to treat radioresistant tumors (Hall and Brenner, 1993). Nevertheless, the use of modern stereotactic radiosurgery systems allows a high dose of radiotherapy to be provided to a tumor, with preservation of normal brain tissue. While these tumors may not respond to lower-dose per fraction radiation therapy, it does not imply that radiosurgery doses are ineffective.

Radioresistant Tumors – Overview

Despite the fact that renal cell, melanoma, and sarcomas have distinct disease biology, several series have evaluated these groups of tumors as a whole. If one extrapolates that radioresistance of these tumors to standard fractionation applies to radiosurgery doses, an initial presumption is that these patients may most benefit from surgical resection. Nevertheless, the ability to perform a surgical resection is often believed to be limited to patients who have a solitary lesion with controlled systemic disease. The use of stereotactic radiosurgery in general is popular as it allows for a minimally invasive procedure that is able to target multiple, even surgically inaccessible lesions (Sin et al., 2009).

Part of the interest in treating patients with radioresistant tumors developed from the common situation where surgical resection is not feasible, and that these patients have been found to have poor outcomes with whole brain radiation therapy alone. Patients with radioresistant tumors treated with whole brain radiation therapy alone have survival ranging from 10 to 20 weeks for patients with melanoma primary tumors compared to 8–37 weeks for patients with renal cell primary tumors. The recursive partitioning analysis (RPA) class, which takes into account age, performance status, and status of extracranial disease, has been found to be an important predictor of overall survival from many different studies (Brown et al., 2002). Additionally, uncontrolled metastatic disease to the brain can result in significant morbidity for patients making local control of importance.

The Mayo clinic experience reported by Brown et al. (2002) reported a series of 41 patients who were treated using a GammaKnife stereotactic radiosurgery system. Patients were treated with a median dose to the tumor margin of 18 Gy (range: 12–25 Gy). The reported local control for patients in this series was 88 %, and overall survival was 14.2 months. These survival rates were improved compared to historical controls treated with whole brain radiotherapy alone (Brown et al., 2002).

At our own institution, Powell et al. (2008), at the State University of New York Upstate Medical University reviewed 76 patients, 50 patients with melanoma, 23 patients with renal cell carcinoma, and 3 patients with sarcoma. Patients were treated to a median margin tumor dose of 18 Gy (range 8–30 Gy). Similar to other reports, we also found that predictors of survival included KPS score, RPA class, and having a single metastatic lesion were all predictors of overall survival. The freedom from local progression was 77.7 % for all patients in the series, with local control for patients with melanoma was found to have 63.0 % compared to 93.6 % for patients with renal cell carcinoma.

Our series also evaluated dosimetric parameters that appeared to improve overall local control. The percent coverage of the prescribed dose to the target volume was also associated with improvements in local control. If the target volume received 90 % or greater of the prescribed dose, then the freedom from local progression was 71 %, compared to 0 % of patients receiving less than 90 % total coverage (Powell et al., 2008).

The largest reported experience of patients with radioresistant primaries is from the University of Texas MD Anderson Cancer Center (Chang et al., 2005). This series included 189 patients with 264 radioresistant metastases. Based on their review, patients with three or fewer metastases each less than 3 cm in diameter were generally considered candidates for stereotactic radiosurgery. They utilized dose constraints for critical structures based on the RTOG 90–05 guidelines. Lesions less than 2 cm were prescribed 20–24 Gy, lesions 2–3 cm 18 Gy, and for lesions

>3 cm, 15 Gy was prescribed. The median minimal peripheral dose was 18 Gy, and the median dose to the isocenter was 21 Gy. The reported local failure for all patients in the study was 27.3 %, with a 1 year overall survival of 30.7 %. Patients with smaller tumors less than 1 cm in diameter had a significantly better probability of local control, even when higher doses utilized to treat smaller metastases are accounted for.

Although most of the experience regarding the treatment of radioresistant primaries is based on retrospective data, prospective data does exist as well. A Phase II study from the Eastern Cooperative Oncology group evaluated patients with 1–3 metastases with renal cell carcinoma in a prospective fashion. In this trial, patients with tumors less than 2 cm in greatest diameter were given a prescription dose of 24 Gy, between 2 and 3 cm a dose of 18 Gy was prescribed, and lesions greater than 3 cm were given 15 Gy, with the dose prescribed to the periphery of the tumor. The investigators found a median survival of 8.3 months was similar to retrospective data, with 19 % of patients dying of intracranial disease progression. However, interestingly local control rates in this study appeared to be worse compared to retrospective data. While many retrospective studies have reported local failure in the 10–20 % range, the 3 and 6 month intracranial disease progression within the original radiosurgery field was 19 and 36 % respectively. The investigators attributed the difference in local control due to possible differences in patient selection, the difficult distinction in tumor necrosis and recurrence, and variations in disease biology (Manon et al., 2005).

A natural question that arises involves the question regarding the use of whole brain radiation therapy in addition to radiosurgery. Whole brain radiation therapy and stereotactic radiosurgery are not mutually exclusive entities, and these treatments can be used in combination with each other. Although in general it appears as if patients who receive whole brain radiation benefit from both local control of the known disease, as well a reduction in failure in remainder of the brain, the addition of whole brain radiation therapy does not result in a survival benefit.

From the surgical literature, it is known that whole brain radiotherapy provides a local control benefit, as well as a reduction in neurological deaths (Patchell et al., 1998). Similar to other reports evaluating whole brain radiotherapy in combination with stereotactic radiosurgery, the Mayo clinic experience in radioresistant tumors suggests that the addition of whole brain radiotherapy improves local control, and neurological progression free survival. However, with extended follow-up in this series it did not appear that there was a reduction in death attributed to neurological causes (Brown et al., 2002). However, in a Phase II prospective study Manon et al. (2005), found that tumor recurrence in the brain was 70 % without whole brain radiation therapy, compared to 18 % with whole brain radiation therapy. Based on their findings, the investigators recommended that if whole brain radiation therapy is omitted, it must be done so cautiously.

Melanoma

Brain metastases continue to pose a significant problem in patients with metastatic melanoma. It is estimated that approximately 50 % of patients found to have metastatic melanoma will eventually develop brain metastases. Various factors have been implicated with an increased risk of brain metastases in patients with melanoma, including patients with ulcerated tumors, mucosal, head and neck, or truncal primaries, and BRAF or NRAS mutations. Factors that are associated with overall poor prognosis include multiple brain metastases, uncontrolled extracranial disease, and elevated lactate dehydrogenase levels (Carlino et al., 2012).

Recent advances in systemic therapy with vemurafenib (Chapman et al., 2011), and ipilumimamb (Hodi et al., 2010), have resulted in a survival benefit in patients with metastatic melanoma. Nevertheless, there is poor penetration of systemic treatments into the central nervous system still necessitates the use of alternative modalities regarding treatment to the central nervous system. Avril et al. (2004) showed a maximum response rate of brain metastases in patients with metastatic melanoma of approximately 10 % to fotemustine. A phase II study with 151 patients evaluating the use of temozolomide

in metastatic melanoma to the brain showed at least a partial response in 6 % of patients, and stabilization in 29 % (Agarwala et al., 2004).

Another alternative compared to chemotherapy is the use of whole brain radiotherapy in patients with metastatic melanoma. An RTOG analysis looking at the use of whole brain radiation therapy in metastatic melanoma showed symptomatic improvement in 76 % patients, and complete resolution of symptoms in 31 % of patients (Carella et al., 1980). Despite symptomatic improvement, local control and overall survival is still poor with metastatic melanoma. A retrospective analysis performed by the Cleveland clinic showed survival rates of 1.1, 2.3, 4.8, 8 months for patients who had no treatment, whole brain radiation therapy alone, aggressive local therapy with radiosurgery or open surgery, and combined aggressive local therapy with whole brain radiation therapy respectively (Buchsbaum et al., 2002).

In the Brown et al. (2002) Mayo clinic experience, patients with melanoma had a worse overall survival of 9.7 months compared to renal cell carcinoma where survival was 17.8 months. A series from the University of Pittsburgh reported a 90 % local control rate following GammaKnife radiosurgery. It was also noted that there was a decreased incidence of new brain metastases by nearly 50 % when whole brain radiation therapy was added to GammaKnife radiosurgery (Mori et al., 1998).

At the University of Southern California, researchers reviewed 45 patients who received stereotactic radiosurgery using the GammaKnife radiosurgery unit. The investigators reported a 98 % local control, and 28 % radiographic resolution following radiosurgery. The complications were acceptable especially compared to open surgery, with a 6 % incidence of seizures, 3 % incidence of nausea and vomiting, and a 3 % incidence of worsening muscle strength. All the patients who were found to have seizures had subtherapeutic levels of antiseizure medications, and the patient who had paresis responded to steroid therapy (Lavine et al., 1999). Patients at this institution were treated to a median dose of 20 Gy (range: 14–24 Gy), depending on the size and location of the metastases. Death was attributed to neurological causes in 34 % of patients. Local control rates following GammaKnife radiosurgery was 90 %, and 1 year survival was 26 %. The strongest predictors of survival were found to be volume of intracranial disease burden and systemic disease burden (Yu et al., 2002).

In the MD Anderson experience, the of radioresistant metastases the investigators found that the rates of hemorrhage were found to be the highest in patients with melanoma (10.5 %), although it is not clear if radiosurgery itself contributes to this or if this is related to the treatment itself (Chang et al., 2005).

Overall it appears that stereotactic radiosurgery for metastatic melanoma improves overall survival. While it is difficult to directly compare the benefit of open surgical resection, WBRT, and stereotactic radiosurgery due to variations in selection of these patients, all of these treatments can be combined with the clinical context of the situation. Patients who have control of systemic disease will benefit more from aggressive treatment of brain metastases. Surgical resection provides the most immediate palliation, and whole brain radiation therapy can be added to improve local control.

Nevertheless based on the retrospective data that we have available, as well as our clinical experience suggest that aggressive treatment to the brain yields a clinical benefit. While surgical resection is indicated for accessible, large lesions, and provides a more immediate relief of symptoms, the more common situation is that many patients may not be candidates for surgery given the location and or number of lesions. The survival benefit is roughly 10 weeks with conservative treatment with WBRT and steroids, however, the survival improves to 6–10 months for a single metastases following stereotactic radiosurgery (Lavine et al., 1999).

Renal Cell Carcinoma

Similar to melanoma, patients with renal cell carcinoma have also been found to have poor outcomes with whole brain radiotherapy alone. A retrospective series of 200 patients from The University of Texas MD Anderson Cancer Center reviewing outcomes for patients who received

whole brain radiation therapy from brain metastases showed that 76 % of patients died of neurological causes, and patients had a 1 year survival of 16.8 %. The authors concluded that based on poor rates of local control with standard whole brain radiation therapy, more aggressive therapy including either surgical resection or radiosurgery may improve patient outcomes (Wrónski et al., 1997). An older series published prior to the more common use of radiosurgery reviewed 34 patients with metastatic renal cell carcinoma. Prognostic factors associated with improved survival were good performance status, and surgical resection. While patients who received surgery did better than patients who did not, all patients who received surgery had good performance status. Nevertheless, the investigators concluded that the data supported surgical resection followed by radiotherapy was associated with improved outcomes (Decker et al., 1984).

Compared to other radioresistant tumors, it appears as if patients with metastatic renal cell carcinoma to the brain have a longer overall survival. In the Mayo clinic series, patients with renal cell carcinoma had the longest overall survival 12.6 months compared to approximately 7 months for both melanoma and sarcoma (Brown et al., 2002). In the MD Anderson experience, patients with renal cell carcinoma had the best overall survival rates with a 1 year survival of 40 %, Patients with renal cell carcinoma are less likely to die of neurological causes (31 %) compared to patients with melanoma (66 %) or sarcoma (60 %) (Chang et al., 2005). Similar to melanoma, as new systemic therapies such as sorafenib emerge (Escudier et al., 2007), providing improved local control to the brain may become even more important. A series by Cochran et al. (2012) evaluated outcomes of GammaKnife radiosurgery in the era of target agents including tyrosine kinase inhibitors, rapamycin inhibitors, and bevacizumab. Patients who received targeted agents had an improvement in overall survival of 16.2 months compared to 7.2 months for patients who were not receiving targeted therapy.

A series from the University of Pittsburgh evaluated patients with metastatic renal cell carcinoma reviewed 69 patients with metastatic renal cell carcinoma with a total of 146 metastases. The authors reported an overall survival of 15 months following GammaKnife radiosurgery. The investigators identified prognostic factors on multivariate analysis that were associated with improved survival following radiosurgery included pre-operative KPS score, radiosurgical dose to the margin as well as to the center, time of initial diagnosis to the time of diagnosis of brain metastases. The overall rate of tumor control was 96 % (Sheehan et al., 2003).

A possible criticism regarding many of the series evaluating the use stereotactic radiosurgery is that better performance status patients are selected, and these patients would do better regardless of the modality chosen. Hernandez et al. (2002), reviewed 29 patients with 92 brain metastases from renal cell carcinoma at Wayne State University. In this series, however, it was found that patients treated with combined whole brain radiotherapy and radiosurgery had survival of 18, 8.5, and 5.3 months for RPA class I, II, and III respectively. Patients who had WBRT alone had survival of 7.1, 4.2, and 2.3 months respectively in this same group.

Based on historical series, untreated brain metastases have a poor survival of 1–2 months, which is improved to 3–6 months followed by conventional radiotherapy techniques, and over 12 months with radiosurgery. Overall patients with metastatic renal cell carcinoma tend to be good candidates for radiosurgery since the metastatic lesions are typically less than 3 cm in greatest dimension, are typically spherical in location, and tend to be well-visualized on imaging studies. The morbidity and mortality of the treatment are low, and treatment tends to preserve quality of life in most of the patients who were treated (Sheehan et al., 2003).

Sarcoma

Brain metastases from sarcoma develop in 1–8 % of patients with sarcoma (Flannery et al., 2010). Additionally, even in series evaluating patients with radioresistant metastases, sarcoma is the most infrequent histology noted. In the Phase II ECOG trial evaluating patients with radioresistant brain metastases, 3/31 (10 %) patients had

metastatic sarcoma (Manon et al., 2005). Even the largest reported series on radioresistant tumors from MD Anderson Cancer Center, only 9 out of 189 patients (5 %) were patients with metastatic sarcoma. Nevertheless, the local control for these patients was 42 % at 1 year, and the 1 year survival of these patients was 22 %. Despite the poor local control, five of these patients who had solitary brain metastases had a median survival of 11 months (Chang et al., 2005). One possibility is that the radiographic appearance of sarcomas following radiosurgery may mimic tumor progression, a phenomena called pseudoprogression. Nevertheless, the small number of patients with sarcoma in these series makes any definitive conclusions difficult.

A series from the University of Pittsburgh reviewed 21 patients with a total of 60 metastases from a sarcomatous primary. In their analysis it was pointed out that patients with metastatic sarcoma to the brain were often in the final stages of their illness, yet there appeared to be a clinical benefit to GammaKnife radiosurgery. In general, patients were considered for stereotactic radiosurgery if the patient has less than 5 total lesions, the individual lesions were less than 3 cm in diameter, and the patient had a Karnofsky performance status greater than 60. Local control following radiosurgery was 88, and 33 % of patients developed new brain metastases. Overall, patients had a median survival of 16 months (Flannery et al., 2010).

Conclusions

The concept of radioresistant metastases is coined from historical data that tumors from patients with melanoma, renal cell carcinoma, and sarcoma do not respond well to standardly fractionationated radiotherapy. Although many mathematical models have been utilized to explain the biology of such tumors, one possibility is that such metastases likely have a lower alpha/beta ratio and therefore, hypofractionation using high radiation dose per fraction is expected to yield a clinical benefit. The precision and high doses that can be provided with modern radiosurgery techniques allows a high level of disease control, while sparing normal brain, thus yielding an overall clinical benefit.

The benefits of stereotactic radiosurgery allows the treatment of multiple, surgically inaccessible lesions. While much of the data regarding the benefit of radiosurgery in this group of patients is based on retrospective data, and good performance status of patients may be a confounding variable, even when controlled for, it still appears that radiosurgery provides a local control, and possibly a survival benefit. Furthermore, controlling intracranial disease provides a palliative benefit and improves overall quality of life.

In general, the approach to patients with brain metastases from a radioresistant primary tumor is that patients should be considered for surgical resection. From a medical standpoint, patients can be placed on steroids if there are neurological symptoms, and anti-seizure medications can be used if the patient develops seizure activity. The role of surgical resection is not only to improve a patient's quality and length of life, but also provides the most immediate relief of symptoms compared to other forms of management. In patients with small metastatic lesions of melanoma, renal cell carcinoma, and sarcoma that are not amenable to surgery, we do recommend stereotactic radiosurgery with or without whole brain radiation therapy. The decision to provide whole-brain radiation therapy should involve a discussion between the patient and the oncologist and the side effects of whole brain radiation therapy should be weighed against the higher rates of local relapse when omitted.

References

Agarwala SS, Kirkwood JM, Gore M, Dreno B, Thatcher N, Czarnetski B, Atkins M, Buzaid A, Skarlos D, Rankin EM (2004) Temozolomide for the treatment of brain metastases associated with metastatic melanoma: a phase II study. J Clin Oncol 22(11): 2101–2107

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(9422):1665–1672

Avril MF, Aamdal S, Grob JJ, Hauschild A, Mohr P, Bonerandi JJ, Weichenthal M, Neuber K, Bieber T, Gilde K, Guillem Porta V, Fra J, Bonneterre J, Saïag P, Kamanabrou D, Pehamberger H, Sufliarsky J, Gonzalez Larriba JL, Scherrer A, Menu Y (2004) Fotemustine compared with dacarbazine in patients with disseminated malignant melanoma: a phase III study. J Clin Oncol 22(6):1118–1125

Brenner DJ (2008) The linear-quadratic model is an appropriate methodology for determining isoeffective doses at large doses per fraction. Semin Radiat Oncol 18(4):234–239

Brown PD, Brown CA, Pollock BE, Gorman DA, Foote RL (2002) Stereotactic radiosurgery for patients with "radioresistant" brain metastases. Neurosurgery 51(3):656–657

Buchsbaum JC, Suh JH, Lee SY, Chidel MA, Greskovich JF, Barnett GH (2002) Survival by radiation therapy oncology group recursive partitioning analysis class and treatment modality in patients with brain metastases from malignant melanoma: a retrospective study. Cancer 94(8):2265–2272

Carella RJ, Gelber R, Hendrickson F, Berry HC, Cooper JS (1980) Value of radiation therapy in the management of patients with cerebral metastases from malignant melanoma: Radiation Therapy Oncology Group Brain Metastases Study I and II. Cancer 45(4):679–683

Carlino MS, Fogarty GB, Long GV (2012) Treatment of melanoma brain metastases: a new paradigm. Cancer J 18(2):208–212

Chang EL, Selek U, Hassenbusch SJ 3rd, Maor MH, Allen PK, Mahajan A, Sawaya R, Woo SY (2005) Outcome variation among "radioresistant" brain metastases treated with stereotactic radiosurgery. Neurosurgery 56(5):936–945

Chapman PB, Hauschild A, Robert C, Haanen JB, Ascierto P, Larkin J, Dummer R, Garbe C, Testori A, Maio M, Hogg D, Lorigan P, Lebbe C, Jouary T, Schadendorf D, Ribas A, O'Day SJ, Sosman JA, Kirkwood JM, Eggermont AM, Dreno B, Nolop K, Li J, Nelson B, Hou J, Lee RJ, Flaherty KT, McArthur GA, BRIM-3 Study Group (2011) Improved survival with vemurafenib in melanoma with BRAF V600E mutation. N Engl J Med 364(26):2507–2516

Cochran DC, Chan MD, Aklilu M, Lovato JF, Alphonse NK, Bourland JD, Urbanic JJ, McMullen KP, Shaw EG, Tatter SB, Ellis TL (2012) The effect of targeted agents on outcomes in patients with brain metastases from renal cell carcinoma treated with Gamma Knife surgery. J Neurosurg 116(5):978–983

Decker DA, Decker VL, Herskovic A, Cummings GD (1984) Brain metastases in patients with renal cell carcinoma: prognosis and treatment. J Clin Oncol 2(3):169–173

Escudier B, Eisen T, Stadler WM, Szczylik C, Oudard S, Siebels M, Negrier S, Chevreau C, Solska E, Desai AA, Rolland F, Demkow T, Hutson TE, Gore M, Freeman S, Schwartz B, Shan M, Simantov R, Bukowski RM, TARGET Study Group (2007) Sorafenib in advanced clear-cell renal-cell carcinoma. N Engl J Med 356(2):125–134

Flannery T, Kano H, Niranjan A, Monaco EA 3rd, Flickinger JC, Kofler J, Lunsford LD, Kondziolka D (2010) Gamma knife radiosurgery as a therapeutic strategy for intracranial sarcomatous metastases. Int J Radiat Oncol Biol Phys 76(2):513–519

Fowler JF (1989) The linear-quadratic model is an appropriate methodology for determining isoeffective doses at large doses per fraction. Br J Radiol 62(740):679–694

Hall EJ, Brenner DJ (1993) The radiobiology of radiosurgery: rationale for different treatment regimes for AVMs and malignancies. Int J Radiat Oncol Biol Phys 25(2):381–385

Hall EJ, Giaccia AJ (2006) Cell survival curves. In: Radiobiology for the radiologist, 6th edn. Lippincott, Philadelphia, pp 30–36

Hernandez L, Zamorano L, Sloan A, Fontanesi J, Lo S, Levin K, Li Q, Diaz F (2002) Gamma knife radiosurgery for renal cell carcinoma brain metastases. J Neurosurg 97:489–493

Hodi FS, O'Day SJ, McDermott DF, Weber RW, Sosman JA, Haanen JB, Gonzalez R, Robert C, Schadendorf D, Hassel JC, Akerley W, van den Eertwegh AJ, Lutzky J, Lorigan P, Vaubel JM, Linette GP, Hogg D, Ottensmeier CH, Lebbé C, Peschel C, Quirt I, Clark JI, Wolchok JD, Weber JS, Tian J, Yellin MJ, Nichol GM, Hoos A, Urba WJ (2010) Improved survival with ipilimumab in patients with metastatic melanoma. N Engl J Med 363(8):711–723

Kirkpatrick JP, Meyer JJ, Marks LB (2008) The linear-quadratic model is inappropriate to model high dose per fraction effects in radiosurgery. Semin Radiat Oncol 18(4):240–243

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(2):427–434

Lassman AB, DeAngelis LM (2003) Brain metastases. Neurol Clin 21(1):1–23

Lavine SD, Petrovich Z, Cohen-Gadol AA, Masri LS, Morton DL, O'Day SJ, Essner R, Zelman V, Yu C, Luxton G, Apuzzo ML (1999) Gamma knife radiosurgery for metastatic melanoma: an analysis of survival, outcome, and complications. Neurosurgery 44(1):59–64

Manon R, O'Neill A, Knisely J, Werner-Wasik M, Lazarus HM, Wagner H, Gilbert M, Mehta M, Eastern Cooperative Oncology Group (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). J Clin Oncol 23(34):8870–8876

Mori Y, Kondziolka D, Flickinger JC, Kirkwood JM, Agarwala S, Lunsford LD (1998) Stereotactic radiosurgery for cerebral metastatic melanoma: factors affecting local disease control and survival. Int J Radiat Oncol Biol Phys 42(3):581–589

Morton GC (2005) The emerging role of high-dose-rate brachytherapy for prostate cancer. Clin Oncol (R Coll Radiol) 17(4):219–227

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(3):299–307

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. N Engl J Med 322(8):494–500

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

Powell JW, Chung CT, Shah HR, Canute GW, Hodge CJ, Bassano DA, Liu L, Mitchell L, Hahn SS (2008) Gamma Knife surgery in the management of radioresistant brain metastases in high-risk patients with melanoma, renal cell carcinoma, and sarcoma. J Neurosurg 109(Suppl):122–128

Rofstad EK (1994) Fractionation sensitivity (alpha/beta ratio) of human melanoma xenografts. Radiother Oncol 33(2):133–138

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(10):2698–2705

Sheehan JP, Sun MH, Kondziolka D, Flickinger J, Lunsford LD (2003) Radiosurgery in patients with renal cell carcinoma metastasis to the brain: long-term outcomes and prognostic factorsinfluencing survival and local tumor control. J Neurosurg 98(2):342–349

Sin AH, Cardenas RJ, Vannemreddy P, Nanda A (2009) Gamma Knife stereotactic radiosurgery for intracranial metastases from conventionally radioresistant primary cancers: outcome analysis of survival and control of brain disease. South Med J 102(1):42–44

Wrónski M, Maor MH, Davis BJ, Sawaya R, Levin VA (1997) External radiation of brain metastases from renal carcinoma: a retrospective study of 119 patients from the M. D. Anderson Cancer Center. Int J Radiat Oncol Biol Phys 37(4):753–759

Yu C, Chen JC, Apuzzo ML, O'Day S, Giannotta SL, Weber JS, Petrovich Z (2002) Metastatic melanoma to the brain: prognostic factors after gamma knife radiosurgery. Int J Radiat Oncol Biol Phys 52(5):1277–1287

Zhivotovsky B, Joseph B, Orrenius S (1999) Tumor radiosensitivity and apoptosis. Exp Cell Res 248(1):10–17

Brain Metastases: Treatment with Stereotactic Iodine-125 Brachytherapy

16

Maximilian I. Ruge, Philipp Kickingereder, and Harald Treuer

Contents

Abstract

The treatment modalities for brain metastases include, in general, stereotactic radiosurgery (SRS) and/or micro-neurosurgical resection combined with external beam radiation therapy (EBRT) as well as whole brain radiation therapy (WBRT) for multiple cerebral tumors. Presently, stereotactic brachytherapy (SBT) is successfully used for the treatment of well circumscribed (low grade) glial tumors, but can also be applied for the treatment of brain metastases. Especially in cases where histological confirmation is requested SBT can be combined with stereotactic biopsy within one minimal invasive and safe surgical procedure. Due to the favorable radiobiology of low dose rate irradiation and a steep dose fall-off from the irradiation center within the tumor towards the periphery SBT represents a highly localized treatment option for not restricting later EBRT/WBRT, not increasing the risk of adverse irradiation effects when applied in case of local tumor recurrence after previous SRS/EBRT treatment, and for tumors >3 cm in diameter. It also has been demonstrated that the overall survival and local control rates are comparable to those after SRS treatment. Thus, SBT is a safe, effective, and minimal invasive local treatment option for selected patients with a single brain metastasis.

M.I. Ruge (✉) • P. Kickingereder • H. Treuer
Department of Stereotaxy and Functional Neurosurgery, University Hospital of Cologne, Kerpener Strate 62, Main Clinic Bldg, 11th Floor, 50937 Cologne, Germany
e-mail: Maximilian.ruge@uk-koeln.de

M.A. Hayat (ed.), *Tumors of the Central Nervous System, Volume 11*,
DOI 10.1007/978-94-007-7037-9_16,

Introduction

Brain metastases represent with increasing incidence the most common intracranial tumors and presently are associated with dismal prognosis. Historically the manifestation of brain metastases has been interpreted as terminal stage of the disease with survival rates of only a few weeks after diagnosis. Kofman et al. (1957) described improvement of symptoms after the administration of steroids, and Chao et al. (1954) introduced whole brain radiation therapy in 1954 as standard therapy increasing survival from 4–6 weeks to 4–6 month. Since then an increased use of magnetic resonance imaging (MRI) has led to earlier and more detailed detection of cerebral disease manifestation and improvement of systemic treatment strategies have enhanced local tumor control rates and overall survival.

Whole brain radiation therapy (WBRT) is still used for multiple brain metastases while treatment regiments for single metastases encompass, depending on localization and size of the metastasis, microsurgical resection in combination with WBRT or more localized treatment concepts as stereotactic radiosurgery (SRS) by modified linear accelerator (LINAC), by Gamma knife or by frameless robotic radiosurgery with Cyberknife. As additional treatment tool with a very long history (stereotactic), brachytherapy (SBT) has been introduced as a safe and minimal invasive treatment option in select cases.

History of Brachytherapy for Brain Tumors

The application of a radium isotope directly into a tumor was first published in 1905 by Danlos followed by reports regarding the utilization of brachytherapy for the treatment of pituitary and glial tumors (Hirsch, 1912; Frazier, 1920). In the 1950s stereotactic guidance for the implantation of radioactive sources was used to precisely treat inoperable brain tumors (Talairach et al., 1955; Mundinger, 1956) and – the beginning of the 1970s – further improved with the introduction of computed tomography (CT) and MRI.

Numerous studies have been published regarding the stereotactically guided application of brachytherapy for the treatment of low- and high-grade glial tumors (WHO grade I–VI) (Gutin et al., 1984; Laperriere et al., 1998; Selker et al., 2002; Kreth et al., 2006; Ruge et al., 2011c) as well as regarding the use for cerebral metastatic disease (Prados et al., 1989; Alesch et al., 1995; Bernstein et al., 1995; Ostertag and Kreth, 1995; Schulder et al., 1997; Bogart et al., 1999; Rogers et al., 2006; Dagnew et al., 2007; Huang et al., 2009; Petr et al., 2009; Ruge et al., 2011a, b, d). The following chapter will discuss principals of stereotactic brachytherapy, indications, surgical technique and published results using this therapy for cerebral metastases.

Principal of Stereotactic Brachytherapy (SBT)

Stereotactic brachytherapy is indicated for well circumscribed tumors with a diameter of <4–5 cm. Brain metastases are generally solid growing tumours which display a relatively clear visible interface of neoplastic extrinsic tissue and non-neoplastic CNS tissue, and, therefore, fulfil one of the major inclusion criteria's for brachytherapy. Stereotactic brachytherapy as well as micro-neurosurgical resection aim toward the devitalisation/removal of the (visible) portion of tumour cells by delivering a lethal irradiation dose (≥200 Gy in the vicinity of the implanted source) from within the tumour while optimally sparing the surrounding tissue. In SBT, Iodine-125-seeds (= small, sealed titanium capsules containing radioactive I-125) are implanted into the tumor. Among other possible radioactive sources, I-125-seeds are used for a variety of reasons:

1. Dose gradient
   The radiation emitted by I-125 has low quantum energy (28–35 keV) and, therefore, is strongly absorbed in the soft tissue (Hubbell and Seltzer, 1995; Ruge et al., 2011d). Together with the steep dose fall-off due to the inverse square law, this strong absorption (half-value layer: 2 cm) results in highly focal dose distributions enabling extremely high doses inside

the tumor, while keeping the dose to the surrounding healthy brain low. The dose gradient in SBT with I-125-seeds is superior to that with SRS (Viola et al., 2006).

2. Shielding
   The low radiation energy makes I-125 also favorable in terms of radiation protection. Since the strong absorption in bone (half-value layer: 3 mm) and lead (half-value layer: 0.02 mm) the radiation exposure of the patient's family and health care personnel can be kept low.
3. Fractionation
   Due to its half-life of 59.4 days (Ruge et al., 2011d) the dose rate of I-125-seeds is rather stable and decreases by as little as 1.16 % per day. This facilitates prolonged irradiation times of several weeks or even longer. For example, the application of a total dose of 50 Gy during 35 days to the tumor border is performed with an initial dose rate of 1.7 Gy/day and still 1.2 Gy/day at the end of treatment. Due to the continuous decay of I-125 a hyper-fractionated treatment regime results with very low dose rates, 7.1–5 cGy/h at the tumor rim, further minimizing the dose effects in neighboring healthy brain tissue.
4. Accuracy
   The steep dose gradient of I-125-seeds makes the accuracy of tumor dosage sensitive to seed position within the target. It was shown that an accuracy of 1.5 mm in seed positioning is required not to inadequately compromise dose accuracy (Treuer et al., 2005). For this purpose stereotactic guidance and localization techniques are used and seeds with radio-opaque markers (Heintz et al., 2001) that allow precise intra-operative localization of the seeds on CT of bi-planar X-rays (Treuer et al., 2004) are used.

   The relation between seed activity and dose output for I-125-seeds has been intensively studied and is well understood today. Reports and recommendations of the American Association of Physicists in Medicine on the dosimetry of interstitial brachytherapy sources are available (Nath et al., 1995; Williamson et al., 2005).
5. Dose conformation
   As in SRS, in stereotactic brachytherapy of brain tumors we attempted to irradiate the target as conformal as possible. For spherical shaped targets like many metastases, this can be simply performed by placing a single seed in the center of the tumor. For complex shaped targets multiple seeds with activities in the range of 0.5–10 mCi are required to create conformal treatment plans for brain tumors by simultaneously keeping the number of seed-catheters low. With this technique, highly conformal treatment plans with a mean conformity index of 70 % (range: 48–79 %) can be created by implanting only 1–3 catheters (mean 1.8) with an average 2.4 seeds per catheter (range: 1–6 seeds/catheter) (Treuer et al., 2005).
6. Safety
   Stereotactic guidance and a low number of catheters to be implanted in the brain minimizes the operative risk of bleeding and infections, and reduces operation time, avoiding problems due to brain shift (Hunsche et al., 2009).

Indications for SBT

The following indications for using I-125 SBT for the treatment of brain metastases are suggested in the literature: (Ostertag and Kreth, 1995; Ruge et al., 2011d)

1. **unclassified histology**: need for stereotactic biopsy in the case of primary diagnosis of an intracerebral lesion in the context of an unknown or undetectable, but suspected, primary systemic disease or an interval between primary diagnosis on systemic cancer and appearance of cerebral disease for >3 years
2. **tumor size**: Metastasis exceeds the limits for SRS (usually a diameter of >3 cm or a volume of >14 cc)
3. **suspecting local recurrence** after WBRT and/or SRS when a new contrast-enhancing lesion appeared in exactly the same site as the treated metastasis after initial complete response, or when Macdonald criteria for progressive disease were fulfilled (increase of >25 % in the pretreated volume on contrast enhanced T1

weighted MR images) (Macdonald et al., 1990). In addition, the patient should not be a candidate for microsurgical tumor removal due to the eloquent and/or deep seated location of the metastasis with only moderate mass effect or the patient refuses to undergo surgery.

Surgical Procedure

The radioactive seed(s) can be placed in different ways. Some authors describe the placement of seeds without stereotactic guidance ("free hand") i.e. into a resection cavity after (gross-total) microsurgical resection of a metastatic lesion (Schulder et al., 1997; Bogart et al., 1999; Dagnew et al., 2007; Huang et al., 2009; Petr et al., 2009). This procedure, however, makes calculation of the applied dose distribution in the tissue very challenging: (1), placement is usually performed first and the evaluation of the distributed dose follows, and (2), the location of the seeds might shift over time in case the resection cavity changes its configuration.

Another approach (also performed by our group) is the placement of the seed(s) under stereotactic guidance. For this procedure a stereotactic computed tomography (CT) compatible frame is adjusted on the patient's head after inducing general or local anesthesia. Next, the CT images, generally not susceptible to distortions, are merged with preoperative axial T1 contrast enhanced and T2 weighted MRI images, which provide better structural resolution of brain and tumor tissue (Fig. 16.1). Depending on the planning software, image fusion can be performed either automatically or by using anatomical landmarks (i.e., vessels). In some cases functional imaging, i.e., functional MRI (fMRI) and/or positron emission tomography (PET) imaging can be added.

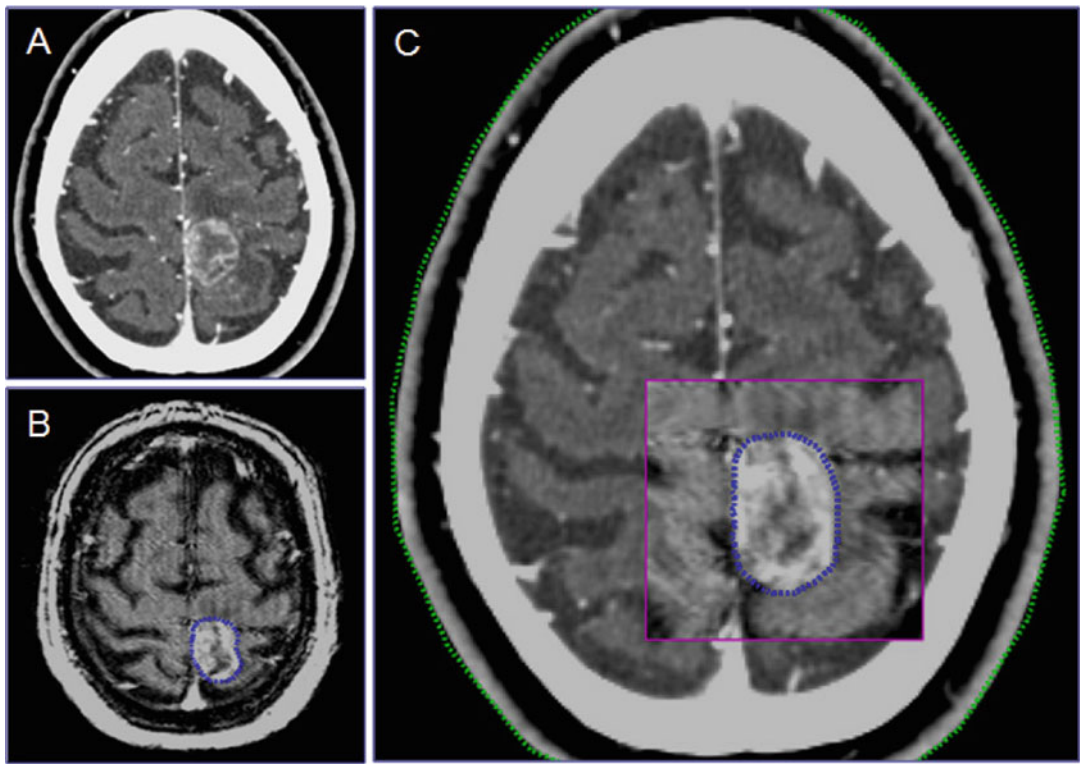

Fig. 16.1 Image fusion of CT and MRI scans. (**a**) CT image; (**b**) MRI image. (**c**) The *blue dotted line* represents the manually outlined tumor margin

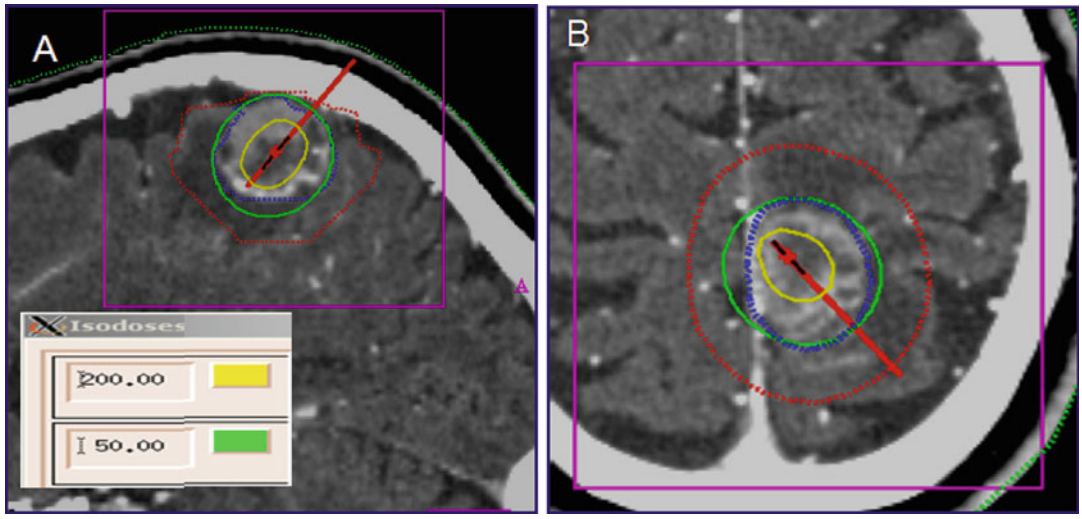

Fig. 16.2 (**a, b**) The SBT computer plan shows one catheter (*red trajectory*) and the marked tumor surface (*dotted blue line*), the 200-Gy isodose (*yellow line*), and the 50-Gy isodose (*green line*). The surface dose was 50 Gy applied for 42 days. The catheter was loaded with three I-125 seeds

The next step is defining the target volume. Using MR (T2-, contrast enhanced T1-, and in some cases FLAIR-weighted images), CT as well as, in specific cases, PET imaging, the visible margins of the tumor are outlined manually. This combination of imaging modalities ensures optimum precision and imaging quality for identifying the tumor. The objective of radiation treatment planning is always to determine a seed configuration with as few seed catheters as possible (to minimize operative risk), and load each catheter (if necessary) with more than one I-125 seeds. Thereby, we tend to select rather more seeds with low activity than one with a high activity to irradiate as conformal as possible. This allows an optimal conformation of the therapeutic isodose with the surface of the target volume. The desired surface dose, implantation time, and trephination point(s) are selected manually and a seed configuration yielding optimal coverage of the tumor with the prescribed dose is calculated automatically by minimization of an appropriate objective function (Fig. 16.2). According to our protocol, we generally applied a cumulative dose of 50 Gy to the surface of the metastatic lesion, with irradiation times ranging from 35 to 42 days at an initial dose rate of 6.2–7.2 cGy/h.

In the operation room, the stereotactic arc is adjusted on a phantom according to the calculated coordinates, and then mounted on the patient's stereotactic frame (Fig. 16.3). After skin incision and placement of a burr hole, the catheters with I-125 seeds (Amersham Buchler GmbH & CoKG, Braunschweig, Germany) are inserted into the tumor. In case histology is requested, a stereotactic biopsy can be performed and evaluated (prior the insertion of the seeds) during the same stereotactically guided procedure (see indications for the combined procedure of stereotactic biopsy and SBT).

To ensure correct placement, intraoperative X-ray images are captured in two planes (anterior/posterior and lateral) with stationary stereotactic X-ray sources, and matched with images of the calculated trajectory. Compared to intraoperative CT or MRI scanning used by some groups, this technique does not require movement of the patient or a time-consuming imaging session. Furthermore, it is comparatively fast, repeatable, and even allows monitoring of the (re-)positioning of the catheters containing I-125 seeds with high precision and with a comparatively low radiation burden for the patient (Treuer et al., 2005). For stabilization, the catheters are

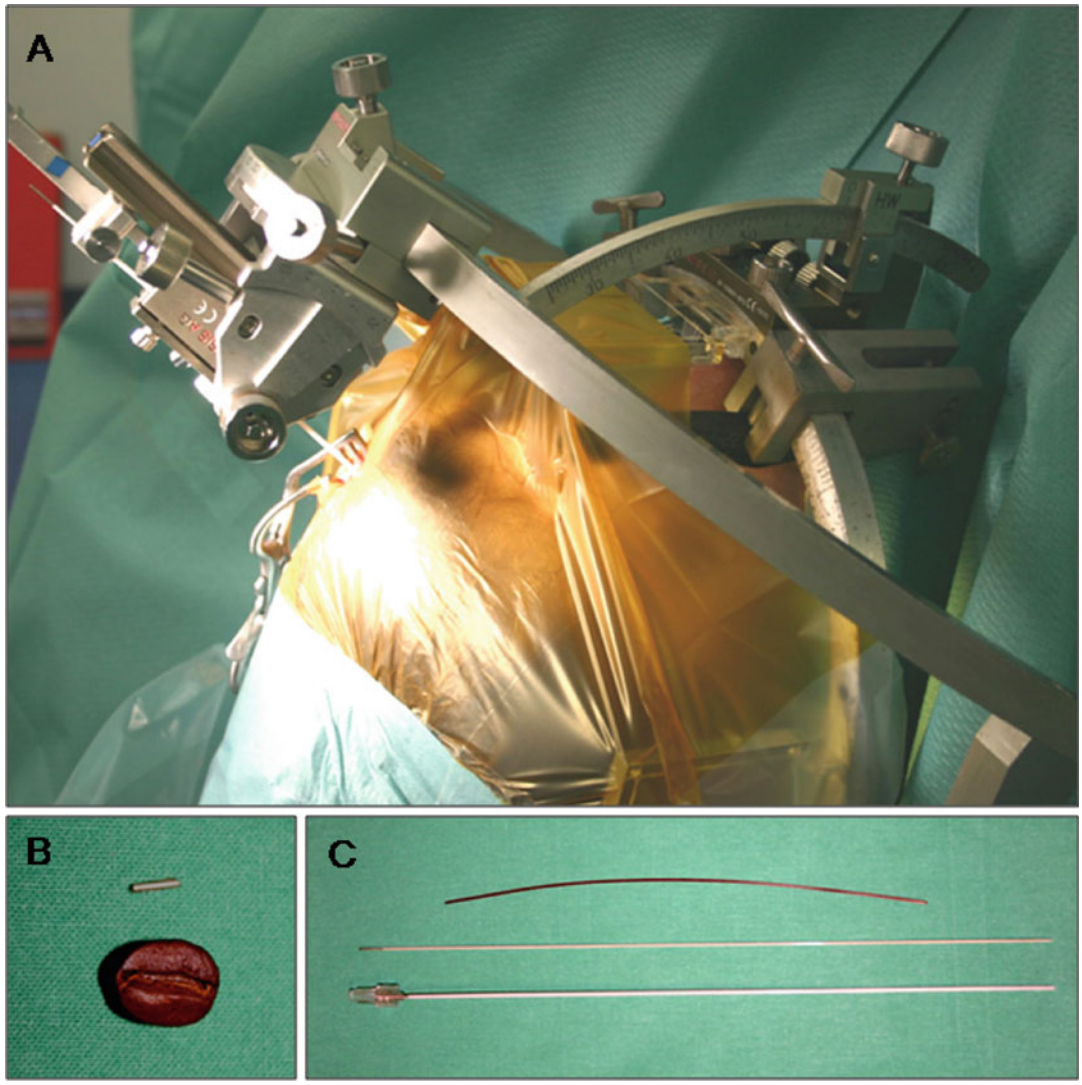

Fig. 16.3 Operative setting with (**a**) the stereotactic frame, the stereotactic arc and the inserted seed catheter. (**b**) Iodine-125 seed compared to a coffee bean. (**c**) The first catheter is placed stereotactically in the target volume (*below*). The second catheter is filled with the calculated seed(s) (*middle*) which are fixed by insertion of a thin tube (*above*) and then placed in the first catheter

fixed within the burr hole using bone cement. In addition, the catheter tip, protruding out of the cement by approximately 3–5 mm, is fixed with a vessel clip to further avoid displacement.

Finally, the emitted radiation was measured at 1 and 2 m distances from the patent's head. In cases where the dose exceeded 2 μSv/h at 1 m distance, the patient had to temporarily wear a lead cap. The duration of the surgical procedure is usually between 40 min and 1.5 h., depending on the number of catheters used. The patient's hospital stay varies between 3 and 5 days.

Seed catheters are removed after 35–42 days under local anesthesia by removing the vessel clip and extracting the catheter, leaving the cement within the burr hole. This procedure requires a hospital stay of 1 day in most cases. At this time every patient receives a follow-up MRI using the same imaging protocol as in the SBT planning to ensure comparability.

Application of Brachytherapy for Cerebral Metastases without Stereotactic Guidance

Several studies reported on the combination of (gross-total) resection of the metastatic lesion followed by placement of I-125 seeds to decrease the rate of local tumor recurrence (Schulder et al., 1997; Bogart et al., 1999; Dagnew et al., 2007; Huang et al., 2009; Petr et al., 2009). The seeds were usually inserted into the resection cavity in a circumferential fashion under visual guidance (non-stereotactically). The majority of studies used permanent implants, and applied a median cumulative dose ranging between 80 and 800 Gy with a median dose rate of 4–39 cGy/h. Median survival ranged between 9.0 and 17.8 months (Schulder et al., 1997; Bogart et al., 1999; Dagnew et al., 2007; Huang et al., 2009; Petr et al., 2009), with 1-year local (resection cavity) control rates in the range of 88 and 96 % (Dagnew et al., 2007; Huang et al., 2009). Symptomatic radiation necrosis developed in 0–23 % of patients, whereas the 23 % as reported in the study by Huang et al. (2009) was probably related to the use of high-dose implants with a dose rate of 39 cGy/h (Huang et al., 2009) (Table 16.1).

Another form of non-stereotactically applied brachytherapy was evaluated by Rogers et al. (2006). They placed a balloon catheter (e.g., GliaSite® Radiation Therapy System) in the resection cavity which was then filled with I-125 solution through a subcutaneous reservoir. In this prospective phase II trial 54 patients with newly diagnosed single brain metastases were evaluated. Following tumor resection, a cumulative dose of 60 Gy was applied at a 1-cm depth of the surrounding balloon surface. They reported a median survival of 40 weeks, and an actuarial 1-year local and distant control rate of 79 and 50 %, respectively. Due to the application of high-dose irradiation by means of 40–60 cGy/h, 17 % of their patients showed histologically confirmed radiation necrosis requiring reoperation. The authors concluded that GliaSite brachytherapy is safe and effective treatment option, comparable to other combined treatment modalities (e.g., surgery combined with WBRT or SRS). However, the high risk for radiation induced necrosis (17 %) was a significant limitation in this study.

Application of Brachytherapy for Cerebral Metastases with Stereotactic Guidance

Prados et al. (1989) published one of the first reports using I-125 SBT for the treatment of brain metastases. This group applied temporary high activity I-125-seeds in 14 patients with recurrent/progressive metastatic brain lesions after previous therapy including WBRT in 13 cases and/or surgical resection in four cases as a salvage treatment. They demonstrated a reasonable overall survival of 20 months and concluded that this technique states a feasible and minimally invasive treatment option for selected cases.

In 1995, Ostertag and Kreth (1995) confirmed the value of this treatment strategy for histologically confirmed (single) cerebral metastases. This group examined retrospectively outcome and procedure related complication of all patients from a single institution who underwent I-125 SBT (in this article referred to as interstitial radiosurgery) using low dose rate implantations (≈10 cGy/h). Three subgroups of patients were identified: (1) SBT with 60 Gy (prescribed to the surface) combined with 40 Gy percutaneous radiotherapy (38 patients), (2) SBT (60 Gy) as stand-alone treatment (34 Patients) and (3) SBT (60 Gy) as salvage for recurrent/progressive tumor after multimodal treatment (radiotherapy, surgery) for 21 patients. Median survival was 17 month (group 1), 15 month (group 2) and 6 months (group 3), respectively. A Karnofsky Performance Score (KPS) $\geq$ 70, the presents of a solitary metastasis, the absence of disseminated systemic disease and a time interval >1 year between diagnosis of primary tumor and appearance of the cerebral metastasis were favorable prognostic factors, while the combination of SBT with adjuvant percutaneous radiotherapy did not prove to be superior to SBT alone. Furthermore, there was no procedure related mortality and the

Table 16.1 Brachytherapy for brain metastases: review of literature

Author	Year	Patients	Intervention	(P)rimary/ (S)alvage group	(T)ransient/ (P)ermanent implants	Surface dose (Gy)	Dose rate (cGy/h)	Median survival (months)	Tumor control	Radiation necrosis	Interval (months)
Prados et al.	1989	14	SBT (Iodine-125) + neoadjuvant WBRT (4/14 pat.)	P (10), S (4)	T (4–6d)	50	50	18.4	n.r.	14 %	12–14
Ostertag and Kreth	1995	38	SBT (Iodine-125) + WBRT (40 Gy)	P	T (n.r.)	65	7	17	n.r.	0 %	–
		34	SBT (Iodine-125)	P				15			
		21	SBT (Iodine-125)	S				6			
Alesch et al.	1995	19	SBT (Iodine-125)	P	T (28d)	60	11	n.r.	LC end of FU: 95 % DC end of FU: 95 %	n.r.	–
Bernstein et al.	1995	10	SBT (Iodine-125)	S	T (n.r.)	70	67	10.6	n.r.	20 %	n.r.
Schulder et al.	1997	13	Rx + Iodine-125 (freehand) + WBRT (9 pre-/4 postimplant)	P (1), S (12)	P	82	4	9	LC end of FU: 82 % DC end of FU: 36 %	15 %	n.r.
Bogart et al.	1999	15	Rx + Iodine-125 (freehand)	P	P	80–160	4–8	14	Median time to recurrence: 9 months	0 %	–
Rogers et al.	2006	54	Rx + GliaSite with Iodine-125	P	n.a.	60	40–60	9.2	1 year LCR: 79 % 1 year DCR: 50 %	17 %	n.r.

Dagnew et al.	2007	26	Rx + Iodine-125 (freehand)	P	P	150	7	17.8	LC after median FU of 1 year: 96 %; DC after median FU of 1 year: 38 %	8 %	6–9
Petr et al.	2009	72	Rx + Iodine-125 (freehand)	P	P	150	7	14	LC end of FU: 92 % DC end of FU: 69 %	6 %	6–32
Huang et al.	2009	40	Rx + Iodine-125 (freehand)	P (19), S (21)	P	R*	39	11.3	1 year RCCR: 88 % 1 year OCR: 37 %	23 %	7.4–40
Ruge et al.	2011d	90	SBT (Iodine-125)	P (61), S (29)	T (35–42d)	50	6	8.5	1 year LCR: 95 % 1 year DCR: 46 %	0 %	–
Ruge et al.	2011a	27	SBT (Iodine-125)	S	T (42d)	50	6	14.8	1 year LCR: 93 % 1 year DCR: 55 %	0 %	–
Ruge et al.	2011b	77	SBT (Iodine-125)	n.r.	T (42d)	50	6	8	1 year LCR: 95 % 1 year DCR: 54 %	0 %	–

Prados et al. (1989), Ostertag and Kreth (1995), Alesch et al. (1995), Bernstein et al. (1995), Dagnew et al. (2007), Ruge et al. (2011a, b, d), Huang et al. (2009), Petr et al. (2009), Rogers et al. (2006), Bogart et al. (1999), Schulder et al. (1997)

Abbreviations:

DC distant control, *DCR* distant control rate, *FU* follow-up, *LC* local control, *LCR* local control rate, *OCR* overall control rate, *RCCR* resection cavity control rate, *Rx* Resection, *WBRT* whole brain radiation therapy, *SBT* stereotactic brachytherapy

Annotations:

Schulder et al. Dagnew et al. Petr et al. Huang et al. did not provide information on the applied dose rate – for these studies we manually calculated the dose rate based on the following formula for permanent implants: *dose rate (cGy/h) = cumulative applied dose (Gy)/2,057 * 100*

30 day post operative complication rate was 2 % of transient neurological deficits. On the long run, there was no surgical relevant radiation necrosis (Ruge et al., 2011d).

The most recent retrospective single center evaluation applying I-125 SBT for singular cerebral metastases was published by Ruge et al. (2011d). Hereby, the outcome of 90 patients was reported utilizing the recursive partitioning analysis (RPA) for survival. In addition, complications as well as local and distant disease control were investigated.

With also no treatment related mortality, a 3.3 % rate of transient complications and a median survival of 8.5 months for all, and 18.1 months for RPA class 1 patients as well as a actuarial incidence of local and distant cerebral relapse of 5.4 and 46.4 % after 1 year. Ruge et al. (2011d) confirmed that SBT represents a safe, minimally invasive, and, compared to SRS and microsurgery, a similarly effective local treatment option regarding survival and cerebral disease control. They furthermore concluded that SBT is less restricted by tumor localization or size, and that it greatly advances local treatment options. Based on its favorable biological irradiation effect, SBT does not limit additional irradiation treatment in the event of disease relapse. The authors also emphasized the possibility of performing a stereotactic biopsy for histological (re-)evaluation and SBT within the same operation (Fig. 16.4).

Stereotactic Biopsy Combined with SBT for Locally Recurrent Brain Metastases

A combined procedure can be of major value especially for those cases where a differentiation between local recurrence or local irradiation induced tissue changes (reappearance/enlargement of contrast enhancement on MRI/computed tomography (CT)) after previous SRS or WBRT treatment is necessary and can often not be solved by magnetic resonance- and nuclear imaging techniques (Huber et al., 2001; Hoefnagels et al., 2009; Ruge et al., 2011a).

Ruge et al. (2011a) published a pilot study evaluating feasibility, safety, and outcome after I-125 SBT as a salvage treatment for patients with local recurrences of previously irradiated brain metastases. Furthermore, this study intended to clarify whether a combined procedure of stereotactic biopsy and SBT within one surgical procedure can reliably distinguish between radiation-induced tissue changes and vital tumor (Table 16.1).

For this investigation all patients with suspected locally recurrent metastases detected by MRI after SRS and/or WBRT treatment were selected for this combined procedure. After stereotactic biopsy, all those patients with a verified vital tumor underwent I-125 SBT (50 Gy surface dose applied for 42 days) during the same surgical procedure. From 30 patients undergoing stereotactic biopsy 27 were treated with SBT for histologically proven tumor recurrence. In this series there was also no treatment-related mortality and the procedure related morbidity was transient and low (6.6 %). Median survival after SBT was 14.8 months. After 1 year the actuarial incidence of local relapse was 6.7 % and there were no grade 3 or 4 CNS toxicities, even among 18.5 % of patients with tumors >30 mm.

Comparison of SBT with Stereotactic Radiosurgery

SRS is a standard treatment option for patients with (single) cerebral metastases. According to available data from prospective, randomized trials (Table 16.2) median survival rates following SRS only are in the range of 8.0–15.2 months, whereas local and distant tumor control rates range from 67.0–96.8 % and 36.3–74.2 % after 1 year, respectively.

Although SRS is a safe and highly effective local treatment option, there are some limitations with regard to this treatment modality:

– SRS cannot provide histological information regarding the treated pathology. This aspect might be important in cases with newly diagnosed, histologically unclassified cerebral lesion(s) lacking information regarding the primary tumor, and also with local tumor recurrences after previous external beam radiation therapy (EBRT), where it can be important to differentiate

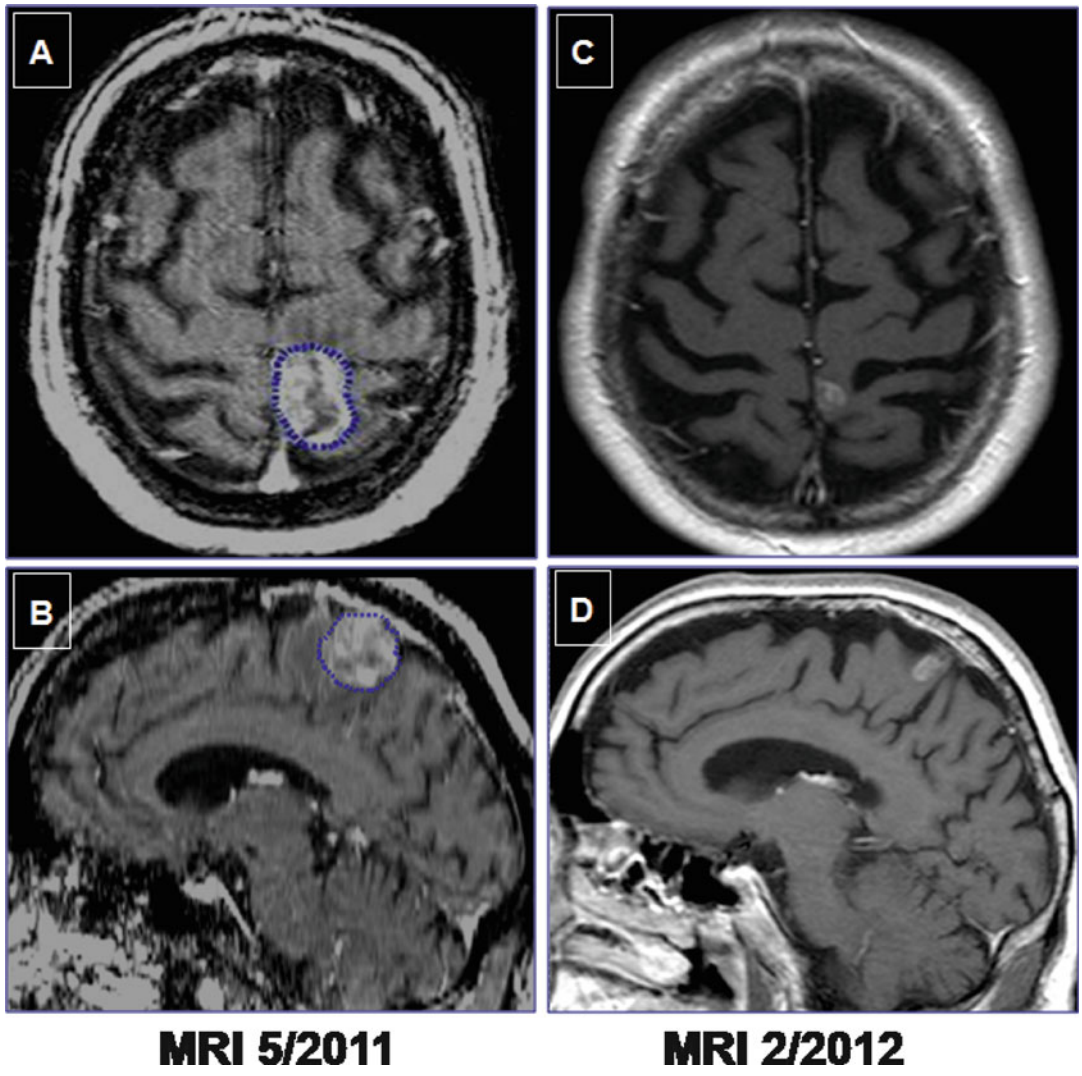

Fig. 16.4 Illustrative case: (**a**, **b**), T1 contrast weighted magnetic resonance imaging (MRI) scans of a 60-year-old male patient with an unknown lesion in the left parietal lobe. According to our protocol he underwent stereotactic biopsy – intraoperative finding showed a metastatic lesion – followed by I-125 SBT within the same surgical procedure (I-125, 50 Gy cumulative surface dose applied for 42 days). Later evaluation revealed an adenocarcinoma of the lung as origin of the metastasis. (**c**, **d**), Follow-up MRI (T1 contrast weighted) reveals partial remission after 9 months. The patient displayed no neurological deficit and had stable systemic disease (KPS 90)

between tumor relapse and radiation induced necrosis (Ruge et al., 2011a).

– Furthermore, one major limitation of SRS is tumor size. Treatment of metastases exceeding a diameter of 3 cm or a volume of 14 cm^3 increases the radiation burden to the surrounding tissue and may increase the risk of edema and/or radiation-induced tissue necrosis (Ruge et al., 2011b).

A recent retrospective study by Ruge et al. (2011b) aimed to compare SRS and SBT for the treatment of singular cerebral metastases. A total of 219 patients were identified, whereas 142 patients were treated with SRS and 77 patients with SBT. Clinical characteristics did not differ significantly between the two treatment groups, except for a lower KPS and larger tumor volume in the SBT subgroup, reflecting the selection criteria

Table 16.2 Randomized trials on stereotactic radiosurgery for brain metastases

Author	Year	Intervention	Patients	No. of BM	Median survival (months)	Local control		Distant control	
Aoyama et al.	2006	SRS	67	1–4	8.0	*88.7 %*	*(1 year)*	*36.3 %*	*(1 year)*
		SRS + WBRT	65		7.5	*72.5 %*	*(1 year)*	*58.5 %*	*(1 year)*
Muacevic et al.	2008	SRS	31	1	10.3	96.8 %	(1 year)	*74.2 %*	*(1 year)*
		Rx + WBRT	33		9.5	82.0 %	(1 year)	*97.0 %*	*(1 year)*
Chang et al.	2009	SRS	30	1–3	*15.2*	*67.0 %*	*(1 year)*	*45.0 %*	*(1 year)*
		SRS + WBRT	28		*5.7*	*100.0 %*	*(1 year)*	*73.0 %*	*(1 year)*
Kocher et al.	2011	SRS	100	1–3	10.9	*69.0 %*	*(2 years)*	*52.0 %*	*(2 years)*
		SRS + WBRT	99		10.7	*81.0 %*	*(2 years)*	*67.0 %*	*(2 years)*

Abbreviation:
BM brain metastases, *Rx* surgical resection, *SRS* stereotactic radiosurgery, *WBRT* whole brain radiation therapy
Annotation:
Italic formatted numbers showed a significant statistical difference between the treatment arms

in favor for SBT. Neither median survival (8.1 vs. 8.0 months) nor local or distant tumor control rates after 1 year (93.6 % vs. 96.7 % and 42.4 % vs. 46.4 %) showed a significant statistical difference between the SRS and SBT subgroups.

Discussion

Currently several standard options are available for the treatment of brain metastases: WBRT with or without boost for patients with multiple brain metastases. More localized treatment regiments encompass SRS for brain metastases ~3 cm in diameter and neurosurgical resection for space occupying, surgically well accessible metastases, followed by EBRT in selected cases. There are, however, cases where tumor localization in highly eloquent brain areas (brainstem, midbrain, motor-or language sensitive cortex) together with a size exceeding the eligibility for SRS and/or the need for histological evaluation do not indicate the above mentioned treatment options. For these cases I-125 (stereotactic) brachytherapy has been introduced. This technique allows histological confirmation and, by stereotactic guidance, the highly precise placement of an irradiation source directly into the tumor. Thereby, a lethal irradiation dose is placed within the tumor which falls off steeply towards the periphery and reduced thereby the radiation burden of the surrounding tissue. While EBRT delivers dose rates in the range of up to 100–200 cGy/min over a defined period of 6–8 weeks SBT provides continuous irradiation with much lower dose rates (initial dose rate 6 cGy/min for 50 Gy surface dose for 42 days) over a far prolonged time period which adapts potentially better to the reproduction cycle of growing tumour cells. These favourable irradiation effects do not narrow the later use of EBRT in case of local/distant relapse, and allows treatment of tumors >3 cm without causing an increased rate of late adverse irradiation effects. The lack of early additional EBRT did not compromise local disease control (Ostertag and Kreth, 1995; Ruge et al., 2011d). Local disease control rate is comparable to the one reported after SRS (Aoyama et al., 2006; Kocher et al., 2011) and superior to those after resection and EBRT (Muacevic et al., 2008). The reason for this might be a provided "safety margin" of irradiation within a millimetre range beyond the therapeutically applied surface isodose around the lesion terminating satellite tumors cells in the vicinity of the visible tumour (Baumert et al., 2006; Ruge et al., 2011a, d). The overall survival rate after application of SBT for cerebral metastases lies in the range of reported outcome after resection combined with WBRT and after SRS only, and the reported procedure related complication rate ranges from 2 to 6.6 % (Ostertag and Kreth, 1995; Ruge et al., 2011d).

For suspected local recurrence after SRS and/or WBRT/EBRT SBT provides in combination with a stereotactic biopsy a highly reliable diagnostic tool as well as a highly effective and safe (regarding further local tumor control and no increased adverse irradiation effects) treatment concept (Ruge et al., 2011a).

In conclusion, stereotactic ^{125}Iodine brachytherapy represents a minimally invasive, safe and feasible method for treating newly diagnosed (single) brain metastasis and/or local recurrences after pervious irradiation treatment, allowing histological confirmation and treatment within one stereotactic procedure. Overall survival and local disease control is comparable to other local treatment methods. The favorable biological effect of the low dose rate irradiation from within the tumor allows future irradiation treatment without causing radiation-induced necrosis. Thus, SBT can be considered in cases "left behind" by surgery or SRS, and might, therefore, close a gap for patients harboring (single) brain metastasis.

References

Alesch F, Hawliczek R, Koos WT (1995) Interstitial irradiation of brain metastases. Acta Neurochir Suppl 63:29–34

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 295:2483–2491

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

Bernstein M, Cabantog A, Laperriere N, Leung P, Thomason C (1995) Brachytherapy for recurrent single brain metastasis. Can J Neurol Sci 22:13–16

Bogart JA, Ungureanu C, Shihadeh E, Chung TC, King GA, Ryu S, Kent C, Winfield JA (1999) Resection and permanent I-125 brachytherapy without whole brain irradiation for solitary brain metastasis from non-small cell lung carcinoma. J Neurooncol 44:53–57

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 10:1037–1044

Chao JH, Phillips R, Nickson JJ (1954) Roentgen-ray therapy of cerebral metastases. Cancer 7:682–689

Dagnew E, Kanski J, McDermott MW, Sneed PK, McPherson C, Breneman JC, Warnick RE (2007) Management of newly diagnosed single brain metastasis using resection and permanent iodine-125 seeds without initial whole-brain radiotherapy: a two institution experience. Neurosurg Focus 22:E3

Danlos H (1905) Quelques considerations sur le traitement des dermatoses par le radium. J Physiother (Paris) 3:98–106

Frazier CH (1920) The effects of radium emanations upon brain tumors. Surg Gynecol Obstet 31:236–239

Gutin PH, Phillips TL, Wara WM, Leibel SA, Hosobuchi Y, Levin VA, Weaver KA, Lamb S (1984) Brachytherapy of recurrent malignant brain tumors with removable high-activity iodine-125 sources. J Neurosurg 60:61–68

Heintz BH, Wallace RE, Hevezi JM (2001) Comparison of I-125 sources used for permanent interstitial implants. Med Phys 28:671–682

Hirsch O (1912) Die operative Behandlung von Hypophysentumoren: Nach endonasalen Methoden. Arch Laryngol Rhinol 26:529–686

Hoefnagels FW, Lagerwaard FJ, Sanchez E, Haasbeek CJ, Knol DL, Slotman BJ, Vandertop WP (2009) Radiological progression of cerebral metastases after radiosurgery: assessment of perfusion MRI for differentiating between necrosis and recurrence. J Neurol 256:878–887

Huang K, Sneed PK, Kunwar S, Kragten A, Larson DA, Berger MS, Chan A, Pouliot J, McDermott MW (2009) Surgical resection and permanent iodine-125 brachytherapy for brain metastases. J Neurooncol 91:83–93

Hubbell JH, Seltzer SM (1995) Tables of X-ray mass attenuation coefficients and mass energy-absorption coefficients 1 keV to 20 MeV for elements Z = 1 to 92 and 48 additional substances of dosimetric interest. Technical report NISTIR 5632, NIST, Gaithersburg, MD 20899

Huber PE, Hawighorst H, Fuss M, van Kaick G, Wannenmacher MF, Debus J (2001) Transient enlargement of contrast uptake on MRI after linear accelerator (linac) stereotactic radiosurgery for brain metastases. Int J Radiat Oncol Biol Phys 49:1339–1349

Hunsche S, Sauner D, Maarouf M, Poggenborg J, Lackner K, Sturm V, Treuer H (2009) Intraoperative X-ray detection and MRI-based quantification of brain shift effects subsequent to implantation of the first electrode in bilateral implantation of deep brain stimulation electrodes. Stereotact Funct Neurosurg 87:322–329

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

Kofman S, Garvin JS, Nagamani D, Taylor SG (1957) Treatment of cerebral metastases from breast carcinoma with prednisolone. J Am Med Assoc 163:1473–1476

Kreth F, Faist M, Grau S, Ostertag C (2006) Interstitial 125I radiosurgery of supratentorial de novo WHO Grade 2 astrocytoma and oligoastrocytoma in adults: long-term results and prognostic factors. Cancer 106:1372–1381

Laperriere NJ, Leung PM, McKenzie S, Milosevic M, Wong S, Glen J, Pintilie M, Bernstein M (1998) Randomized study of brachytherapy in the initial management of patients with malignant astrocytoma. Int J Radiat Oncol Biol Phys 41:1005–1011

Macdonald DR, Cascino TL, Schold SC Jr, Cairncross JG (1990) Response criteria for phase II studies of supratentorial malignant glioma. J Clin Oncol 8:1277–1280

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

Mundinger F (1956) Eine einfache Methode der lokalisierten Bestrahlung von Großhirngschwülsten mit radioaktivem Gold. Münch Med Wschr 98:23–25

Nath R, Anderson LL, Luxton G, Weaver KA, Williamson JF, Meigooni AS (1995) Dosimetry of interstitial brachytherapy sources: recommendations of the AAPM Radiation Therapy Committee Task Group No. 43. American Association of Physicists in Medicine. Med Phys 22:209–234

Ostertag CB, Kreth FW (1995) Interstitial iodine-125 radiosurgery for cerebral metastases. Br J Neurosurg 9:593–603

Petr MJ, McPherson CM, Breneman JC, Warnick RE (2009) Management of newly diagnosed single brain metastasis with surgical resection and permanent I-125 seeds without upfront whole brain radiotherapy. J Neurooncol 92:393–400

Prados M, Leibel S, Barnett CM, Gutin P (1989) Interstitial brachytherapy for metastatic brain tumors. Cancer 63:657–660

Rogers LR, Rock JP, Sills AK, Vogelbaum MA, Suh JH, Ellis TL, Stieber VW, Asher AL, Fraser RW, Billingsley JS, Lewis P, Schellingerhout D, Shaw EG (2006) Results of a phase II trial of the GliaSite radiation therapy system for the treatment of newly diagnosed, resected single brain metastases. J Neurosurg 105:375–384

Ruge MI, Kickingereder P, Grau S, Hoevels M, Treuer H, Sturm V (2011a) Stereotactic biopsy combined with stereotactic (125)iodine brachytherapy for diagnosis and treatment of locally recurrent single brain metastases. J Neurooncol 105:109–118

Ruge MI, Kocher M, Maarouf M, Hamisch C, Treuer H, Voges J, Sturm V (2011b) Comparison of stereotactic brachytherapy (125 iodine seeds) with stereotactic radiosurgery (LINAC) for the treatment of singular cerebral metastases. Strahlenther Onkol 187:7–14

Ruge MI, Simon T, Suchorska B, Lehrke R, Hamisch C, Koerber F, Maarouf M, Treuer H, Berthold F, Sturm V, Voges J (2011c) Stereotactic brachytherapy with iodine-125 seeds for the treatment of inoperable low-grade gliomas in children: long-term outcome. J Clin Oncol 29:4151–4159

Ruge MI, Suchorska B, Maarouf M, Runge M, Treuer H, Voges J, Sturm V (2011d) Stereotactic 125Iodine brachytherapy for the treatment of singular brain metastases: closing a gap? Neurosurgery 68:1209–1219

Schulder M, Black PM, Shrieve DC, Alexander E 3rd, Loeffler JS (1997) Permanent low-activity iodine-125 implants for cerebral metastases. J Neurooncol 33:213–221

Selker RG, Shapiro WR, Burger P, Blackwood MS, Arena VC, Gilder JC, Malkin MG, Mealey JJ Jr, Neal JH, Olson J, Robertson JT, Barnett GH, Bloomfield S, Albright R, Hochberg FH, Hiesiger E, Green S (2002) The Brain Tumor Cooperative Group NIH Trial 87–01: a randomized comparison of surgery, external radiotherapy, and carmustine versus surgery, interstitial radiotherapy boost, external radiation therapy, and carmustine. Neurosurgery 51:343–355; discussion 355–347

Talairach J, Ruggiero G, Aboulker J, David M (1955) A new method of treatment of inoperable brain tumours by stereotaxic implantation of radioactive gold; a preliminary report. Br J Radiol 28:62–74

Treuer H, Hunsche S, Hoevels M, Luyken K, Maarouf M, Voges J, Sturm V (2004) The influence of head frame distortions on stereotactic localization and targeting. Phys Med Biol 49:3877–3887

Treuer H, Klein D, Maarouf M, Lehrke R, Voges J, Sturm V (2005) Accuracy and conformity of stereotactically guided interstitial brain tumour therapy using I-125 seeds. Radiother Oncol 77:202–209

Viola A, Major T, Julow J (2006) Comparison of (125)I stereotactic brachytherapy and LINAC radiosurgery modalities based on physical dose distribution and radiobiological efficacy. Radiat Res 165:695–702

Williamson JF, Butler W, Dewerd LA, Huq MS, Ibbott GS, Mitch MG, Nath R, Rivard MJ, Todor D (2005) Recommendations of the American Association of Physicists in Medicine regarding the impact of implementing the 2004 task group 43 report on dose specification for 103Pd and 125I interstitial brachytherapy. Med Phys 32:1424–1439

Stereotactic Radiosurgery for Skull Base Meningiomas

17

Daniel M.S. Raper, Robert M. Starke,
and Ricardo J. Komotar

Contents

Abstract

Complete resection of meningiomas occurring at the skull base may be difficult, due to the proximity of critical neurovascular structures. Due to the benign nature of these lesions, most patients with skull base meningiomas have an extended life expectancy. The goal of treatment for these lesions, therefore, revolves around long-term tumor control without worsening neurological function. Stereotactic radiosurgery is one of three main treatment options for the treatment of cranial base meningiomas, and has been shown to have similar rates of tumor control with safe administration within 3–5 mm of cranial nerves and brainstem. In this chapter, we review the literature reporting outcomes following use of stereotactic radiosurgery for these lesions, and the rationale for decision-making about treatment for these lesions.

Introduction

Meningiomas occurring at the skull base represent a neurosurgical challenge. Although most often histologically benign, these tumors typically continue to grow unless treated, and cause symptoms due to compression of cranial nerves, vessels or through mass effect. The location of these tumors at the skull base, with the close proximity of vital neural and vascular tissues, makes complete surgical resection according to

D.M.S. Raper, M.B.B.S • R.M. Starke, M.D., M.Sc. (✉)
Department of Neurosurgery, University of Virginia Health System, Box 800212, Charlottesville, VA 22908 FL, USA
e-mail: rms6bx@hscmail.mcc.virginia.edu

R.J. Komotar, M.D.
Department of Neurosurgery, University of Virginia Health System, Box 800212, Charlottesville, VA 22908, USA

Department of Neurosurgery, University of Miami, Miami, FL, USA

M.A. Hayat (ed.), *Tumors of the Central Nervous System, Volume 11*,
DOI 10.1007/978-94-007-7037-9_17,

the principles of oncological cure difficult. Presence of tumor in the cavernous sinus, associated with the ICA and/or optic nerves and chiasm, or extending along the dura of the anterior or middle cranial fossae, all represent instances in which complete surgical resection may be associated with an unacceptably high risk of morbidity. Because of this, treatment aimed at achieving local control of tumor growth with relief or stabilization of neurological deficits has been increasingly investigated.

External beam radiation therapy and stereotactic radiosurgery (SRS) are two logical treatment options within this altered paradigm of treatment for skull base meningiomas. Meningiomas have been an obvious target for SRS due to their clear demarcation from surrounding neural tissue and bone on modern imaging modalities. The rationale for treatment is to provide long-term control with a lower risk of damage to surrounding structures due to a rigorous planning algorithm with sharp drop-off of radiation dose at the margin of the tumor. Radiosurgery, as originally conceived in the 1950s by Leksell, combined the principles of radiotherapy with stereotactic neurosurgery to provide a precise focus of radiation via gamma rays in a predetermined trajectory in 3-dimensional space. The intersection of small-diameter beams allows focused delivery of radiation with a sharp fall-off of dose gradient outside the target (Vesper et al., 2009). Today, a number of different radiosurgical systems are available that incorporate both framed and frameless stereotactic delivery. A detailed review of these is beyond the scope of this chapter, but results from each system appear to be similar, and differentiation between systems will require rigorous comparative studies with long-term follow up (Andrews et al., 2006). The stereotactically modified linear accelerator (LINAC), protons, and gamma knife modalities have been historically most widely used. CyberKnife is a frameless radiosurgical system that uses inverse planning with non-isocentric radiation delivery, and represents another option for delivery of stereotactic radiosurgery in one or more fractions (Adler et al., 1997). Though all systems achieve precise stereotaxy, framed systems may provide peace of mind in the localization of high doses of radiation near the cranial nerves at the skull base.

General Principles

Stereotactic radiosurgical principles began to be applied to skull base meningiomas in the early 1990s (Starke et al., 2012). As radiosurgical treatment has evolved, with improved conformality and more predictable dose fall-off, smaller doses have been used in order to minimize long-term toxicity while maintaining efficacy. It is possible to maintain therapeutic doses to the tumor with highly accurate conformality, using multiple isocenters of different size and configuration, with differential weighting and selective beam blocking. Practical guides to creating radiosurgical plans for irregularly shaped skull base tumors have been recently published (Kondziolka et al., 2008a). The radiation tolerance of the cranial nerves and optic apparatus continue to be a subject of debate, particularly in the setting of multisession radiosurgical plans using CyberKnife, Novalis, and Gamma Knife Extend systems (Leber et al., 1998; Tuniz et al., 2009). Although individual treatment planning varies with the precise characteristics of each tumor, some general guidelines are outlined below, bearing in mind that in modern series, doses of 12–14 Gy have been shown to be as effective as larger doses, while allowing limited exposure of sensitive structures:

1. The optic nerve and apparatus should not receive more than 10–12 Gy; some groups aim for <8.5 Gy to the optic apparatus, and the target may be more safely 8–10 Gy depending on the volume of nerve involved.
2. For the brainstem, there is little reliable data but doses ≤15 Gy appear to be reasonable.
3. Tumor margin dose at the CPA should be 12–13 Gy at most, with lower limits for patients in whom hearing preservation is the goal of treatment.
4. Limits of 12–14 Gy have been used around other cranial nerves without high incidence of post-radiosurgical deficits.

Stereotactic Radiosurgery for Skull Base Meningiomas

Anterior and Middle Cranial Fossa Meningiomas

SRS may be used either as a primary treatment option or as an adjuvant therapy following surgical resection. After using GKS as a primary treatment option, rates of local control vary from 85 to 98 % at 5 years, and 73 to 97 % at 10 years (Starke et al., 2012). In a combined series of meningiomas at different intracranial locations, tumor control of 93 % at 5 years and 87 % at 10 and 15 years was reported (Kondziolka et al., 2008b). Actuarial 5- and 10-year control rates of 91 and 87.6 %, respectively, were reported in a recent systematic review of GKRS for skull base meningiomas (Minniti et al., 2009). The reported rates of tumor shrinkage vary widely, between 8 and 66 % depending on series. In the majority of cases, tumor volumes remain stable, with a minority of patients experiencing either tumor shrinkage or expansion on long-term follow up imaging.

In a large cohort study, there were no differences in long-term survival between 384 patients treated with postoperative SRS compared with 488 patients who underwent primary SRS (Kondziolka et al., 2008b). Factors associated with poorer outcome include larger tumor volumes, inadequate conformity index, and tumor recurrence. For larger tumors, there may be a tendency to formulate more conservative treatment plans due to closer association with radiosensitive structures, thus resulting in lower control rates. In either case, location is obviously of paramount importance in predicting the tumor response and risk of cranial neuropathies. Tumors located in the cavernous sinus may be more likely to improve after radiosurgery than at other skull base locations.

The risk of neurological complications ranges between 3 and 40 % depending on series, most commonly in the range of 3 % for transient and 5 % for permanent neurological complications. There is a risk of secondary neoplasia developing after radiosurgery, but this is rarely observed in retrospective or prospective series. The reported incidence is 0–3 per 200,000 patients (Starke et al., 2012), which is similar to the rate of spontaneous development of cancer in the general population. Though the absolute risk is low, it should be considered particularly for young patients with slow-growing, benign processes such as skull base meningiomas. If cranial neuropathies develop, after radiosurgical treatment, from tumor progression, it is an indication that inadequate radiation has been dosed to the tumor margin. The optic apparatus, for example, has generally been limited to a dose of 8–10 Gy, but if markedly lower doses are administered in an attempt to limit morbidity, there is a risk of inadequate tumor control.

SRS may be used in the setting of regrowth after previous treatment. Conservative treatment remains a primary option, especially for older patients who experience growth of a previously treated meningioma, whether treated by primary surgical or radiosurgical means. Radiosurgery does not make subsequent resection more technically challenging. Alternatively, SRS may be attempted again, although growth at this location often makes planning more difficult due to the close proximity of cranial nerves and vessels and the likelihood that these structures have already been exposed to radiation during previous treatments.

Posterior Fossa Meningiomas

Many of the issues surrounding use of SRS at the anterior skull base also apply to the treatment of posterior fossa meningiomas. Proximity of these lesions to the brainstem, as well as venous sinuses and prominent vessels, makes surgical resection difficult, although some degree of microsurgical resection may be essential to relieve mass effect or hydrocephalus. Rates of complete surgical resection vary from 40 to 96 %, with morbidity and mortality ranging from 0 to 13 % and 13 to 40 %, respectively (Starke et al., 2011). As with other skull base meningiomas, there has been an increasing recognition that preservation of neurological function may be best achieved through a

more conservative surgical approach, combined with adjuvant radiation therapy or radiosurgery. Particular to the posterior fossa, it is essential to limit the radiation exposure of the brainstem to ≤12 Gy, as these doses even at volumes as low as 0.1 cm^3 have been shown to result in new neurological deficits (Sharma et al., 2008). Likewise, SRS has been used successfully as a primary treatment in certain circumstances. Because of the lower incidence of posterior fossa meningiomas compared to those occurring at other skull base locations, reports of these lesions in the literature often combine a variety of skull base locations (including sellar, sphenoid, cavernous sinus, olfactory groove, optic sheath and foramen magnum). In our experience treating posterior fossa meningiomas with primary SRS, 36 % had no change in tumor volume, and 51 % had a decrease at last follow-up, with 91 % of patients experiencing stable or improved clinical symptoms (Starke et al., 2011). Characterization of long-term tumor control following primary SRS, as well as the potential neurocognitive effects of radiosurgery at and around the brainstem, require ongoing investigation. SRS remains, however, a viable alternative for primary treatment in patients who are poor surgical candidates, and as an alternative to radiotherapy for residual or recurrence after primary surgical resection.

Comparison with Surgical Resection and Radiotherapy

Historically, the gold standard for meningiomas at any intracranial location has been total resection along with the dural tail and any involved bone. This can be impossible to achieve in practice, contributing to the observation that these lesions tend to recur after surgery. Resection or biopsy are the only options that offer the potential for formal histological diagnosis of skull base meningiomas. Though these lesions have a characteristic appearance on MR/CT imaging, there are other pathologies that may occur in this area and that may mimic the appearance of meningioma, which would be the target of different treatment strategies. Additionally, the finding of a more aggressive histological grade than WHO Grade I meningioma warrants consideration for adjuvant radiotherapy even in the setting of gross total resection.

A variety of skull base approaches have been developed, and long-term control after Simpson Grade I resection is very high (Linskey et al., 2005; Pollock et al., 2003), but achieving this can be extremely difficult without risking significant morbidity. Gross total resection rates range from 20 to 87.5 % (Bassiouni et al., 2006; Chi and McDermott, 2003; Otani et al., 2006; Sanna et al., 2007; Voss et al., 2000). In earlier surgical series, postoperative complication rates were high (on the order of 30–40 %), with mortality of up to 7 %. More recent series report much lower complication rates. Along with improvements in microsurgical technique, incorporation of stereotactic planning and intraoperative monitoring and imaging, there may be an increasing comfort with the concept of leaving residual tumor to be treated with adjuvant therapies such as SRS. Combining microsurgery with SRS appears to improve long-term local control rates, with 5-year control rates of upwards of 90 % (Davidson et al., 2007; Duma et al., 1993; Ichinose et al., 2010; Iwai et al., 2001, 2008; Lunsford, 1994; Zachenhofer et al., 2006). Again, the precise location of the lesion is important in treatment planning. For instance, for a parasellar meningioma involving both intra- and extra-cavernous locations, a microsurgical approach for the extracavernous lesion and radiosurgical approach for the intracavernous portion may offer the greatest potential for reduction of tumor burden with minimal risk of neurovascular injury (Williams et al., 2011).

Radiotherapy represents a third treatment option for skull base meningiomas. As with fractionated SRS (see below), dividing radiotherapeutic treatment may allow time for normal tissue to heal between treatments. In fact, modern stereotactic radiotherapy is very similar to SRS, utilizing similarly precise dose localization and steep dose gradients. The major difference is the number of fractions, and the total delivered radiation dose. A variety of regimens have been employed, most commonly delivering 50–55 Gy over 30–33 fractions. Five and ten-year local control rates

range from 75 to 95 % in different studies; actuarial combined control rates are 90 % at 5 years and 83 % at 10 years (Condra et al., 1997; Dufour et al., 2001; Elia et al., 2007; Goldsmith et al., 1994; Hasegawa et al., 2007; Mendenhall et al., 2003; Nutting et al., 1999). Symptomatic improvement is reported in 69–100 % (Dufour et al., 2001; Maire et al., 1995; Mendenhall et al., 2003; Nutting et al., 1999), but complications occur in up to 24 % of cases (Minniti et al., 2009). Cranial nerve injury, including radiation injury to the optic apparatus, occurs in 0–3 % of cases. Newer techniques such as intensity-modulated radiotherapy and stereotactic radiotherapy use smaller treatment volumes and image guidance, and have demonstrated safety in and around the skull base. Overall, outcomes and toxicity are both very similar between fractionated SRT and SRS (Elia et al., 2007). The rate of permanent treatment-related morbidity is similar to that seen after SRS, and is reported at 0–3 % (Lo et al., 2002; Metellus et al., 2005). In addition to neurological deficits as discussed above, toxicity includes fatigue, skin erythema and alopecia.

Decision Making in Treatment of Skull Base Meningiomas

The selection of appropriate treatment for patients with presumed or histologically proven skull base meningiomas should be undertaken with the goal of achieving long-term tumor control without additional neurological morbidity. Patients should initially be evaluated in a center with expertise in neurosurgery, radiosurgery and radiation oncology. Decisions should always be made in a multidisciplinary fashion and must be individualized based on imaging characteristics, anatomic features, tumor location, size, and patient preference. For patients with large skull base tumors who present with neurological deficit or symptoms from mass effect, microsurgical resection is the initial treatment of choice, as it allows histological diagnosis and relief of compression with the potential for some neurological recovery. SRS may be appropriate as a primary or adjunctive treatment for a variety of skull base meningiomas, as outlined above. One approach, which we have found to be effective and well tolerated, has been to limit the use of SRS to tumors <3 cm in diameter, with 3–5 mm margin between the tumor limit and radiosensitive skull base structures. Fractionated SRT may be best suited for instances in which SRS is limited, such as for larger lesions, or for optic nerve sheath lesions (Elia et al., 2007). Finally, a more conservative approach of careful observation may be the best option for some older patients with small skull base meningiomas.

The development of frameless radiosurgical alternatives has led to the investigation of staged or "hypofractionated" radiosurgery, which may also be useful for skull base meningiomas. Theoretically, fractionation allows differentiation of response between abnormal tumor tissue and surrounding normal neurovascular structures. Assuming that normal tissue recovers faster from the toxic effects of radiation, fractionation may allow the delivery of slightly lower radiation doses over time while maintaining a cumulative "radiosurgical" effect. Benign tumors at the skull base, including a number of meningiomas, have been treated using this treatment strategy with high rates of tumor control and low morbidity, albeit in small series to date (Adler et al., 2006). Characterization of the optimal lesions for treatment with staged radiosurgery remains to be fully elucidated.

Conclusions

Stereotactic radiosurgery is a safe and effective treatment option, either as primary or adjuvant therapy, for skull base meningiomas. Neurological preservation and control of symptoms may be more commonly observed after radiosurgical treatment of petroclival, parasellar, and cerebellopontine angle lesions than at other anterior skull base locations. Lesions larger than 3 cm in diameter, or <3 mm from the optic apparatus, may be more safely treated with fractionated treatments, be they radiosurgical or radiotherapeutic. Overall rates of tumor control are comparable between SRS, SRT and microsurgery.

References

Adler JR, Chang SD, Murphy MJ, Doty J, Geis P, Hancock SL (1997) The Cyberknife: a frameless robotic system for radiosurgery. Stereotact Funct Neurosurg 69:124–128

Adler JR, Gibbs IC, Puataweepong P, Chang SD (2006) Visual field preservation after multisession CyberKnife radiosurgery for perioptic lesions. Neurosurgery 59:244–254

Andrews DW, Bednarz G, Evans JJ, Downes B (2006) A review of 3 current radiosurgery systems. Surg Neurol 66:559–564

Bassiouni H, Asgari S, Stolke D (2006) Tuberculum sellae meningiomas: functional outcome in a consecutive series treated microsurgically. Surg Neurol 66:37–45

Chi JH, McDermott MW (2003) Tuberculum sellae meningiomas. Neurosurg Focus 14(6):E6

Condra KS, Buatti JM, Mendenhall WM, Friedman WA, Marcus RB Jr, Rhoton AL (1997) Benign meningiomas: primary treatment selection affects survival. Int J Radiat Oncol Biol Phys 39:427–436

Davidson L, Fishback D, Russin JJ, Weiss MH, Yu C, Pagnini PG, Zelman V, Apuzzo ML, Giannotta SL (2007) Postoperative Gamma Knife surgery for benign meningiomas of the cranial base. Neurosurg Focus 23(4):E6

Dufour H, Muracciole X, Metellus P, Regis J, Chinot O, Grisoli F (2001) Long-term tumor control and functional outcome in patients with cavernous sinus meningiomas treated by radiotherapy with or without previous surgery: is there an alternative to aggressive tumor removal? Neurosurgery 48:285–296

Duma CM, Lunsford LD, Kondziolka D, Harsh GR IV, Flickinger JC (1993) Stereotactic radiosurgery of cavernous sinus meningiomas as an addition or alternative to microsurgery. Neurosurgery 32:699–705

Elia AEH, Shih HA, Loeffler JS (2007) Stereotactic radiation treatment for benign meningiomas. Neurosurg Focus 23(4):E5

Goldsmith BJ, Wara WM, Wilson CB, Larson DA (1994) Postoperative irradiation for subtotally resected meningiomas. A retrospective analysis of 140 patients treated from 1067 to 1990. J Neurosurg 80:195–201

Hasegawa T, Kida Y, Yoshimoto M, Koike J, Iizuka H, Ishii D (2007) Long-term outcomes of Gamma Knife surgery for cavernous sinus meningioma. J Neurosurg 107:745–751

Ichinose T, Goto T, Ishibashi K, Takami T, Ohata K (2010) The role of radical microsurgical resection in multimodal treatment for skull base meningioma. Clinical article. J Neurosurg 113:1072–1078

Iwai Y, Yamanaka K, Nakajima H (2001) The treatment of skull base meningiomas – combining surgery and radiosurgery. J Clin Neurosci 8:528–533

Iwai Y, Yamanaka K, Ikeda H (2008) Gamma Knife radiosurgery for skull base meningioma: long-term results of low-dose treatment. Clinical article. J Neurosurg 109:804–810

Kondziolka D, Flickinger JC, Lunsford LD (2008a) The principles of skull base radiosurgery. Neurosurg Focus 24(5):E11

Kondziolka D, Mathieu D, Lunsford LD, Martin JJ, Madhok R, Niranjan A, Flickinger JC (2008b) Radiosurgery as definitive management of intracranial meningiomas. Neurosurgery 62:53–60

Leber KA, Bergloff J, Pendl G (1998) Dose–response tolerance of the visual pathways and cranial nerves of the cavernous sinus to stereotactic radiosurgery. J Neurosurg 88:43–50

Linskey ME, Davis SA, Ratanatharathorn V (2005) Relative roles of microsurgery and stereotactic radiosurgery for the treatment of patients with cranial meningiomas: a single-surgeon 4-year integrated experience with both modalities. J Neurosurg 102(Suppl):59–70

Lo SS, Cho KH, Hall WA, Kossow RJ, Hernandez WL, McCollow KK, Gerbi BJ, Higgins PD, Lee CK, Dusenbery KE (2002) Single dose versus fractionated stereotactic radiotherapy for meningiomas. Can J Neurol Sci 29:240–248

Lunsford LD (1994) Contemporary management of meningiomas: radiation therapy as an adjuvant and radiosurgery as an alternative to surgical removal? J Neurosurg 80:187–190

Maire JP, Caudry M, Guerin J, Celerier D, San Galli F, Causse N, Trouette R, Dautheribes M (1995) Fractionated radiation therapy in the treatment of intracranial meningiomas: local control, functional efficacy, and tolerance in 91 patients. Int J Radiat Oncol Biol Phys 33:315–321

Mendenhall WM, Morris CG, Amdur RJ, Foote KD, Friedman WA (2003) Radiotherapy alone or after subtotal resection for benign skull base meningiomas. Cancer 98:1473–1482

Metellus P, Regis J, Muracciole X, Fuentes S, Dufour H, Nanni I, Chinot O, Martin PM, Grisoli F (2005) Evaluation of fractionated radiotherapy and gamma knife radiosurgery in cavernous sinus meningiomas: treatment strategy. Neurosurgery 57:873–886

Minniti G, Amichetti M, Enrici RM (2009) Radiotherapy and radiosurgery for benign skull base meningiomas. Radiat Oncol 4:42

Nutting C, Brada M, Brazil L, Sibtain A, Saran F, Westbury C, Moore A, Thomas DG, Traish D, Ashley S (1999) Radiotherapy in the treatment of benign meningioma of the skull base. J Neurosurg 90:823–827

Otani N, Muroi C, Yano H, Khan N, Pangalu A, Yonekawa Y (2006) Surgical management of tuberculum sellae meningioma: role of selective extradural anterior clinoidectomy. Br J Neurosurg 20:129–138

Pollock BE, Stafford SL, Utter A, Giannini C, Schreiner SA (2003) Stereotactic radiosurgery provides equivalent tumor control to Simpson Grade I resection for patients with small- to medium-size meningiomas. Int J Radiat Oncol Biol Phys 55:1000–1005

Sanna M, Bacciu A, Falcioni M, Taibah A, Piazza P (2007) Surgical management of jugular foramen meningiomas: a series of 13 cases and review of the literature. Laryngoscope 117:1710–1719

Sharma MS, Kondziolka D, Khan A, Kano H, Niranjan A, Flickinger JC, Lunsford LD (2008) Radiation tolerance limits of the brainstem. Neurosurgery 63:728–733

Starke RM, Nguyen JH, Rainey J, Williams BJ, Sherman JH, Savage J, Yen CP, Sheehan JP (2011) Gamma Knife surgery of meningiomas located in the posterior fossa: factors predictive of outcome and remission. J Neurosurg 114:1399–1409

Starke RM, Williams BJ, Hiles C, Nguyen JH, Elsharkawy MY, Sheehan JP (2012) Gamma Knife surgery for skull base meningiomas. J Neurosurg 116:588–597

Tuniz F, Soltys SG, Choi CY, Chang SD, Gibbs IC, Fischbein NJ, Adler JR Jr (2009) Multisession cyberknife stereotactic radiosurgery of large, benign cranial base tumors: preliminary study. Neurosurgery 65:898–907

Vesper J, Bölke E, Wille C, Gerber PA, Matuschek C, Peiper M, Steiger HJ, Budach W, Lammering G (2009) Current concepts in stereotactic radiosurgery – a neurosurgical and radiooncological point of view. Eur J Med Res 14:93–101

Voss NF, Vrionis FD, Heilman CB, Robertson JH (2000) Meningiomas of the cerebellopontine angle. Surg Neurol 53:439–447

Williams BJ, Yen CP, Starke RM, Basina B, Nguyen J, Rainey J, Sherman JH, Schlesinger D, Sheehan JP (2011) Gamma Knife surgery for parasellar meningiomas: long-term results including complications, predictive factors, and progression-free survival. J Neurosurg 114:1571–1577

Zachenhofer I, Wolfsberger S, Aichholzer M, Bertalanffy A, Roessler K, Kitz K, Knosp E (2006) Gamma-knife radiosurgery for cranial base meningiomas: experience of tumor control, clinical course, and morbidity in a follow-up of more than 8 years. Neurosurgery 58:28–36

Part IV

Spinal Cord Tumors

Pediatric Spinal Cord Tumors

18

Chiazo Amene, Michael Levy, and John Crawford

Contents

C. Amene • M. Levy
Department of Neurosurgery, University of California, San Diego, Rady Children's Hospital, 9500 Gilman Drive, La Jolla, CA 92093-0662, USA

J. Crawford (✉)
Department of Neurosciences and Pediatrics, Division of Child Neurology and Hematology-Oncology, University of California, San Diego, Rady Children's Hospital, 9500 Gilman Drive, La Jolla, CA 92093-0662, USA
e-mail: jrcrawford@ucsd.edu

Abstract

Pediatric spinal cord tumors comprise a rare but challenging subset of neoplasms with regards to neurosurgical and neuro-oncologic management. Spinal cord tumors may present with more common findings of weakness or back pain in older children or with more subtle findings of early handedness or head tilt in younger children and infants. An understanding of the diverse presentation of pediatric spinal cord tumors, their radiographic features and management strategies is crucial as delayed diagnosis may affect clinical outcome. While the vast majority of pediatric spinal cord tumors are histologically benign, their anatomic location often makes them a challenge to treat, both surgically and medically, as there is no universal consensus of the management of these children. Gross total surgical resection is the mainstay of therapy whenever feasible, however, intramedullary tumors pose a unique set of challenges for the neurosurgeon. Adjuvant chemotherapy plays a lesser role in the management of spinal cord tumors compared to their cerebral counterparts. Radiation therapy is a very important adjuvant therapy in the treatment of spinal cord tumors. However, depending on the age of the child and extent of radiation field, this may carry future risks of scoliosis or future secondary malignancy. There has been a relative lack of progress in non-surgical management of children with spinal cord tumors. The rarity of pediatric spinal cord

M.A. Hayat (ed.), *Tumors of the Central Nervous System, Volume 11*,
DOI 10.1007/978-94-007-7037-9_18,

tumors, together with small tissue sizes obtained during surgery portends a lesser understanding of the biologic mechanism of this disease. In this chapter, we will present the most common pediatric spinal cord tumors, their clinical and neuroradiographic features, as well as tumor biology and treatment strategies.

Introduction

Pediatric spinal cord tumors are an uncommon entity, with an incidence of 0.64 per 100,000 person years as reported by the Central Brain Tumor Registry of the United States (2011). They make up anywhere from 1 to 10 % of all pediatric central nervous system tumors (Nadkarni and Rekate, 1999; Wilson et al., 2007). The variation in reported prevalence may be attributed to small sample sizes and the assignment of developmental tumors or bony tumors to this category. Spinal cord tumors can be grossly classified into three types based on anatomic location: intramedullary, intradural extramedullary and extradural. Intramedullary refers to the area within the spinal cord parenchyma, intradural extramedullary is the area outside the spinal cord but within the dura and extradural refers to the space between the dura and the bony elements (Fig. 18.1). Intramedullary tumors are the most common subtypes, making up approximately 35 % of all pediatric spinal cord tumors, and approximately 55 % of intradural neoplasms (Constantini et al., 1996; Kothbauer, 2007). The intradural extramedullary type rarely occurs in the pediatric population, which is in direct contradiction to the adult spinal cord neoplasms where the most common tumors are in this region and include meningiomas, schwannomas and neurofibromas. Epidermoids and dermoid lesions are also in this group and although they are not considered true neoplastic lesions, their natural history mimic that of other slow-growing benign tumors with expansile and compressive features and they are therefore, included in this chapter. Extradural tumors include secondary metastases from distant sites, "drop" metastases from elsewhere in the craniospinal system and bony tumors. For the sake of this chapter, tumors of the bony elements are excluded.

Most studies have seen no difference in distribution between the male and female populations, while some, like Baysefer et al. (2004), report that spinal cord tumors are more prevalent in boys. Some series report up to 12 % of pediatric spinal tumors occur in the first year of life. However, if congenital/developmental lesions are excluded, tumor occurrence is evenly distributed throughout the first 15 years of life. In regards to cranio-caudal levels of the spine, the thoracic region is the most common site for spinal tumors (Crawford et al., 2009), followed closely by the cervical spine and then with the lumbar and sacral/cauda equina regions having relatively equal distributions.

Genetic associations exist in some cases of pediatric spinal cord tumors. The syndromes of Neurofibromatosis types 1 and 2 (NF1 and 2) and von Hippel-Lindau Disease (VHL) are well-known disease entities that are associated with schwannomas and neurofibromas in the former and hemangioblastomas in the latter. Lee et al. (1996) showed that spinal astrocytomas were more associated with NF1 and ependymomas were more often found in children with NF2. These two classes of intramedullary tumors have often been grouped in the same categories as their cerebral counterparts, but emerging evidence suggests that there are distinct differences in the genetics and molecular biology of these tumors. However, secondary to the rarity of pediatric spinal cord tumors in general, very little is known about the molecular and genetic basis of these specific entities.

Although uncommon, pediatric spinal cord tumors represent a particularly daunting diagnosis due to their close proximity to the densely packed fiber tracts in the spinal cord and the devastating neurological deficits they can incur, either by their presence alone or consequently due to surgical manipulation. Specific treatment modality largely depends on the type of tumor, location and the extent of neurological deficits. Historically, it was felt that treatment should be conservative to minimize morbidity, especially

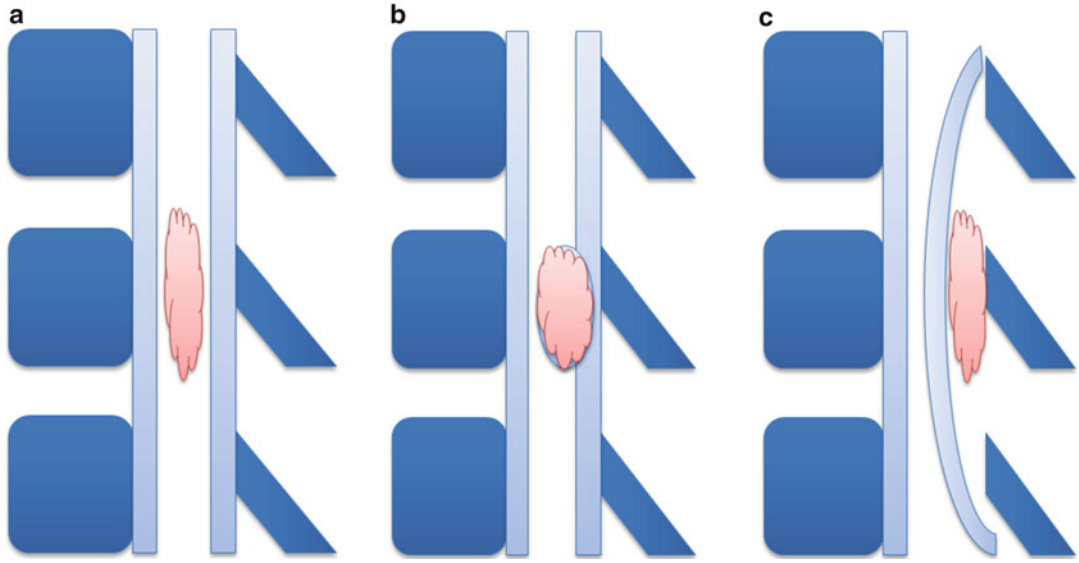

Fig. 18.1 Depiction of classification of spinal cord tumors based on location. (**a**) Intramedullary, (**b**) Intradural extramedullary, (**c**) Extradural

in regards to intramedullary tumors, with the traditional approach limited to biopsy, dural decompression and radiation therapy. However, recent reports consistently call for a more aggressive surgical approach with attempts at gross total resection and adjuvant therapy where indicated.

Clinical Presentation

The signs and symptoms of spinal cord tumors vary depending on location, type of the tumor and age of the patient (Fig. 18.2). Neck or back pain was the most common presenting symptomatology in most series, including Constantini et al. (1996), Crawford et al. (2009) and Wilson et al. (2007), occurring in approximately two-thirds of patients. Onset of pain is often insidious and tends to be diffuse rather than radicular in distribution. Pain is often more severe on recumbent positioning, thus more severe during nighttime. This phenomenon of nighttime pain was postulated by Kothbauer (2007) to be secondary to mild venous congestion in the horizontal position, which causes increased tissue pressure on the spinal cord and results in further meningeal irritation or activation of pain pathways. Another theory is that fewer stimuli are present at nighttime to distract the child from the pain. Pain that awakens a child from sleep should be a heralding symptom for all practitioners to obtain appropriate imaging. However, pain is a symptom that may be difficult to delineate in infants and younger children and the only pointer may be irritability, general fussiness or, in some cases, abdominal

Symptoms	Signs
Back (or neck) pain	Motor weakness
Gait abnormalities	Atrophy
Kyphoscoliosis	Reflex changes
Torticollis	Tenderness
Early handedness	Sensory level
Urinary dysfunction	Decreased rectal tone

Fig. 18.2 Common signs and symptoms of spinal cord tumors

discomfort. The most common etiology of childhood back pain remains musculoskeletal in origin. However, atypical features, associated neurologic deficits, or persistent duration should warrant an inclusion of spinal cord tumors in the differential diagnosis.

Motor signs and symptoms are not uncommon in association with pediatric spinal cord tumors. Spinal cord tumors may manifest as a delay in motor development or early hand preference in younger patients, motor regression and refusal to ambulate in slightly older patients, and extremity weakness or frequent falls in adolescents. Tumors in the cervical region may result in head tilt or torticollis. When the upper extremities are involved, early handedness may occur where a child switches hand dominance. Constantini et al. (1996) found that in children less than 3 years old, head tilt and motor delay were common presenting factors, although pain was still more prevalent, presenting in 42 % of patients under 3 years of age. A variability of reflexes (hyper vs. hyporeflexia, positive Babinski response) may be present in up to 50 % of pediatric patients with spinal cord tumors, as seen in the series by Baysefer et al. (2004), however, no reproducible correlation was noted between this and tumor location and/or grade in another series by Crawford et al. (2009). This lack of localization is noted more frequently in children than in adults, where a lesion can cause a combination of upper and lower motor neuron signs. Therefore, the neurologic examination should be comprehensive and also include assessment of the bulk and tone of all muscle groups.

Bowel or bladder dysfunction may be difficult to delineate in very young children, especially prior to toilet training. Urinary retention, however, should be readily identified and appropriate work-up carried out. Pre- and post-treatment urinary function should be followed periodically with urodynamic studies. Bowel and/or bladder problems are often present in patients with lesions of the cauda equina or filum terminale as reported by Bagley et al. (2009).

Spinal deformity, specifically kyphoscoliosis, was present in about 24 % of cases in the series by Constantini et al. (1996) of children under 3 years of age with intramedullary tumors. This finding is more common in intramedullary tumors than tumors in other locations and the physiologic reason for this appears to be the inequality between signaling to both sides of the spine and paraspinal muscles resulting in discrepancy in paraspinal muscle strength. As will be discussed later, this issue of spinal deformity becomes more problematic in the post-treatment phase in these patients with some requiring spinal fusion surgeries.

Sensory complaints are uncommon in the pediatric population but, when present, tend to be observed later in the course of spinal cord tumors. Some patients may be misdiagnosed as having Guillain-Barre syndrome or transverse myelitis especially when sensory problems are accompanied by hypo or absent reflexes. Some patients may present with a Horner's syndrome when the tumor is in the cervico-thoracic region and this is often seen in neuroblastomas where the lesion extends from the paravertebral area through the neural foramen causing disruption of the third order neurons.

Occasionally, symptoms manifest after a minor traumatic injury. This occurrence may be due to exacerbation of the underlying pathology by the trauma or by a previously unrecognized symptom like clumsiness resulting in a fall. The variability in symptoms and duration of symptoms may provide a challenge in diagnoses of these tumors. Although there has been no overt correlation between duration of symptoms and outcome in more benign tumors, malignant tumors tend to have a more aggressive course and a shorter duration in symptoms as noted in Crawford et al. (2009). Symptoms tend to be slowly progressive in all but a few cases. An acute change in spinal cord function may sometimes be encountered in cases of acute hemorrhage in the tumor, bony collapse or compression causing spinal cord ischemia and infarct.

Radiographic Features

Plain Radiographs

Plain radiographic images may be the initial imaging obtained when a pediatric patient complains of back pain or when a structural deformity is noted. Although spinal x-rays often do not

show tumors, they do show the overall alignment of the vertebral column and are necessary in the diagnosis of kyphoscoliosis. Expansion of the neural foramen in cases of peripheral nerve sheath tumors or neuroblastomas can be seen on lateral spine X-rays. If treatment involves instrumentation and fusion, it is also important to obtain spine X-rays post-operatively and periodically to evaluate and follow any changes in alignment. All patients with abnormal plain radiographs require a thorough neurologic examination to exclude a spinal cord tumor.

Ultrasonography

Due to the advent of superior imaging techniques and the poor penetration of sound waves through bone, ultrasonography has been largely discarded in the diagnosis and evaluation of spinal tumors. However, it remains a valuable tool during resection of spinal tumors, especially intramedullary tumors. The echogenicity of the tumor tends to defer from surrounding parenchyma and helps guide extent of the resection. Even in the world of intra-operative MRI image-guidance it has been found that lesions in the spinal cord may migrate during positioning and therefore, ultrasonography remains a simple, yet useful tool.

Bone Scans

Bone scans are useful in determining the extent of metastatic disease or detecting a primary lesion. They may also yield useful information regarding the response of disseminated disease to chemotherapy or radiation therapy.

Angiography

Digital subtraction angiography is an important tool when vascular lesions are suspected and is the gold standard for diagnosing arteriovenous malformation and dural arteriovenous fistulae. Their main use in tumors, however, is limited to evaluation and possible embolization of hemangioblastomas to limit intra-operative blood loss.

Computed Tomography (CT)/ Myelogram

CT scans may be necessary to evaluate the extent of bony involvement of some tumors or the structural relationship between the tumor and normal bony structures to better plan surgical approaches. A 3-D reconstruction may be required for planning. The use of CT scans in young children has been controversial secondary to the level of ionizing radiation exposure and its possibility for causing secondary malignancies. Compared to most other imaging modalities that use ionizing radiation (radiographs, angiography), CT scans have a disproportionately higher level of ionizing radiation and in children with growing tissue and a higher life expectancy in which to manifest potential cancers, poses a higher risk for causing a malignancy. In a recent clinical report, Brody et al. (2007) analyzed the current literature on the risks of ionizing radiation, specifically CT scans and found that the consensus was that the use of CT scans in the right settings far outweigh the potential risk of future cancers. Therefore, if a CT is essential for diagnosis and surgical planning in a pediatric patient with a known or suspected spinal cord tumor, the benefits far outweigh the risks for future oncologic manifestations. A CT with a myelogram may be used when an MRI is contraindicated and is useful in delineating leptomeningeal dissemination of tumors.

Magnetic Resonance Imaging (MRI)

MRI is the modality of choice for evaluating patients with suspected spinal cord tumors and the different sequences and protocols are well reviewed in Khanna et al. (2003). Since the innovation of this mostly non-invasive image modality, the time to diagnosis of various forms of spinal cord tumors in children has decreased and this modality has largely replaced all other forms of diagnostic imaging. MRI should be performed without and with a gadolinium-based compound. T1-weighted images must be performed in multiple planes and this best evaluates the solid components of the tumor. T2-weighted images provide information on any associated cysts,

cerebrospinal fluid and any syrinx, if present. The T2-weighted images may be further suppressed to provide information on the presence of edema and its extent. Contrast-enhanced images are necessary to precisely determine the extent of the lesion, and provide a theoretical likelihood of its histologic diagnosis. The disadvantages of MRI are two-fold. First is the need for sedation in young children. Although the American Association of Pediatrics (AAP) has published guidelines, these are not mandatory and careful examination of the patient before and after the study is completed is important to avoid any sedation-associated complications. The second disadvantage of MRI is that this modality does not fully evaluate the bony components around the tumor.

The MRI features of intramedullary spinal cord tumors vary depending on type of tumor. Low-grade glial tumors are often hypodense on T1, non-enhancing and expand the cord. As mentioned earlier, a syrinx may be associated with these and is hypointense on T1 and hyperintense on T2-weighted images. Juvenile pilocytic astrocytomas and hemangioblastomas may present as a cystic lesion with a mural contrast-enhancing nodule. Most other spinal cord tumors, including those of the intradural, extramedullary origin, enhance strongly with contrast administration. However, the absence of gadolinium enhancement should not exclude tumor from the differential diagnosis. Complete neural axis imaging (brain and spine MRI) is often required in pediatric patients with spinal cord tumors, to determine whether the known lesion is as a result of metastasis from another primary source or if dissemination has occurred. Representative neuroimaging features of pediatric spinal cord tumors are shown in Fig. 18.3.

Pathology and Biology

Intramedullary Tumors

Astrocytoma

Astrocytomas are glial-derived tumors that represent the most common tumors of the spine, making up approximately 35 % of intramedullary tumors in the pediatric population as reported by Constantini et al. (2000). Astrocytomas are grouped into four different types based on the World Health Organization (WHO) guidelines. Juvenile pilocytic astrocytomas (JPA) are considered WHO Grade I and are relatively common in the pediatric cranio-spinal axis. When they are present in the spine, they often occur in the cervico-medullary junction or cervical spine. Imaging reveals a well-defined expansile mass, which has an associated cyst and often enhances with contrast administration. They are non-infiltrative, with well-defined borders and are, therefore, curable via complete surgical resection. This is in direct contradistinction to Grade II-IV astrocytomas. Although both WHO Grade I pilocytic astrocytomas and WHO Grade II diffuse astrocytomas are grouped under ‘low-grade astrocytomas’, these are two distinct, unrelated entities and pilocytic astrocytomas are not considered a lower grade version of diffuse astrocytomas, nor are they part of a continuum. Histologically, they are characterized by biphasic areas of compact tissue with elongated, piloid (hair-like) cells and coarse cytoplasmic processes, alternating with loosely knit spongy areas with microcysts. They may possess brightly eosinophilic Rosenthal fibers (in compact areas) and eosinophilic granular bodies (in compact and spongy areas).

Most spinal astrocytomas are fibrillary astrocytomas (WHO Grade II) and are diffusely infiltrative. MRI of a diffuse astrocytoma often shows an eccentrically located lesion, typically in the cervico-thoracic spine that widens the spinal cord and possesses heterogeneous signal intensities and minimal contrast enhancement. They often span multiple spinal segments and may involve the entire spinal cord, sometimes presenting as a holocord tumor. Kyphoscoliosis and pain are the most common presenting symptoms and as mentioned earlier, symptoms are insidious and diagnosis may be delayed. Though they are diffusely infiltrative, attempts at total resection has been shown in small case studies, including Constantini et al. (2000) and Nakamura et al. (2008), to be superior to biopsy or partial resection with or without radiation therapy. Hematoxylin and eosin staining reveal fibrillary and/or

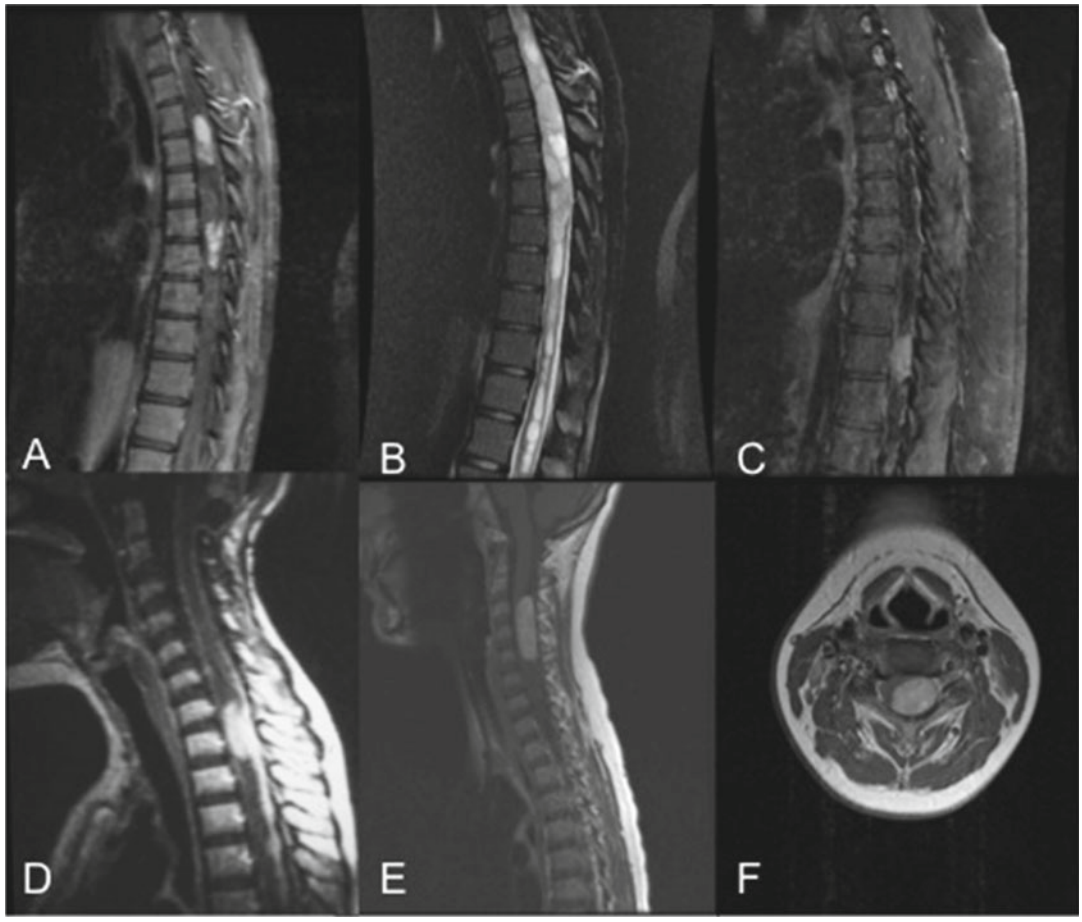

Fig. 18.3 Representative MRI sequences showing different pediatric spinal cord tumors. (**a**) Post-enhancement T1 sequence of an intradural JPA. (**b**) Same tumor on T2-weighted image showing extensive cysts and syrinx. (**c**) Intradural extramedullary meningioma, post-Gd enhancement. (**d**) Diffuse metastatic PNET with a large nodule and meningeal enhancement. (**e** & **f**) Sagittal and Axial post-enhancement images of a cervical spine schwannoma

gemistocytic astrocytes with increased cellularity and pleomorphism. They are infiltrative into surrounding cord but often do not contain mitotic cells. There are few published reports on the molecular and cytogenetic analysis of these tumors and most are inferred from studies of their intracranial counterparts. Chi et al. (2006) noted that a mutation in p53 likely played a role in the transition of astrocytes to astrocytoma, in addition to losses in Chromosomes 17p, which would explain the association with NF1.

Anaplastic astrocytomas (WHO Grade III) and glioblastoma (WHO Grade IV), collectively called high-grade or malignant glioma, are very rare in the pediatric population and make up approximately 10–15 % of all spinal astrocytomas (Binning et al., 2007). Clinically, they present with a more aggressive course and a shorter duration of symptoms. MRI usually does not differentiate between low and high-grade neoplasms. Similar to their intracranial counterparts, the hematoxylin and eosin stains show diffuse infiltration, microvascular proliferation, increase in mitotic activity and necrosis. They may disseminate widely in the subarachnoid space prior to diagnosis. Although surgical treatment is still recommended in these cases, less aggressive resection is usually undertaken secondary to their aggressive course and is then supplemented with adjuvant radiation therapy after surgery, as seen

in Nakamura et al. (2008). There are no studies reporting any significant improvement in outcome with adjuvant chemotherapy.

Ependymoma

Ependymomas are neuroectodermal tumors that are thought to arise from the ependymal lining of the spinal canal and ventricles. In children, ependymomas are more frequently found in the ventricular system than in the spinal cord and the reverse is true for adults. Therefore, the incidence of spinal cord ependymoma increases with age. Ependymomas are the second most common intramedullary tumors after astrocytomas in the pediatric population and are clinically and sometimes radiographically indistinguishable from astrocytomas. They can be grouped into three types; myxopapillary ependymoma (WHO Grade I), benign (typical) ependymoma (WHO Grade II) and anaplastic ependymoma (WHO Grade III). Secondary to the unique location of the myxopapillary type of the tumor, they will be discussed in the section reserved for intradural, extramedullary tumors. Spinal ependymomas are usually of the benign variety (WHO Grade II), are well-circumscribed and, in contrast to diffuse astrocytomas, are typically curable with gross total resection. However, neurosurgeons often report a focal loss of the cord/tumor cleavage plane. Typical MRI characteristics of ependymomas include a centrally located lesion, often in the cervical spine, with more symmetric expansion and more intense and homogenous enhancement than astrocytomas as described by Miyazawa et al. (2000). Hsu et al. (2009) also reports that they may be sausage-shaped and more often than not, have a rostral and/or caudal cyst associated with them. T2- weighted images reveal a dark-rim of hemosiderin deposits and some edema in the cord. Spinal cord ependymomas, like schwannomas and neurofibromas, are associated with NF2 and Birch et al. (1996) found that the majority of sporadic spinal ependymomas had a mutation in the NF2 transcript. Hematoxylin and eosin stains show areas of decreased cellularity (paucicellular) intermixed with areas of dense cellularity. Almost pathognomic of intracranial ependymomas are perivascular pseudorosettes, as nuclei tend to respect perivascular zones, leaving a region of cell processes that converge on the vessels. Perivascular pseudorosettes are not as inconspicuous in spinal ependymomas and this may result in some confusion with diagnosis. They may also contain dense, collagenous tissue and induce piloid gliosis in adjacent cord. The anaplastic type (WHO Grade III) exhibits a more aggressive course with diagnosis being made histologically with presence of mitosis and increased cellularity and often, accompanying microvascular proliferation. Necrosis and intratumoral hemorrhage are frequent but often do not lend to a more aggressive grade.

As mentioned earlier, treatment of spinal ependymomas is surgical resection and it is clear in the literature that extent of resection is directly linked to long-term survival. Benesch et al. (2010) and Lonjon et al. (1998) report up to 85–90 % progression-free survival at 5 years after gross total resection. If residual tumor is seen on post-operative imaging, consideration should be given to re-exploration and attempts at gross total resection. Radiotherapy is often not indicted unless there are signs of dissemination at the time of diagnosis or recurrence occurs. Recurrence, when present, is usually local and focal radiotherapy may then be administered as discussed in the review by Hsu et al. (2009). Similar to high-grade astrocytomas, adjuvant radiation therapy is usually administered after resection of anaplastic ependymomas although no long-term follow-up supporting this is available.

Ganglioglioma

Gangliogliomas are uncommon intramedullary tumors that are clinically indistinguishable from low-grade astrocytomas and make up 1.1 % of intramedullary spinal tumors (Jallo et al., 2004). They are comprised of both glial (astrocytes) and mature neuronal components and have an indolent course with low mortality. When they occur in the spinal cord, they are more common in the cervical spine and in a review of 27 reported cases, Patel et al. (1998) found that gangliogliomas extended over more vertebral segments than astrocytomas or ependymomas. MRI analysis

often shows a well-defined, eccentrically located cystic mass spanning 4–8 vertebral segments with mixed hypo and hyper-intensity signals and little peritumoral edema. Contrast administration reveals patchy to no enhancement. On hematoxylin and eosin stains, clusters of large cells with two vesicular nuclei, the so-called ganglion cells, mixed with astrocytes in a desmoplastic, reticulin-rich background is noted. Treatment of choice of spinal cord gangliogliomas is gross total resection, which is associated with low morbidity and mortality. Jallo et al. (2004) reported an 88 % 5 year survival rate with a 65 % progression-free survival. Adjuvant radiotherapy should be avoided unless in the setting of recurrent disease. Even then, a second surgical procedure has not been shown to increase morbidity and is encouraged.

Hemangioblastoma

Hemangioblastomas of the spinal cord are very uncommon in pediatric population, even when associated with von Hippel-Lindau Disease (VHL). VHL disease is an autosomal dominant disease with high penetrance which results from the loss of a tumor suppressor gene on Chromosome 3. The syndrome results in multiple tumors including CNS hemangioblastomas, renal cysts, retinal angiomas, pancreatic cysts and pheochromocytomas. Sporadic spinal hemangioblastomas occur evenly throughout all levels of the spine but those associated VHL show a predilection for the cervical cord. Hemangioblastomas tend to have a pial attachment and are located on the dorsal or dorsolateral aspect of the cord and this results in the higher incidence of sensory-related symptoms seen in these cases compared to other intramedullary tumors. On MRI, the tumor is isointense on T1-weighted images and enhance strongly and homogenously with contrast administration. Rostral and caudal cysts are very common and often make up the bulk of the mass. They are hyperintense on T2-weighted sequences with the presence of flow voids. They are almost always associated with extensive edema and syrinxes. Histologically, a highly vascular mass is seen with numerous capillaries lined with endothelial cells and pericytes. In between the capillaries are lipid-laden 'foamy' stromal cells. This is the one tumor type where preoperative angiography may be useful in defining the feeding vessels and possibly enable embolization prior to surgical resection, although most centers, including that reported in Lonser and Oldfield (2006) report no advantage in using diagnostic arteriography or selective embolization prior to resection. Unlike most other intramedullary tumors, hemangioblastoma should be resected in a circumferential pattern and care should be taken to avoid breaching the wall of the mass as attempts at debulking from within could result in uncontrollable hemorrhage. Also, unlike most other tumors that may be followed expectantly in the absence of symptoms, asymptomatic spinal hemangioblastomas should be treated as they often result in unpredictable and extensive neurologic deterioration.

Intradural Extramedullary Tumors

As mentioned earlier, while intradural extramedullary tumors are the more prevalent spinal cord tumors in adults, they only make up about 25 % of all spinal tumors in children. Meningiomas and peripheral nerve sheath tumors are often associated with Neurofibromatosis types 1 and 2.

Meningioma

Spinal meningiomas make up less than 5 % of all spinal cord tumors in the pediatric population. When they are present, it should herald a possible diagnosis of NF2. The established higher incidence in adult females, almost 10:1, is not reproduced when looking at children and this may lend to a different biology of these tumors. In fact, there is a slight male predominance as reported in Sheikh et al. (1996). They most commonly occur in the cervical and thoracic regions and are situated ventrolaterally. Symptoms, usually of the motor variety, are gradual and are caused by compression of the underlying cord and exiting nerve root. MRI imaging shows a well-circumscribed lesion that is isointense on T1- and T2-weighted images, enhances strongly and homogenously with contrast administration and possesses a

dural tail, although this is not a universal finding. There is usually little to no edema in the adjacent cord. Imaging of the entire cranio-spinal axis is warranted in a pediatric patient with diagnosis of spinal meningioma to evaluate for NF2. The histologic subtypes seen in pediatric spinal meningiomas are the same as in adults. However, the psammomatous type appears to be the most common subtype noted. Most fall under the WHO Grade I heading but when present in the lumbar region, it is often the clear cell type that is by definition, a WHO Grade II meningioma. Anaplastic or malignant meningiomas are very rare but do occur with higher prevalence in children than adults.

Gross total surgical excision is the primary treatment for spinal meningiomas and this is accomplished with less difficulty than in intramedullary tumors. From a neurosurgical standpoint, resection of the dural–based component is crucial, as this determines recurrence and subtotal resection may result in up to a 90 % recurrence rate. This may be a difficult endeavor in ventrally-located tumors, but when accomplished, the defect can be reconstructed with a dural substitute. Repeat surgery should be considered for recurrence prior to radiation as there have been reports of radiation-induced meningiomas in children, especially in the setting of NF2.

Peripheral Nerve Sheath Tumors

Peripheral nerve sheath tumors (PNSTs) are common in the setting of NF1 and 2 and include neurofibromas, schwannomas and malignant PNSTs. They account for approximately 10 % of spinal tumors in children and 30 % of all intradural extramedullary neoplasms. Neurofibromas involve proliferation of both Schwann cells and mesenchymal cells of fibroblastic origin within nerves. Schwannomas, on the other hand, involve a proliferation of the Schwann cells around but not within the nerve roots. These lesions usually arise from the sensory nerve roots and as such, do not cause motor dysfunction unless significant compression is present. In addition to pain, patients may present with a sensory dysesthesias with a distinct level on physical examination. Nerve sheath tumors expand the neural foramen, a finding that can be noted on lateral spinal x-rays and sagittal MRI sequences. MRI often reveals a dumb-bell shaped lesion extending out from the neural foramen that is isointense on T1 and T2-weighted images and enhances homogenously with contrast administration. They often have both intradural and extradural components, although this is more common with schwannomas. Surgery is the treatment of choice and secondary to this bipartitioning, a 2-stage procedure may be required, first, a laminectomy with decompression of the extradural component, and then, an intradural procedure to complete the resection. Hematoxylin and eosin staining of schwannomas show the prototypical elongated cells arranged in densely packed Antoni A regions and more loosely associated Antoni B areas with Verocay bodies, striking palisades resulting from stacked arrays of nuclei alternating with anucleate zones of cell processes, present in the Antoni A areas. Neurofibromas have a wavy appearance with the Schwann cells separated by a loose, mucoid matrix. Interwoven axons with or without myelin are noted.

Malignant degeneration may occur in neurofibromas and schwannomas, although this occurs less frequently in schwannomas. An association with NF1 is seen in 50–60 % of MPNSTs while up to 5 % of patients with NF1 go on to develop a MPNST (Binning et al., 2007). MPNSTs have a poorer prognosis as they are more aggressive and are locally invasive. Surgical treatment remains a first-line therapy and radiation therapy should play a limited role in treatment of these and benign neurofibromas and schwannomas in the setting of NF1 as this has been shown to increase the incidence of malignant degeneration.

Myxopapillary Ependymomas

Myxopapillary ependymomas have a unique location from all other spinal ependymomas. They arise from the filum terminale and often involve multiple nerve roots in the cauda equina or may infiltrate the conus medullaris. They are slow-growing and are histologically classified as WHO Grade I. However, as reported in multiple series, including Bagley et al. (2009) and Fassett et al. (2005), they notoriously recur at the local

site after resection and have been known to exhibit meningeal dissemination. Multiple chromosome abnormalities different from those in other spinal ependymomas have been identified in myxopapillary ependymomas, the most common being gains in chromosomes 7 and 9, as well as losses on chromosomes 1 and 2 (Binning et al., 2007). MRI reveals an isointense lesion on T1, hyperintense on T2 and an avidly and homogenously enhancing sausage-shaped lesion on contrast images. Hematoxylin and eosin stains reveal a delicately encapsulated lesion with columnar epithelial cell and microcysts and extensive intercellular mucin deposits. Radical surgical excision is the treatment of choice for myxopapillary ependymomas with a favorable outcome noted in both children and adults in the series of 53 patients reported in Bagley et al. (2009). However, this may be difficult to achieve in cases where the tumor invades the conus or is intimately entwined with nerve roots of the cauda equina. Meticulous care must be taken to separate these and find a cleavage plane and avoid overt manipulation of nerve roots as this may result in disastrous neurologic compromise. When gross total resection cannot be achieved, post-surgical radiation therapy may be utilized as many studies have shown a reduction long-term recurrence of these tumors (Al-Halabi et al., 2010; Fassett et al., 2005). On the other hand, Al-Halabi et al. (2010) also advocated for the use of adjuvant radiotherapy, regardless of the extent of resection in children, secondary to the aggressive nature of this disease in younger children. In the event of local recurrence, surgery is still superior to radiation therapy alone and adjuvant radiotherapy should be considered. No chemotherapeutic regimen has been known to show any clinical benefits and there are currently no protocols in use for this disease.

Dermoid and Epidermoid Tumors

Although by definition dermoid and epidermoid tumors are not neoplastic lesions, they should be mentioned secondary to their slow growth and compressive properties that liken them to other benign neoplastic lesions. In the series by Baysefer et al. (2004), they make up approximately 33 % of all intraspinal tumors in children. Epidermoid cysts contain a stratified epithelial lining with a fibrous capsule and are ectodermal in origin. Dermoid cysts contain both ectodermal and mesodermal components that include an epithelial lining and capsule, but also sweat glands and hair follicles that are orderly arranged. Dermoids are often associated with a congenital dermal sinus tract. These lesions are thought to form from failure in separation of the invagination of the normal ectoderm that occurs during formation of the neural tube and may be found anywhere along the neural axis, although they predominantly occur at the level of the conus medullaris or cauda equina. Epidermoids may be formed iatrogenically after a lumbar puncture in the neonatal period, often when a small-gauge needle is introduced without a stylet, leading to the introduction of epidermal components to the intradural space. In addition to compressive features, dermoids and epidermoids may cause neurologic dysfunction by inflammation of the surrounding neural structures and, in the case of dermoids, infection. Often, dermoids may go undiagnosed until the child presents with a meningitis or intradural abscess. The diagnosis of dermoids is clinical, but MRI is helpful in delineating extent of the tract. Imaging is characteristic with a cystic non-enhancing lesion with heterogeneous signal intensity. There may be restricted diffusion secondary to keratinaceous debris. Malignant degeneration of epidermoids or dermoids does not occur. Treatment is surgical, with great stakes taken to achieve complete resection as any remnant often results in recurrence. If infection is already present, the patient may be treated with antibiotics and resection delayed to reduce inflammation.

Primitive Neuroectodermal Tumors (PNETs)

PNET is a controversial term that may be used to describe different small cell embryonal tumors which are histologically similar but may be present anywhere in the central nervous system or even occur peripherally. When present in the CNS, they are the most likely to disseminate throughout the subarachnoid space via the

cerebrospinal fluid. The most common type is located in the cerebellum and referred to as medulloblastoma. In the spinal cord, the most common instance of PNETs is as drop metastases from primary intracranial PNETs, although there have been reports of primary intramedullary PNETs, as discussed in Ellis et al. (2011), and also of the intradural extramedullary and extradural subtype. MRI is often variable depending on location and CSF cytology is extremely helpful. Histologically, these tumors show a poorly-differentiated cell population with nuclear pleomorphism and a large number of mitotic figures. Treatment is surgical excision with adjuvant chemotherapy and radiation but prognosis remains poor with median survival between 1 and 2 years.

Extradural Tumors

Tumors in the spinal extradural space could include metastatic tumors, bony tumors like osteoblastoma or sarcomas causing compression of the neural element. Metastatic spinal tumors occur in about 3–5 % of systemic malignancies and spinal compression is the primary symptom in about 50 % of these cases. This entity includes both drop metastases from intracranial tumors and metastases from distant sites like abdominal or long bone tumors. The most common culprits include Ewing's sarcoma, osteosarcoma, neuroblastoma, leukemias and lymphomas. The tumors with a bony origin are not included in this chapter.

Neuroblastoma

Neuroblastomas are an embryonal malignancy that may be considered a better-differentiated form of PNETs and are a derivative of neural crest cells. They are the most common solid malignancy in infancy and childhood. Neuroblastomas originate anywhere along the sympathetic chain and are the most common cause of spinal compression in the pediatric population. They either arise from the abdominal area and extend through the neural foramen to compress the spine (so-called dumbbell neuroblastomas), or may arise primarily in the intraspinal location, usually in the thoracic area. Neuroblastomas may be divided into three categories: neuroblastomas, ganglioneuroblastomas and ganglioneuromas, with the latter on the more benign end of the spectrum. Characteristic neurologic manifestations include Horner's syndrome when there is involvement of the cervical ganglion, opsoclonus-myoclonus-ataxia syndrome, a paraneoplastic autoimmune reaction, CNS metastases and cord compression. MRI may portray an abdominal or paraspinal mass extending through the foramen that enhances with contrast administration. Histologically, there are sheets of blue cells similar to a PNET, but with a higher abundance of fibroblastic stroma. Binning et al. (2007) in their review discussed that first-line chemotherapy often resulted in decrease in size of these tumors and surgical excision is reserved for those patient with rapid neurologic decline secondary to acute compression of neural elements or those in which there was no response to chemotherapy or radiation. Aydin et al. (2010) in their series found that CNS involvement was a poor prognosis with a 7.9 months median time to death. The incidence of post-treatment scoliosis was also reported to be very high in neuroblastoma, even with radiotherapy alone, ranging from 30 to 70 %. Thus, these patients require aggressive follow-up with post-treatment spinal x-rays to evaluate and treat the deformity.

Leukemias/Lymphoma

Leukemias and lymphomas are the most common malignancies in children and can affect any organ system. Spinal involvement is generally rare, occurring in about 4 % of patients presenting with lymphomas in one series by Chahal et al. (2003). However, because the general incidence is so high, this makes up a significant amount of pediatric spinal cord tumors. The most common sites of spread are the extradural and paravertebral areas but metastases can occur to any site. CSF cytology is very useful in diagnosis and eventual follow-up. These disease entities differ from other spinal cord tumors in one very important aspect. First line therapy is chemotherapy and radiation as they are often very chemo-responsive. Surgical decompression is indicated only in the instances of acute neurologic

deterioration, failure of first-line therapy and or when a primary is unknown and tissue is needed to make a diagnosis.

Treatment

Management of the spinal cord tumors in the pediatric population can be complex and depends on the several factors, including age, baseline neurologic function, location, tumor subtype and extent of tumor. Overall prognosis largely depends on the response of the tumor to various modalities, namely surgical resection, radiation and/or chemotherapy and also on spinal stability. The goals for treatment should be three fold; first, to maximize tumor resection, second, to decompress the spinal cord and lastly, to avoid neurologic compromise. Due to the rarity of spinal cord tumors in children, there is limited data in terms of multi-centered controlled trials as compared to other childhood CNS malignancies.

Steroids

While use of steroids have become commonplace in the initial management of spinal cord tumors, there have been no studies specifically studying the effects of steroid use pre- and post-operatively in pediatric patients with intramedullary spinal cord tumors. Pre-operative steroid administration presumably decreased tumor-associated inflammation and cord edema. McGirt et al. (2008a, b) reported in their series of 16 patients that pre-operative steroid use was associated with markedly increased likelihood of improvement in neurological status after surgical resection.

Surgical Treatment/Technique

For extradural compressive tumors, the goal for surgery is often decompression of the spinal cord. A decompressive laminectomy is usually sufficient and all exposed tumor can be resected. Pursuing tumor masses ventral to the cord is often not recommended secondary to the high risk of cord injury and, in these cases, adjuvant therapy may be utilized. The treatment of intradural extramedullary tumors is also primarily surgical as mentioned earlier. Spinal meningiomas and PNSTs often possess a distinct margin from surrounding tissue that allows them to be totally excised. Dermoids may be associated with a sinus tract that extends to the skin surface and these need to followed and completely excised to avoid infectious sequelae.

The patient is positioned prone with the head fixated in the neutral position, with the Mayfield head-holder in the case of cervical or cervicothoracic tumors. For lower thoracic or lumbar lesions, the patient's head may be placed on a headrest, with care taken to avoid pressure on the eyes. For intramedullary tumors, a laminectomy or osteoplastic laminotomy (laminoplasty) starting at the midportion of the tumor and extending rostrally and caudally to access the solid component of the tumor is needed. Cysts associated with tumor need not be fully exposed. If performing a laminectomy, care must be taken to avoid compromising the facet joints. Ultrasonography may be used prior to dural opening to evaluate extent of the tumor. Astrocytomas and gangliogliomas have similar characteristics to the cord but expand cord while ependymomas tend to be hyperechogenic and readily distinguishable from the spinal cord. Once the dura is opened, thickened arachnoid is often encountered. The exposed cord should be closely inspected to identify midline as some tumors may rotate the cord. A myelotomy is then performed at this midline area using microsurgical techniques. The advent of the Cavitron Ultrasonic Aspirator (CUSA) and the microsurgical laser has vastly improved resection of intramedullary tumors. The CUSA uses high-frequency ultrasound to fragment the tumor while aspirating it at the same time and the microsurgical laser, specifically the Nd-YAG (neodymium:yttrium-aluminium-garnet) Contact Laser System can act as a scalpel especially in areas where the tumor is firm, and in both cases, avoids overt manipulation of adjacent cord. The laser may also be used to perform the myelotomy. Care must be taken in areas where the tumor infiltrates the cord parenchyma and resection is

deemed complete when the interface with white matter is noted or if a sustained decrease in motor-evoke potentials is seen (see next section). Tumor–associated syrinxes or cysts need not be manipulated. After resection, the dura is closed in a watertight fashion using non-absorbable sutures.

The use of intraoperative neurophysiologic monitoring (INM) is paramount in the resection of intramedullary tumors. Sala et al. (2002) reviewed the literature on intraoperative neurophysiologic monitoring in the pediatric population and, in the case of spinal cord surgery, recommended that INM be used in all cases. They reviewed the evidence on somatosensory-evoked potentials (SSEPs) and motor-evoked potentials (MEPs) and concluded that MEPs were a better determinant of function during surgery, as SSEPs may be lost during the myelotomy or preserved during surgery, with apparent 'false-negative' plegia noted post-operatively, as they do not accurately reflect the motor pathways which are especially vulnerable during surgery.

Radiation Therapy

A common finding in most reported pediatric series is that gross total resection is superior to partial resection or biopsy with radiation therapy in the treatment of spinal cord tumors, with a few exceptions. Observation with serial imaging is then utilized without adjuvant radiation therapy. Goh et al. (1997) concluded that radical surgery was often enough in the treatment of intramedullary tumors and that radiotherapy should be avoided in the pediatric population secondary to the vulnerability of the immature and growing nervous system, the increased tendency of subluxation and kyphotic deformity after irradiation of the apophyseal plates of the immature skeleton and the risk of development of secondary malignancies. Radiation therapy is therefore, reserved for cases of high-grade astrocytomas (after surgical resection), disseminated disease, and some cases of recurrence after maximal resection. Different modalities of radiation therapy are available including intensity-modulated photon radiotherapy and conformal proton beam radiotherapy, but there is no evidence supporting any one modality over others in the treatment of pediatric spinal cord tumors.

Outcomes

For intramedullary tumors, the histology of the tumor and the patient's pre-operative neurologic function are the most important prognostic factors in predicting outcome in multiple studies including Constantini et al. (2000) and Goh et al. (1997). The extent of initial resection also played a major role in outcome in the series by Crawford et al. (2009) and Nakamura et al. (2008). When including extradural and intradural extramedullary tumors, the patient's presenting neurologic status was the most predictive factor on outcome. This reinforces the need for a swift and accurate diagnosis in these patients.

Immediate post-operative complications may include infection, hematoma formation or CSF fistula. A significant delayed complication of laminectomies is a progressive kyphosis, with anywhere from 25 to 100 % of pediatric patients who undergo laminectomy for resection of an intramedullary tumor developing a deformity. About 15 % of these require a stabilization procedure. Some surgeons preferably use a laminoplasty to approach these tumors as this is thought to preserve the posterior tension band and therefore, a normal alignment. A laminectomy, however, is less time-consuming than a laminotomy, which is an important consideration in what could already be a very lengthy procedure. In a 2008 retrospective study looking at laminectomy vs. laminoplasty for intramedullary tumor removal, McGirt et al. (2008b) found that 5 % of the laminoplasty group required fusion vs. 30 % in the laminectomy group, although there was no difference in functional outcome. Unfortunately, until there are specific multicenter clinical trials for pediatric spinal cord tumors, we will not fully understand the interplay between tumor biology, extent of resection and adjuvant therapies with regards to overall and event free survival.

Future Challenges

The most fundamental challenge in advances in the study of pediatric spinal cord tumors is a lack of understanding of the biology of the tumors and, in most cases, it is naïve to presume that biological pathways that govern the development of these tumors in the spinal cord parallels those in the brain. However, secondary to the rarity of these lesions and the often small tissue size obtained at the time of resection, these handicaps are not easily overcome. Some ongoing trials in the treatment of spinal cord tumors include those on intratumoral chemotherapy, chemotherapy plus peripheral stem cell transplantation and proton-beam radiotherapy. However, large collaborative centers are needed to be able to obtain the power necessary to make significant advances in the understanding and treatment of these tumors.

References

Al-Halabi H, Montes JL, Atkinson J, Farmer JP, Freeman CR (2010) Adjuvant radiotherapy in the treatment of pediatric myxopapilary ependymomas. Pediatr Blood Cancer 55:639–643

Aydin GB, Kutluk MT, Buyukpamukcu M, Akyuz C, Yalcin B, Varan A (2010) Neurological complications of neuroblastic tumors: experience of a single center. Childs Nerv Syst 26:359–365

Bagley CA, Wilson S, Kothbauer KF, Bookland MJ, Epstein F, Jallo GI (2009) Long term outcomes following surgical resection of myxopapillary ependymomas. Neurosurg Rev 32:321–334; discussion 334

Baysefer A, Akay KM, Izci Y, Kayali H, Timurkaynak E (2004) The clinical and surgical aspects of spinal tumors in children. Pediatr Neurol 31:261–266

Benesch M, Weber-Mzell D, Gerber NU, von Hoff K, Deinlein F, Krauss J, Warmuth-Metz M, Kortmann RD, Pietsch T, Driever PH, Quehenberger F, Urban C, Rutkowski S (2010) Ependymoma of the spinal cord in children and adolescents: a retrospective series from the HIT database. J Neurosurg Pediatr 6:137–144

Binning M, Klimo P, Gluf W, Goumnerova L (2007) Spinal tumors in children. Neurosurg Clin N Am 18:631–658

Birch BD, Johnson JP, Parsa A, Desai RD, Yoon JT, Lycette CA, Li YM, Bruce JN (1996) Frequent type 2 neurofibromatosis gene transcript mutations in sporadic intramedullary spinal cord ependymomas. Neurosurgery 39:135–140

Brody AS, Frush DP, Huda W, Brent RL, Radiology AAoPSo (2007) Radiation risk to children from computed tomography. Pediatrics 120:677–682

Central Brain Tumor Registry of the United States, CBTRUS (2011) Primary brain and central nervous system tumors diagnosed in the United States, statistical report, 2004–2007 years data collected. Central Brain Tumor Registry of the United States, Chicago

Chahal S, Lagera JE, Ryder J, Kleinschmidt-DeMasters BK (2003) Hematological neoplasms with first presentation as spinal cord compression syndromes: a 10-year retrospective series and review of the literature. Clin Neuropathol 22:282–290

Chi JH, Cachola K, Parsa AT (2006) Genetics and molecular biology of intramedullary spinal cord tumors. Neurosurg Clin N Am 17:1–5

Constantini S, Houten J, Miller DC, Freed D, Ozek MM, Rorke LB, Allen JC, Epstein FJ (1996) Intramedullary spinal cord tumors in children under the age of 3 years. J Neurosurg 85:1036–1043

Constantini S, Miller DC, Allen JC, Rorke LB, Freed D, Epstein FJ (2000) Radical excision of intramedullary spinal cord tumors: surgical morbidity and long-term follow-up evaluation in 164 children and young adults. J Neurosurg 93:183–193

Crawford JR, Zaninovic A, Santi M, Rushing EJ, Olsen CH, Keating RF, Vezina G, Kadom N, Packer RJ (2009) Primary spinal cord tumors of childhood: effects of clinical presentation, radiographic features, and pathology on survival. J Neurooncol 95:259–269

Ellis JA, Rothrock RJ, Moise G, McCormick PC, Tanji K, Canoll P, Kaiser MG (2011) Primitive neuroectodermal tumors of the spine: a comprehensive review with illustrative clinical cases. Neurosurg Focus 30:E1

Fassett DR, Pingree J, Kestle JR (2005) The high incidence of tumor dissemination in myxopapillary ependymoma in pediatric patients. Report of five cases and review of the literature. J Neurosurg 102:59–64

Goh KY, Velasquez L, Epstein FJ (1997) Pediatric intramedullary spinal cord tumors: is surgery alone enough? Pediatr Neurosurg 27:34–39

Hsu W, Pradilla G, Constantini S, Jallo GI (2009) Surgical considerations of spinal ependymomas in the pediatric population. Childs Nerv Syst 25:1253–1259

Jallo GI, Freed D, Epstein FJ (2004) Spinal cord gangliogliomas: a review of 56 patients. J Neurooncol 68:71–77

Khanna AJ, Wasserman BA, Sponseller PD (2003) Magnetic resonance imaging of the pediatric spine. J Am Acad Orthop Surg 11:248–259

Kothbauer KF (2007) Neurosurgical management of intramedullary spinal cord tumors in children. Pediatr Neurosurg Switz 3:222–235

Lee M, Rezai AR, Freed D, Epstein FJ (1996) Intramedullary spinal cord tumors in neurofibromatosis. Neurosurgery 38:32–37

Lonjon M, Goh KY, Epstein FJ (1998) Intramedullary spinal cord ependymomas in children: treatment, results and follow-up. Pediatr Neurosurg Switz 4:178–183

Lonser RR, Oldfield EH (2006) Spinal cord hemangioblastomas. Neurosurg Clin N Am 17:37–44

McGirt MJ, Chaichana KL, Atiba A, Attenello F, Woodworth GF, Jallo GI (2008a) Neurological outcome after resection of intramedullary spinal cord tumors in children. Childs Nerv Syst 24:93–97

McGirt MJ, Chaichana KL, Atiba A, Bydon A, Witham TF, Yao KC, Jallo GI (2008b) Incidence of spinal deformity after resection of intramedullary spinal cord tumors in children who underwent laminectomy compared with laminoplasty. J Neurosurg Pediatr 1:57–62

Miyazawa N, Hida K, Iwasaki Y, Koyanagi I, Abe H (2000) MRI at 1.5 T of intramedullary ependymoma and classification of pattern of contrast enhancement. Neuroradiology 42:828–832

Nadkarni TD, Rekate HL (1999) Pediatric intramedullary spinal cord tumors. Critical review of the literature. Childs Nerv Syst 15:17–28

Nakamura M, Ishii K, Watanabe K, Tsuji T, Takaishi H, Matsumoto M, Toyama Y, Chiba K (2008) Surgical treatment of intramedullary spinal cord tumors: prognosis and complications. Spinal Cord Engl 4:282–286

Patel U, Pinto RS, Miller DC, Handler MS, Rorke LB, Epstein FJ, Kricheff LL (1998) MR of spinal cord ganglioglioma. AJNR Am J Neuroradiol 19(5):879–887. (PMID 9613504)

Sala F, Krzan MJ, Deletis V (2002) Intraoperative neurophysiological monitoring in pediatric neurosurgery: why, when, how? Childs Nerv Syst 18:264–287

Sheikh BY, Siqueira E, Dayel F (1996) Meningioma in children: a report of nine cases and a review of the literature. Surg Neurol 45:328–335

Wilson PE, Oleszek JL, Clayton GH (2007) Pediatric spinal cord tumors and masses. J Spinal Cord Med 30(Suppl 1):S15–S20

Radiosurgery for Intramedullary Spinal Cord Tumors

19

Anand Veeravagu, Cassie Ludwig, Bowen Jiang, and Steven D. Chang

Contents

Abstract

Intrinsic intramedullary spinal cord tumors (ISCTs) account for 8–10 % of all primary spinal cord tumors, while intramedullary spinal cord metastases (ISCMs) account for less than 5 % of all spinal tumors. While the overall survival of patients with primary ISCTs varies greatly with histology, ISCMs maintain a poor prognosis with a median overall survival of 4 months following diagnosis. Standard of care for both primary ISCTs and ISCMs often includes a combination of surgical resection, conventional external beam radiation therapy (EBRT), steroids, chemotherapy, hormonal therapy, and stereotactic radiosurgery (CyberKnife, LINAC, Gamma Knife). With greater access and application of stereotactic radiosurgery (SRS) in the treatment of ISCTs, data is beginning to accrue regarding patient outcomes. In this chapter, the authors review the present literature surrounding the safety and efficacy of SRS in the treatment of ISCTs and present a sample institutional experience of CyberKnife SRS.

Introduction

Intramedullary spinal cord tumors (ISCTs) may be classified as primary tumors or as metastases originating from a systemic diagnosis. Parsa et al. (2005) reported that ISCTs account for 8–10 % of all primary spinal cord tumors, while

A. Veeravagu • C. Ludwig • B. Jiang
Department of Neurosurgery, Stanford University Medical Center, 300 Pasteur Drive, Room R-225, Stanford, CA 94305, USA

S.D. Chang (✉)
Department of Neurosurgery, Robert C. and Jeannette Powell Professor in the Neurosciences, Stanford University, 300 Pasteur Drive, Room R-225, Stanford, CA 94305, USA
e-mail: sdchang@stanford.edu

M.A. Hayat (ed.), *Tumors of the Central Nervous System, Volume 11*,
DOI 10.1007/978-94-007-7037-9_19,

Edelson et al. (1972) found that intramedullary spinal cord metastases (ISCMs) account for <5 % of all spinal metastases. Intramedullary spinal cord metastases are considered even more rare and tend to present late during the course of a systemic cancer. According to these authors, ~25–35 % of all cases of ISCMs are found in patients with previously unidentified cancer (1972). In a recent 20-year retrospective study of 293 ISCM cases, Sung et al. (2012) found that ISCMs are approximately evenly distributed throughout the three spinal cord segments (cervical 41 %, thoracic 34 %, and lumbar 38 %). The slight increase in distribution in the cervical cord has been suggested to correspond to the greater size and vascular supply of the cord in this region.

Histology

It was reported by Parsa et al. (2005) that histologically, 80–90 % of primary ISCTs are gliomas in origin, of which 60–70 % are ependymomas and 30–40 % are astrocytomas. These are followed in frequency by hemangioblastomas, 3–8 %. Of these, Lonser et al. (2003) stated that 15–25 % are associated with von-Hippel-Lindau (VHL) syndrome, an autosomal-dominant disorder caused by a mutation of the VHL tumor-suppressor gene.

Sung et al. (2012) reported that the most frequent primary sources of ISCMs were lung (47.8 %) and breast (15.9 %) cancers. The next most frequent sources included, but were not limited to, melanoma (5.9 %), renal cell carcinoma (5.6 %), colorectal carcinoma (5.3 %), lymphoma (4.7 %), and drop metastases from a primary brain tumor (3.7 %).

Diagnosis

Recent clinical series have documented the distinct differences in the presentation of ISCTs and ISCMs. The most common presenting symptom for primary ISCTs is pain (88 % of patients) as described by Raco et al. (2005) whereas for ISCMs it is weakness (72 %) as described by Sung et al. (2012). The next most common presenting symptoms for primary ISCTs are motor deficit (55 %), sensory loss (39 %) and sphincter disturbance (15 %). Similar symptoms exist for ISCMs but at different rates, with the next most common presenting symptoms being sensory loss (73 %), local or radicular pain (60 %), bowel and bladder dysfunction (43 %) and Brown-Sequard syndrome (19 %).

Both primary ISCTs and ISCMs are best diagnosed radiographically via contrast-enhanced MRI of the spine (Fig. 19.1). Crasto et al. (1997) described primary ISCTs as often having focal and sometimes holocord spinal expansion while Abul-Kasim et al. (2008) reported that ISCMs tend to be small, isolated, oval-shaped lesions with little spinal cord deformity. However, these features alone cannot be used to definitively diagnose a primary ISCT versus a metastatic lesion.

Prognosis

Unlike ISCMs, the majority of primary ISCTs have benign courses. As they grow in size and extend into local structures, though, they may induce neurologic deficit. In a long-term study by Constantini et al. (2000) of 155 adults and children post-radical excision of ISCT, the 3-, 5-, and 10-year survival rates were 80 % (0.74–0.86), 76 % (0.69–0.83), and 70 % (0.61–0.79), respectively. Intramedullary spinal cord metastases, however, generally harbor an unfavorable prognosis, as they tend to present late in the course of a systemic disease process. The overall survival of ISCMs is poor with a median of 4 months following diagnosis according to Sung et al. (2012).

Treatment

Management options for ISCTs include a combination of open surgical resection, conventional external beam radiation therapy (EBRT), steroids, chemotherapy, hormonal therapy, and SRS (CyberKnife, LINAC, Gamma Knife). It is important to treat primary ISCTs and ISCMs

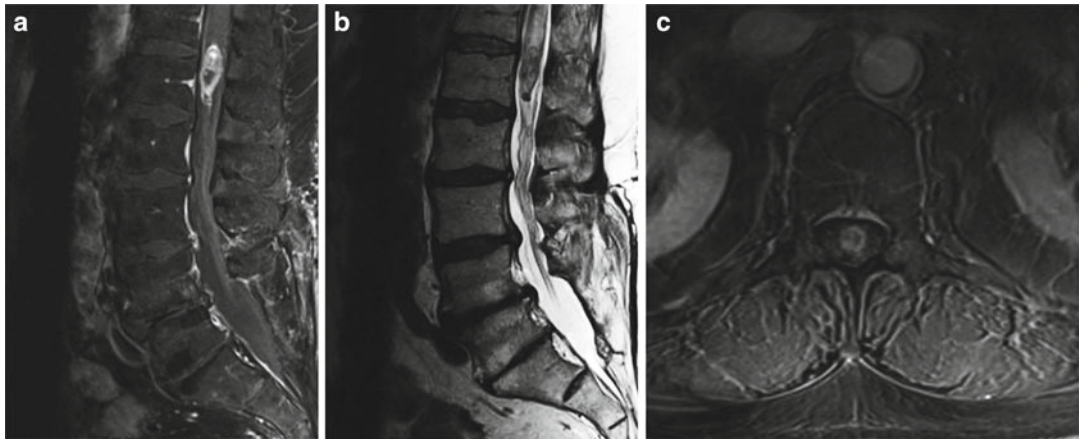

Fig. 19.1 MRI with contrast enhancement at T1/T2 weightings. Pre-SRS MRI studies done by Lieberson et al. (2012) obtained in a patient with adenocarcinoma of the prostate. Sagittal contrast-enhanced T1-weighted (**a**) and T2-weighted (**b**) images show a spindle-shaped, irregularly enhancing, intramedullary lesion of the conus medullaris. The lesion appears partially cystic. Axial contrast-enhanced T1-weighted magnetic resonance image (**c**) demonstrates the same irregularly enhancing lesion

appropriately to both extend overall survival and increase quality of life for palliative treatment. Here, we review the safety and efficacy of EBRT and SRS in the treatment of ISCTs.

Conventional Radiotherapy (EBRT)

Radiation therapy is useful in patients with multiple lesions or those who are poor surgical candidates. Limitations of radiation therapy include adverse side effects such as radiation myelitis, radiation necrosis, spinal kyphosis or subluxation, induction of additional lesions and the potential development of worsened permanent or transient neurologic deficit.

Primary Tumors

Just as in surgery, tumor histology plays an important role in dictating the appropriate use of EBRT in the treatment of ISCTs. Generally favorable for surgical resection, low grade ependymomas are often treated with surgery alone, whereas Schiff and O'Neill (1996) reported that EBRT is indicated for partially resected WHO grade 2 or malignant grade 3 ependymomas. Postoperative EBRT has been shown by Isaacson (2000) to improve survival and local control in intramedullary ependymomas and astrocytomas. For astrocytomas, as complete resection is rare, radiotherapy is indicated for patients with high-grade histology and progressive disease. A retrospective review by Minehan et al. (2009) of 136 patients with intramedullary astrocytomas treated with postoperative radiotherapy found that EBRT improved survival for patients with infiltrative (WHO grades 2–4) but not pilocytic (WHO grade 1) tumors. This may be secondary to the theory reported by Raco et al. (2005) that gross total resection is more likely to be achieved with pilocytic tumors. The role of radiotherapy is limited for hemangioblastomas with the exception of patients with VHL and/or multiple lesions. In these cases, as described by Jeffreys (1975), radiotherapy may help to reduce morbidity and mortality associated with surgical resection.

Metastases

In the appropriate setting, radiation may aid in halting tumor growth and preventing further neurologic decline. Radiation is ideally suited for patients with radiosensitive tumors including lymphoma, breast and small cell lung carcinoma. Lee et al. (2007) and Dam-Hieu et al. (2009)

reported that renal cell carcinoma and melanoma have demonstrated poor radiosensitivity. In the aforementioned study by Schiff and O'Neill (1996), median survival among patients with EBRT was 4 months. Additionally, 35 of the 40 patients maintained the same ambulatory status as admission, three experienced neurological improvement, and two suffered neurological deterioration. In the study by Lee et al. (2007) of 12 patients with ISCMs from breast and lung cancer treated with EBRT only, median survival was 3.9 months and neurologic status deteriorated rapidly in all patients. No patients experienced recovery of motor function.

Stereotactic Radiosurgery

SRS (CyberKnife, LINAC, Gamma Knife) is a noninvasive and convenient way of delivering large and highly conformal doses of radiation to localized, surgically untreatable ISCTs. It minimizes the radiation to healthy tissue with its mobilization, and high degree of collimation. Dose limits to the spinal cord are an important consideration when designing a treatment plan for patients with primary or metastatic ISCTs. Ryu et al. (2007) determined that the dose of intramedullary SRS should be limited to 10 Gy to 10 % of local spinal cord volume, defined as extending 6 mm above and below the superior and inferior limits of SRS target volume. Veeravagu et al. (2012) confirmed this dose-curve as safe and effective in a recent retrospective review of treatment of 11 ISCM in 9 patients with SRS at Stanford University Hospital and Clinics (Stanford, CA, USA).

Current literature on the use of SRS as treatment for both primary and metastatic ISCTs is limited due to the rarity of these tumors. There has yet to be a randomized clinical trial comparing two therapies for spinal cord tumors. The literature on the use of SRS for the treatment of primary ISCTs is limited to expert opinion, case series and literature review. There is only one case report by Sahgal et al. (2007) and two retrospective reviews by Ryu et al. (2003) and Moss et al. (2009). The only studies on the use of SRS for treatment of ISCMs are three case reports by Parikh and Heron (2009), Lieberson et al. (2012) and Dewas et al. (2011) and two small retrospective reviews by Shin et al. (2009) and Veeravagu et al. (2012). Even the most recent comprehensive review by Sung et al. (2012) failed to include a study of SRS as treatment for ISCM. Therefore, it is important to critically evaluate the utility of SRS as treatment for both primary and metastatic ISCTs.

Primary Tumors

In general, surgical resection is indicated for patients with intramedullary ependymomas, as it provides a favorable long-term survival. However, as reported by Clover et al. (1993), only one in four intramedullary ependymomas undergoes complete resection and intramedullary ependymomas may recur locally. In these cases, EBRT used post-operatively has been shown to be effective in providing a favorable long-term outcome, and more recent studies have demonstrated that SRS is similarly effective and safe. These studies are summarized in Table 19.1.

Ryu et al. (2003) performed a retrospective review of ten intramedullary spinal tumors in four men and three women treated with SRS at Stanford University Medical Center (Stanford, CA, USA). These patients received SRS secondary to tumor recurrence, had undergone several previous surgeries, had medical contraindications to surgery or had declined open surgical resection. The patients' mean age was 38 years (range 19–61 years). Seven of the ISCTs were hemangioblastomas, three were ependymomas and four of the five patients with hemangioblastomas also had a diagnosis of VHL. The patients were prescribed a dose of 18–25 Gy (mean 21 Gy) to the tumors in one to three stages. Ryu et al. (2003) found that one ependymoma and two hemangioblastomas were smaller on follow-up neuroimaging, one each at 5-, 10- and 12-month review. The rest of the tumors were stable at follow-up imaging. Thus, SRS appeared to be safe and effective in treatment of both ependymomas and hemangioblastomas when alternative therapies

Table 19.1 SRS on primary ISCTs

Authors & year	Intervention	Number of patients	Number of tumors	Mean marginal dose	Mean size of tumor	Outcome
Moss et al. (2009)	Frame based LINAC and CyberKnife RS	12	16	21 Gy	1.8 cm^3	Among all 16 spinal lesions, 6 regressed, 9 remained unchanged and 1 grew
Sahgal et al. (2007)	CyberKnife RS	1	1	13 Gy	NA	MRI revealed two cysts treated via steroids and cystectomy at 2 and 4 months post-SRS. Following the second cystectomy and gross tumor resection, the patient had no radiographic evidence of cyst or disease and had minimal residual left hand dysfunction
Ryu et al. (2003)	CyberKnife RS	7	10	21 Gy	Only range available: 0.47–9.8 cm^3	Mean radiographic and clinical follow-up duration was 12 months. For ependymomas, 1/3 regressed and 2/3 were stable. For hemangioblastomas, 2/7 smaller and 5/7 were stable

were not feasible. It is important to note, though, that according to Wen et al. (1991), myxopapillary and high-grade cellular intramedullary ependymomas are more likely to recur remotely and therefore may benefit more from wider field irradiation.

Similar to intramedullary ependymomas, surgical resection is primarily indicated for intramedullary hemangioblastomas due to the well-defined margins that often allow for complete resection. However, SRS provides an alternative for patients with recurrent or surgically inaccessible tumors. SRS minimizes long-term radiation toxicity by attempting to spare normal brain and spinal cord parenchyma. Furthermore, the high prevalence of VHL in patients with hemangioblastomas leads to a high likelihood of multiple and recurrent lesions. Multiple surgeries can lead to discomfort and possible morbidity; therefore, SRS is an effective alternative for additional treatment in these cases.

In a long-term retrospective review, Moss et al. (2009) examined the effectiveness of treatment of 92 hemangioblastomas in 31 patients with CyberKnife between 1991 and 2007. Twelve of these patients had 16 spinal cord lesions and were treated with a mean radiation dose to margins of 21 Gy. Whether these were intramedullary was not specified. However, previous research by Lonser et al. (2003) has demonstrated that approximately 25 % of spinal cord hemangioblastomas are completely intramedullary. On follow-up, one of these lesions progressed, while nine stabilized and six regressed. There were no clinical complications but two patients were found to have local edema following SRS. Local control rates at 3 and 5 years were 85 and 82 %, respectively. Nine patients in the study died of causes unrelated to their treated hemangioblastomas. Thus, overall, SRS has been shown to be a safe and effective alternative or adjunct treatment for patients with intramedullary hemangioblastomas.

Metastases

Two retrospective reviews have been completed on the treatment of ISCMs with SRS. The most recent was the aforementioned review of the treatment of 11 ISCM in 9 patients with SRS at Stanford University Hospital and Clinics by Veeravagu et al. (2012). The patients had a

median of 63 years (range 33–77 years), tumor size had a median of 0.48 cm^3 (range 0.12–6.4 cm^3), and seven patients were female while two were male. Five metastases were from breast carcinoma, two from non-small cell lung cancers, one was a cystic adenocarcinoma and one was from an epithelioid hemangioepithelioma. All patients had progressive systemic metastases and three had simultaneous metastatic lesions in the brain at the time of presentation. Patients were treated with a median of 21 Gy (range 14–27 Gy) in one to five fractions and dexamethasone was administered to all patients at the time of treatment. One patient remained alive at the time of study, 14 months after therapy while eight died with a median survival of 4.1 months (range 1.1–9.1 months). This is similar to the length of survival found by Sung et al. (2012) in patients with ISCMs who received surgery and/or EBRT. The poor survival is largely due to systemic disease burden and the fact that ISCMs appear late in the disease process. Thus, the authors concluded that SRS appears to be safe and to have prevented local recurrences.

Prior to this study was a smaller retrospective review of nine patients with four intradural extramedullary and seven intramedullary lesions reported by Shin et al. (2009) between 2001 and 2008. The patients had a median of 50 years (range 14–71 years) and six patients were female while three were male. Three metastases originated in the breast, two in the lung, one in the brain, one in the kidney and one was dermal. All patients suffered from simultaneous metastatic lesions in the brain, and among them, two also had progressive systemic metastases. Patients were treated with a median of 13.8 Gy (range 10–16 Gy), however the spinal cord dose exceeded the guideline of 10 Gy to the 10 % volume. Shin et al. (2009) allowed a higher radiation dose to the spinal cord directly adjacent to tumor. The study is complicated by the fact that chemotherapy was continued post-SRS in patients capable of safely accepting treatment. The median survival time after SRS was 8 months (range 2–19 months) and overall tumor control was achieved in eight cases (89 %). No radiation toxicity was detected clinically, however, the survival may be too short to detect such toxicity.

Two case studies have also been written on the treatment of ISCMs with SRS. The most recent, by Lieberson et al. (2012) describes a 68-year-old man with a Gleason grade 4 + 3 prostate adenocarcinoma who presented with new-onset saddle anesthesia and fecal incontinence. MRI showed a spindle-shaped intramedullary lesion in the conus medullaris that was subsequently treated with a 27 Gy dose of SRS. At 3 months follow-up the patient remained neurologically stable without new neurologic deficits. Thus, the authors concluded that SRS might be as safe and effective as conventional EBRT while reducing risk of toxicity to normal cord parenchyma.

Parikh and Heron (2009) similarly reported treating a 50-year-old with a C5 ISCM from renal cell carcinoma with SRS. The patient presented with bilateral should pain and upper extremity paresthesias but was a poor surgical candidate due to his performance status and anatomic configuration of his spinal cord changes. The patient experienced progressive symptoms in spite of previous EBRT and so was treated with SRS at a dose 15 Gy delivered in three fractions over 5 days. The patient was still alive and fully functional with no pain 26 months following treatment. However, he still experienced rare paresthesias in his fingers and toes as well as tinnitus and balance difficulties. This study, along with others summarized in Table 19.2, reveal the role of SRS in ISCM tumor control or regression with low complication rates.

Alternative Treatments

Surgical Resection

Surgical resection carries the benefit of good long-term outcomes for both primary ISCTs and ISCMs. Disadvantages to surgery include a possible impaired quality of life, high risk of post-operative neurological deficit and lack of complete resection, which may lead to recurrence. There are also many medical contraindications to surgery that may prevent it from being a viable treatment option. Furthermore, there is a risk of paralysis and a concern for post-operative spinal deformity especially in the pediatric population.

Table 19.2 SRS on ISCMs

Authors & year	Intervention	Number of patients	Number of tumors	Mean marginal dose	Mean size of tumor	Outcome
Veeravagu et al. (2012)	CyberKnife RS	9	11	21 Gy	0.48 cm^3	Tumor size decreased in 2 patients and was stable in 2 patients. Of 8 deceased, survival ranged from 1.1 to 9.1 months (median 4.1 months, SD 2.6).
Dewas et al. (2011)	CyberKnife RS	1	1	20 Gy	NA	Two months after the end of treatment, neurological examination remained unchanged. Radiographic evidence showed a stable lesion 2 months post-SRS. The patient was still alive 11 months post-SRS
Lieberson et al. (2012)	CyberKnife RS	1	1	27 Gy	NA	Patient remained neurologically stable with no new deficits or lesions at 3 months follow-up
Shin et al. (2009)	Novalis RS	9	11	13.8 Gy	3.4 cm^3	Tumor control was achieved in 8 cases. Tumors were drastically smaller in 2/9 cases, partially reduced in 3/9, stable in 3/9 and larger in 1/9
Parikh and Heron (2009)	Gamma Knife RS	1	1	15 Gy	NA	Twenty six months following treatment, the patient was still alive, fully functional, and reported no pain and rare paresthesias in fingers and toes. He had decreased head, neck, and shoulder pain 1 month post-treatment. He reported tinnitus and balance difficulties, but no other new neurological deficits

Tumor histology plays an important role in dictating best treatment option for patients with primary ISCTs. It was reported by Cooper and Epstein (1985) that surgery is the most effective treatment of ependymomas, with local control rates of 90–100 %. One retrospective review by Wen et al. (1991) of 33 patients showed a 10-year survival rate of 86 % after treatment with surgery and/or EBRT. However, Clover et al. (1993) found that a majority of patients undergo subtotal resection necessitating additional forms of treatment. Complete resection is rare for astrocytomas. Nevertheless, a recent case report by Ewelt et al. (2010) described the cordectomy of an anaplastic astrocytoma ISCM resulting survival greater than 15 months. Similar to ependymomas, resection is the primary treatment for intramedullary hemangioblastomas and has proven highly effective as described by Eskridge et al. (1996) and Montano et al. (2008).

In cases of ICSMs, surgery is often used for younger patients who otherwise maintain good performance status but suffer progressive neurological deficits and/or when tissue diagnosis is necessary. It is more likely to be used when there are limited systemic metastases and in cases considered unusual for the primary tumor. Sung et al. (2012) found that survival in surgical patients is 6 months, whereas survival in conservatively managed patients is 5 months. In a retrospective review by Dam-Hieu et al. (2009) of 18 patients with ISCM treated with surgery in a single institution in France, median survival was 6.1 months. Gasser et al. (2005) found that in a retrospective

review of 13 patients with ISCM, neurological status remained stable in 11 patients and worsened in 2. Median survival was similarly 7.1 months. In another study by Schiff and O'Neill (1996), 35 patients with ISCM underwent EBRT whereas five underwent surgery. Median survival among surgical patients was 8 months whereas median survival among patients with EBRT was 4 months. Therefore, when feasible, it appears that surgery may extend overall survival in patients with ISCMs.

Discussion

The treatment of ISCTs continues to necessitate a multi-dimensional, dynamic approach catered to the status of each individual patient. While complete tumor resection may lead to an increase in overall survival, this may not always be feasible pending anatomic location and medical comorbidities. Thus, adjuvant radiation, chemotherapy and hormone therapy have been utilized to reduce risk of surgical complications, prevent recurrence and increase quality of life. Literature increasingly demonstrates that SRS is an effective and safe alternative to conventional radiation. It allows for the delivery of high dose, highly conformal radiation to lesions with a reduction in radiation exposure to normal tissue. In several multi-institutional studies and case series, SRS has been found to be associated with tumor control and symptomatic improvement without adverse radiation-related side effects.

References

Abul-Kasim K, Thurnher MM, McKeever P, Sundgren PC (2008) Intradural spinal tumors: current classification and MRI features. Neuroradiology 50(4):301–314

Clover LL, Hazuka MB, Kinzie JJ (1993) Spinal cord ependymomas treated with surgery and radiation therapy. A review of 11 cases. Am J Clin Oncol 16(4): 350–353

Constantini S, Miller DC, Allen JC, Rorke LB, Freed D, Epstein FJ (2000) Radical excision of intramedullary spinal cord tumors: surgical morbidity and long-term follow-up evaluation in 164 children and young adults. J Neurosurg 93(2 Suppl):183–193

Cooper PR, Epstein F (1985) Radical resection of intramedullary spinal cord tumors in adults. Recent experience in 29 patients. J Neurosurg 63(4): 492–499

Crasto S, Duca S, Davini O, Rizzo L, Pavanello IG, Avataneo T, Cirillo S, Regge D, Soffietti R (1997) MRI diagnosis of intramedullary metastases from extra-CNS tumors. Eur Radiol 7(5):732–736

Dam-Hieu P, Seizeur R, Mineo JF, Metges JP, Meriot P, Simon H (2009) Retrospective study of 19 patients with intramedullary spinal cord metastasis. Clin Neurol Neurosurg 111(1):10–17

Dewas S, Le Rhun E, Duhem R, Dansin E, Prevost B, Lartigau E (2011) Solitary intramedullary metastasis from malignant pleural mesothelioma treated with CyberKnife(R): a case report. Rev Neurol 167(2): 185–186

Edelson RN, Deck MDF, Posner JB (1972) Intramedullary spinal cord metastases. Neurology 22(12):1222

Eskridge JM, McAuliffe W, Harris B, Kim DK, Scott J, Winn HR (1996) Preoperative endovascular embolization of craniospinal hemangioblastomas. AJNR Am J Neuroradiol 17(3):525–531

Ewelt C, Stummer W, Klink B, Felsberg J, Steiger HJ, Sabel M (2010) Cordectomy as final treatment option for diffuse intramedullary malignant glioma using 5-ALA fluorescence-guided resection. Clin Neurol Neurosurg 112(4):357–361

Gasser T, Sandalcioglu IE, El Hamalawi B, van de Nes JA, Stolke D, Wiedemayer H (2005) Surgical treatment of intramedullary spinal cord metastases of systemic cancer: functional outcome and prognosis. J Neurooncol 73(2):163–168

Isaacson SR (2000) Radiation therapy and the management of intramedullary spinal cord tumors. J Neurooncol 47(3):231–238

Jeffreys R (1975) Clinical and surgical aspects of posterior fossa haemangioblastomata. J Neurol Neurosurg Psychiatry 38(2):105–111

Lee SS, Kim MK, Sym SJ, Kim SW, Kim WK, Kim SB, Ahn JH (2007) Intramedullary spinal cord metastases: a single-institution experience. J Neurooncol 84(1): 85–89

Lieberson RE, Veeravagu A, Eckermann JM, Doty JR, Jiang B, Andrews R, Chang SD (2012) Intramedullary spinal cord metastasis from prostate carcinoma: a case report. J Med Case Rep 6(1):139

Lonser RR, Weil RJ, Wanebo JE, Devroom HL, Oldfield EH (2003) Surgical management of spinal cord hemangioblastomas in patients with von Hippel—Lindau disease. J Neurosurg 98(1): 106–116

Minehan KJ, Brown PD, Scheithauer BW, Krauss WE, Wright MP (2009) Prognosis and treatment of spinal cord astrocytoma. Int J Radiat Oncol Biol Phys 73(3):727–733

Montano N, Doglietto F, Pedicelli A, Albanese A, Lauretti L, Pallini R, Lauriola L, Fernandez E, Maira G (2008) Embolization of hemangioblastomas. J Neurosurg 108(5):1063–1064

Moss JM, Choi CY, Adler JR, Soltys SG, Gibbs IC, Chang SD (2009) Stereotactic radiosurgical treatment of cranial and spinal hemangioblastomas. Neurosurgery 65(1):79–85; discussion 85

Parikh S, Heron DE (2009) Fractionated radiosurgical management of intramedullary spinal cord metastasis: a case report and review of the literature. Clin Neurol Neurosurg 111(10):858–861

Parsa A, Chi J, Acosta F, Ames C, McCormick P (2005) Intramedullary spinal cord tumors: molecular insights and surgical innovation. Clin Neurosurg 52:76–84

Raco A, Esposito V, Lenzi J, Piccirilli M, Delfini R, Cantore G (2005) Long-term follow-up of intramedullary spinal cord tumors: a series of 202 cases. Neurosurgery 56(5):972–981; discussion 972–981

Ryu SI, Kim DH, Chang SD (2003) Stereotactic radiosurgery for hemangiomas and ependymomas of the spinal cord. Neurosurg Focus 15(5):E10

Ryu S, Jin JY, Jin R, Rock J, Ajlouni M, Movsas B, Rosenblum M, Kim JH (2007) Partial volume tolerance of the spinal cord and complications of single-dose radiosurgery. Cancer 109(3):628–636

Sahgal A, Chou D, Ames C, Ma L, Lamborn K, Huang K, Chuang C, Aiken A, Petti P, Weinstein P, Larson D (2007) Image-guided robotic stereotactic body radiotherapy for benign spinal tumors: the University of California San Francisco preliminary experience. Technol Cancer Res Treat 6(6):595–604

Schiff D, O'Neill BP (1996) Intramedullary spinal cord metastases: clinical features and treatment outcome. Neurology 47(4):906–912

Shin DA, Huh R, Chung SS, Rock J, Ryu S (2009) Stereotactic spine radiosurgery for intradural and intramedullary metastasis. Neurosurg Focus 27(6):E10

Sung W, Sung M, Chan J, Manion B, Song J, Dubey A, Erasmus A, Hunn A (2012) Intramedullary spinal cord metastases: a 20-year institutional experience with a comprehensive literature review. World Neurosurg 79:576–584

Veeravagu A, Lieberson RE, Mener A, Chen YR, Soltys SG, Gibbs IC, Adler JR, Tian AG, Chang SD (2012) CyberKnife stereotactic radiosurgery for the treatment of intramedullary spinal cord metastases. J Clin Neurosci 19(9):1273–1277

Wen BC, Hussey DH, Hitchon PW, Schelper RL, Vigliotti AP, Doornbos JF, VanGilder JC (1991) The role of radiation therapy in the management of ependymomas of the spinal cord. Int J Radiat Oncol Biol Phys 20(4):781–786

Novalis Spinal Radiosurgery

20

David Ly, Christopher J. Anker, and Meic H. Schmidt

Contents

Abstract

Stereotactic radiosurgery (SRS) is a noninvasive approach to delivering high doses of conformal radiation. The majority of spinal tumors are metastatic lesions, and it is estimated that 30–90 % of cancer patients will develop metastatic spinal lesions. The potential benefit of spinal SRS may arise in cases of reirradiation where conformal dose distribution and a noninvasive approach are desired. Current techniques require a high degree of precision with patient simulation. Retrospective studies have favored a spinal SRS fractionation schema of ≥14 Gy in one fraction in previously unirradiated patients, with the majority of 1-year local and pain control estimates above 80 %. Radiation-induced myelopathy from spinal SRS is exceedingly rare, but may occur 6–12 months after treatment. Follow-up after spinal SRS is important since intervention after radiation-induced myelopathy may alleviate neurologic symptoms. Randomized clinical trials are examining the feasibility and ability of spinal SRS to deliver improved outcomes for pain relief compared with conventional three-dimensional conformal external beam radiotherapy.

D. Ly • C.J. Anker
Department of Radiation Oncology,
Huntsman Cancer Hospital, University of Utah,
1950 Circle of Hope, Salt Lake City, UT 84112, USA

M.H. Schmidt (✉)
Department of Neurosurgery, Huntsman Cancer Institute, University of Utah, 175 N. Medical Drive East, Salt Lake City, UT 84132, USA
e-mail: meic.schmidt@hsc.utah.edu

Introduction

History of Spinal Irradiation

The development of stereotactic radiosurgery (SRS) arose from the desire to ablate intracranial

M.A. Hayat (ed.), *Tumors of the Central Nervous System, Volume 11*,
DOI 10.1007/978-94-007-7037-9_20,

targets with a nonsurgical approach. It was thought that "stereotaxis," or localization of the target lesion relative to a three-dimensional system, would be required. In 1951, Dr. Leskell published the first account of SRS using a noninvasive approach. His idea involved multiple cross-firing beams of radiation aimed at a central target. Stereotaxis of the target lesion utilized a frame. Refinements of this instrument in the 1960s utilized proton beams and, subsequently, Cobalt-60. The rise of SRS in intracranial applications prompted the development of extracranial radiosurgical applications, which are termed stereotactic body radiation therapy (SBRT). The first use of SRS in the spine was described by Hamilton et al. (1995). In a cohort of patients previously irradiated with spinal cord tolerance doses, patients were treated to 10 Gy in a single fraction utilizing a linear accelerator (LINAC)-based treatment. Further progression of methods to deliver SRS, including advances in target delineation and dosimetric calculations, have led to the increasing use of radiosurgery.

The American Society of Radiation Oncology (ASTRO) applies the term SRS only to intracranial and spinal targets, as opposed to SBRT, which applies to extracranial or extraspinal targets. According to the American College of Radiology (ACR) and ASTRO guideline definitions, SRS is defined as involving between one and five high-dose fractions. A stabilizing device that identifies a target relative to a reference system is necessary so that delivery of treatment is accurate to within 1 mm (ASTRO, 2011).

Radiobiology

Radiation is thought to affect cells through DNA damage by direct and indirect mechanisms. Radiation causes direct DNA damage through the breaking of the bonds that hold DNA together. Radiation can also cause indirect DNA and cellular damage through the creation of free radicals. These highly reactive molecules have an unpaired electron that can cause structural changes and create harmful chemical compounds. When conventional three-dimensional conformal external beam radiation therapy (3D-CRT) is given at 1.8–2.0 Gy per fraction, the DNA damaged by the above processes contributes to cell death when the cells undergo mitosis. Although mitotic cell death predominates, cells may also experience apoptosis. Cellular mechanisms of single-strand break repair are efficient and therefore represent sublethal damage. Double-strand breaks are irreversible and lethal; this is described by a linear quadratic formula by the following model:

$$SF = e^{-(\alpha D + \beta D^2)} \tag{1}$$

where SF is the fraction of cells surviving a dose of radiation (D) expressed in Gy, α is the coefficient related to a single-event cell killing, and β is the coefficient related to cell killing through the interaction of sublethal events. The proportion of the relative contributions of these two components to overall cell kill is the α/β ratio. Conventional 3D-CRT is typically fractionated, meaning that the total radiation dose is given in multiple fractions. By fractionating the dose, normal tissues (which typically have a lower α/β than tumor cells) receive a lower dose and have time to recover before the next dose (Fig. 20.1). When the number of fractions increases, however, the total dose also needs to be increased to obtain the same biological effect. In spinal SRS, a lower overall dose is used because the treatment is delivered in one to five fractions.

The cellular mechanisms that occur in radiosurgery are not well understood, but it appears that radiation dose plays a role. A study has shown that at high doses of radiation (18–20 Gy), tumor cell death is independent of endothelial apoptosis, unlike in doses of less than 10 Gy. The traditional methods that are used to calculate biologic equivalent dose (BED) no longer apply when higher doses of radiation per fraction are delivered, as in SRS. The linear quadratic model of BED (below) overestimates the effect of radiation at high doses (Fig. 20.2). In this equation,

$$BED\left(Gy_{\frac{\alpha}{\beta}}\right) = nd\left(1 + \frac{d}{\frac{\alpha}{\beta}}\right) \tag{2}$$

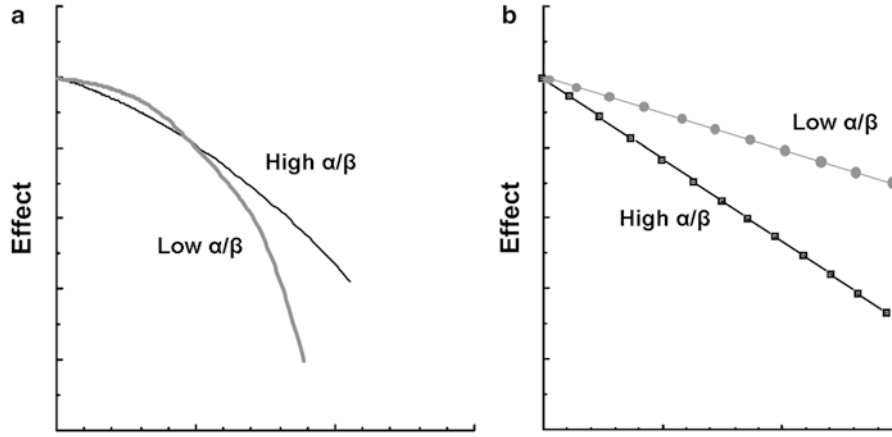

Fig. 20.1 (**a**) Graph showing the biological effect (i.e., cell survival) for a single fraction as dose is increased for low and high α/β tissues. (**b**) Graph showing the biological effect of fractionated treatment as dose is increased for low and high α/β tissues. By fractionating the dose as seen in (**b**), the small advantage observed in the low-dose range sparing low α/β tissues as depicted in (**a**) is amplified (Figure is courtesy of Anker and Shrieve, 2009)

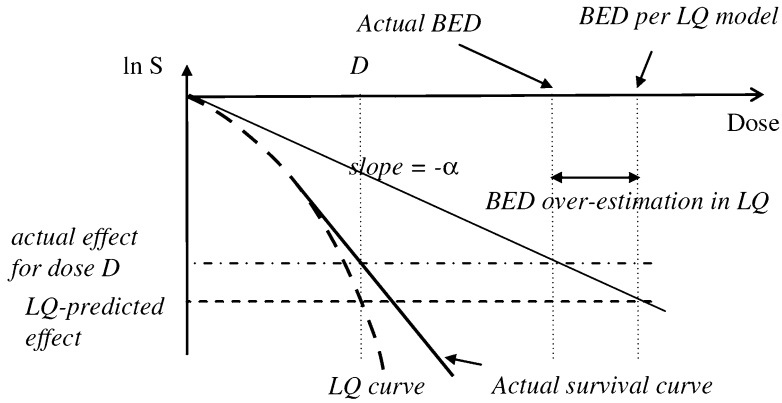

Fig. 20.2 Graph showing how the biological effect as modeled by the linear quadratic (LQ) equation [2] overestimates the actual biological effect at higher radiation doses as determined by actual survival curves by in vitro experiments (Figure is courtesy of Park et al. 2008)

BED is expressed in $Gy_{\alpha/\beta}$ to indicate that it should be used only to compare effects in tissues with the same α/β, *n* is the number of fractions, *d* is the radiation dose, and *nd* is, therefore, the total radiation dose (*D*). Because this equation is an overestimate at high doses, a universal survival curve was developed to better depict the relationship between biologic effect and higher radiation doses (Park et al., 2008). The universal survival curve was based on laboratory and clinical data, but has not been fully validated as only prospective trials can fully characterize the actual BED.

Despite the potential inaccuracies, the standard BED equation is often algebraically manipulated to describe various spinal SRS regimens. Single-fraction BED (SFBED) and single-session equivalent dose (SSED) are different nomenclatures that both describe the BED of a treatment course if the radiotherapy is given in a single fraction, typically denoted with the units [Gy_3].

Another common method to describe the BED of a spinal SRS regimen is with the equivalent BED for a radiotherapy course delivered in 2-Gy fractions, using an α/β ratio of 2. This is denoted by the units [$Gy_{2/2}$].

Indications for Spinal Radiosurgery

External beam radiation therapy may be indicated for the palliation of spinal bone or soft tissue primary tumors or metastases to the spine. Palliation may be beneficial for patients with neurological symptoms, pain, or impending fracture. Spinal SRS may be indicated when the advantages of SRS over traditional 3D-CRT are preferred, namely, when conformal dose distribution and a shortened course of treatment are important. A more conformal dose distribution can limit dose to organs at risk (OARs) such as the spinal cord, kidneys, heart, and lungs. In addition, the conformality of SRS can treat limited parts of a vertebral body to spare bone marrow, which may be helpful in patients with anemia, thrombocytopenia, or neutropenia. A shortened course of treatment may be beneficial to patients who have limited access to radiation therapy or have a limited life expectancy. Some data suggest that compared with standard 3D-CRT, spinal SRS may decrease time to pain relief, increase the durability of pain relief, and more effectively treat pain (Ryu et al., 2008). A Phase III clinical trial (RTOG 0631) has been designed to investigate the validity of these potential benefits.

Retrospective studies have examined the feasibility of using spinal SRS in patients with spinal cord compression and in cases of spinal reirradiation (Choi et al., 2010; Garg et al., 2011; Mahadevan et al., 2011; Sahgal et al., 2012). Consideration for spinal SRS as a definitive therapy may be made in patients with spinal cord compression who are poor surgical candidates. Spinal SRS has also been used in the postoperative setting, with results showing that it is well tolerated with minimal morbidity (Moulding et al., 2010). Patients with previous irradiation to the spine at or close to spinal cord tolerance may also benefit from spinal SRS. Spinal SRS may be considered in patients with extenuating physical or social limitations in which a shorter course of treatment is favored. There are some situations in which the use of spinal SRS should be seriously weighed. The ASTRO Task Force suggests that SRS not be the primary mode of treatment for tumors of the vertebral body in patients with metastatic epidural spinal cord compression (MESCC) (ASTRO, 2011). Recurrent or progressive vertebral body lesions, which have been previously irradiated, may benefit from SRS; however, the Task Force suggests that the use of SRS for vertebral body lesions be considered in the context of a clinical trial (ASTRO, 2011).

Metastatic Tumors of the Spine

The spine is the most frequent site of metastatic disease after pulmonary and/or hepatic metastases (Sciubba and Gokaslan, 2006). It is estimated that between 30 and 90 % of patients with a malignancy will develop metastases to the spine (Sciubba and Gokaslan, 2006). Metastatic epidural spinal cord compression, defined as displacement of the spinal cord, is estimated to occur in 5–10 % of patients (Sciubba and Gokaslan, 2006). The most common primary tumors that metastasize to the spine include breast (16.5 %), lung (15.6 %), and prostate (9.2 %) (Petteys et al., 2009). Spinal metastases may be classified by their anatomic location including intramedullary, intradural-extramedullary, or extradural. Extradural metastases are the most common form, which can present as disease in the vertebral body with possible extension into the posterior elements. The most common location of metastatic tumors of the spine is within the thoracic region, where 60 % of MESCC events occur. This is followed by the lumbosacral region at 25, and 15 % in the cervical region (Cole and Patchell, 2008). The location, extent of disease and symptoms of the patient will guide management of their disease.

Primary Tumors of the Spine

Primary tumors of the spine are much more rare than metastatic lesions and are estimated to account for 10 % of all malignant tumors of the spine (Ropper et al., 2012). Primary malignant tumors of the spine can arise from hematologic, soft tissue, or osseous origin. Of those with osseous origins, the most common are chordomas, which represent a fifth of all cases. Less common osseous tumors are chondrosarcoma, Ewing sarcoma, and osteosarcoma. Multiple myeloma may account for up to 26 % of vertebral body tumors (Ropper et al., 2012). Soft tissue tumors may include soft tissue sarcomas and benign tumors of the spine such as bone cysts, chondromas, hemangiomas, osteoid osteomas, and hemangioblastomas. Intradural tumors are very rare with limited data on incidence but may include astrocytomas, ependymomas, neurofibromas, schwannomas, hemangiomblastomas, and meningiomas. A multidisciplinary approach to treatment is recommended including input from neurosurgery, medical oncology, and radiation oncology.

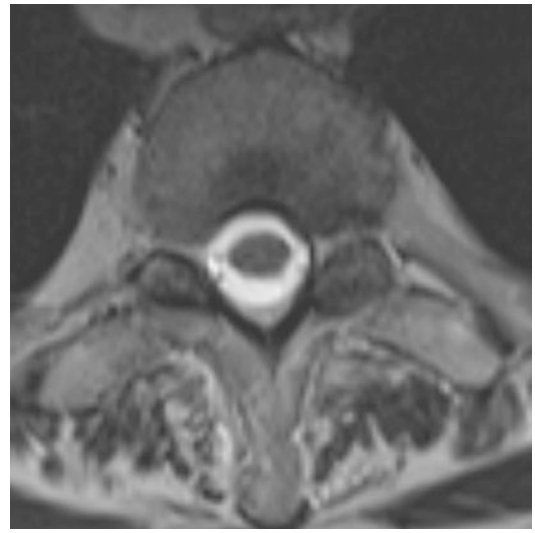

Fig. 20.3 T2-weighted axial MR image of the thoracic spine showing mild compression of the anterior left thecal sac by an extradural metastasis, with 5 mm of space to the cord

Treatment of the Spine

Non-radiosurgical Treatments

Surgery

For primary extradural and epidural tumors of the spine, surgery is considered the primary mode of treatment as part of a multidisciplinary approach. The surgical goal is for a gross total tissue removal by either an en-bloc resection or piecemeal resection. En-bloc resections may be favored because of a lower recurrence rate; however, adjuvant therapy should be considered since recurrence rates are still high. Intradural spine tumors are less common, but since they arise from the meninges or dura, neurologic function may be prioritized over total tissue removal.

In the case of metastatic tumors of the spine, it is important to determine if there is neurologic compromise, spinal instability, or MESCC. In these cases, stabilizing and/or decompressive surgery may be favored. Spinal instability may be assessed using a spinal instability neoplastic score (SINS), which scores instability by location, pain, type of bone lesion, degree of spinal alignment, vertebral body collapse, and posterolateral involvement (Fourney et al., 2011). A score of greater than 13 denotes instability, while a score of greater than 7 warrants neurosurgical consultation. This classification system was validated using clinical and radiographic data with a sensitivity of 95.7 %. To determine the degree of MESCC, a grading system has been developed. Bilsky et al. (2010) validated the grading scale using T2-weighted magnetic resonance (MR) images; this grading scale may aid in determining surgical and radiosurgical candidates. Patients whose MESCC is designated Grade 1a (epidural impingement without deformation of the thecal sac) or Grade 1b (deformation of the thecal sac but without spinal cord abutment) are often eligible for SRS, as long as the spinal cord can be kept within specified dose limits. This is often achievable when there is at least 3 mm of space from the thecal sac edge to the spinal cord (Fig. 20.3).

For years after the introduction of 3D-CRT as a therapeutic modality, patients with MESCC were treated with 3D-CRT alone because studies did not

show additional benefit with laminectomy. After the development of more advanced surgical techniques, Patchell et al. (2005) demonstrated that patients who had decompressive surgery followed by 3D-CRT retained their ability to walk for 122 days whereas those treated with 3D-CRT alone retained the ability only 13 days ($p=0.003$). In addition, patients who had surgery in addition to 3D-CRT were continent for longer (156 days vs. 17 days; $p=0.016$) and had an increase in overall survival (OS) from 100 to 126 days ($p=0.033$). On the basis of the results of this randomized trial, patients with MESCC should be evaluated by a neurosurgeon for decompressive surgery. Resection of metastatic spinal tumors without spinal cord compression is not favored in most circumstances unless the diagnosis is questioned or if there is neurologic compromise or spinal instability.

External Beam Radiotherapy

The effectiveness of 3D-CRT in relieving pain has been estimated at between 50 and 75 % for spinal lesions. Standard 3D-CRT schedules include 8 Gy in 1 fraction, 20 Gy in 5 fractions, 30 Gy in 10 fractions, and 37.5 Gy in 15 fractions. Previous trials that have randomized patients with skeletal metastases have shown equivalency in pain relief for single fraction (i.e., 8 Gy) versus multifraction schedules, and subgroup analyses have not shown differences in effectiveness in the case of spinal metastases (Yarnold, 1999). Limited studies have investigated the use of 3D-CRT for reirradiation of spinal lesions. One series of eight patients initially treated to a median of 38 Gy were retreated to a median of 30 Gy (Grosu et al., 2002). Complete pain relief was experienced in four of the seven patients who had reirradiation because of pain, and retreatment was tolerated with no acute or long-term side effects; however, because of the limited series size, the authors could not give clear recommendations on dose and scheduling. On the basis of reirradiation data from 40 patients, Nieder et al. (2006) completed an analysis using a linear-quadratic model. For reirradiation of the spinal cord, they recommended a BED limit of 98 Gy_2 per each treatment course, a 6-month elapsed time period between the two treatment courses, and a total BED $\leq$135.5 Gy_2. The authors noted that only 1 out of 30 patients developed myelopathy using these guidelines, which manifested as hemihypoesthesia.

Radiosurgical Treatments

Non-LINAC-Based Treatments

The earliest SRS utilized a frame-based system for intracranial targets, which acted as a fiducial for target localization and delivery of dose. Multiple cobalt sources focused their beamlets of radiation through a collimator helmet. The helmet was surgically attached to the skull to ensure that the target was stationary. Although the risks of this Gamma Knife SRS procedure were low, because the frame-based system was fixed to a collimator helmet, extracranial lesions could not be treated.

LINAC-Based Treatments

Because of the limitations of non-LINAC based systems, the focus for treatment of extracranial lesions shifted to LINAC-based systems. Hamilton et al. (1995) described the novel use of SRS utilizing an invasive rigid frame affixed to the spine and a modified LINAC to treat metastatic tumors of the spine. The invasive nature of this set-up, however, was a detriment, and frameless LINAC-based systems were subsequently developed for SRS treatment. The first account of a noninvasive fixation system utilizing a LINAC for SRS of extracranial targets was published by Lohr et al. (1999). The two main systems that have been developed for LINAC-based SRS are the CyberKnife and the Novalis systems. Spinal SRS can also be accomplished by other LINAC-based systems such as the TrueBeam by Varian, Tomotherapy by Tomotherapy, and Synergy by Elekta.

The CyberKnife system was initially developed to treat intracranial targets, but because of its flexibility, it has also been used to treat spinal targets. The highlights of the CyberKnife system include the compactness of the LINAC arm, which allows for maneuverability and real-time imaging that compensates with adaptive beam

pointing. The treatment of each spinal lesion utilizing the CyberKnife system divides each radiation fraction into 100 or more beams called nodes. The system will compare the target and send feedback for corrective directions for each node. Depending on the frequency and quantity of corrections that are made, the system will make more or less frequent corrections. Extracranial SRS has also been achieved utilizing the Novalis system, which is a LINAC that utilizes a multileaf collimator to shape the beam. It has capabilities to conform the beam shape while delivering radiation in the form of an arc. The Novalis system has a single-energy, 6-MV photon beam. In addition, its patient positioning system uses keV imaging, which is then fused to reference images. Deviations in isocenter position are determined by the ExacTrac system, which uses infrared cameras to detect fiducial markers; the couch can then automatically reposition using the deviations noted from the ExacTrac system. Both the Novalis and the CyberKnife treatment systems are accurate to within approximately 1 mm, but because it has a single collimator that can dynamically conform to the entire target volume, beam-on times for the Novalis system are shorter than for the CyberKnife. This review will focus on the Novalis-based treatment system, and will describe the techniques that are employed to perform SRS in depth.

Clinical Considerations

Stereotactic radiosurgery of the spine may be considered in patients with 1–3 regions of MESCC or painful spinal metastases (defined as Numerical Rating Pain Scale scores ≥5) with a maximal regional involvement of two contiguous vertebral bodies, as recommended in RTOG 0631 (http://www.rtog.org/ClinicalTrials/ProtocolTable/StudyDetails.aspx?study=0631). In addition, in certain cases, SRS may considered as a boost to 3D-CRT in patients who have diffuse spine metastases but have focal areas that have MESCC or severe pain. Although a computed tomography (CT) scan may sufficiently show a vertebral body, epidural, or dural-based tumor, MR imaging should be performed for any patient undergoing SRS as it is more sensitive in showing the extent of the lesion. Furthermore, the full extent of disease throughout the length of the spine is better defined with MR imaging, and more extensive disease may be more appropriately treated with conventional fractionated radiation. Should spinal cord compression be of concern, MR imaging of the spine best assists in determining spinal canal compromise. In cases of spinal cord compression, neurosurgeons should be involved in the assessment of the patient, as previous studies have shown improved outcomes with surgery (Patchell et al., 2005). At the initial consultation, a history and physical examination should be performed. During the history, it is important to understand whether the patient is symptomatic (back/leg pain, neurologic symptoms, urinary retention, saddle anesthesia, fecal incontinence, etc.) and how long symptoms have lasted. The patient's comorbidities, social situation, and performance status should be carefully assessed. The examination should include a complete neurologic and musculoskeletal examination. Spinal SRS should generally be considered in the context of a clinical trial. Previous studies have shown the feasibility of spinal SRS in patients with spinal cord compression (Ryu et al., 2010) and reirradiation of the spine (Choi et al., 2010; Garg et al., 2011; Mahadevan et al., 2011; Sahgal et al., 2012). Steroids should be administered immediately in patients with spinal cord compression. Analgesics should be optimized in those with pain. Evaluation of a patient's performance status, expected tolerance of treatment, extent of disease, and projected survival should be completed when considering spinal SRS. Relative exclusion criteria include a history of connective tissues disorder, inability to tolerate treatment (to lie flat and still potentially for >1 h), and instability of the spine.

Simulation

Prior to radiation therapy planning, patients must undergo CT imaging in the treatment position with the proper immobilization devices. Spinal SRS systems such as BrainLab by Novalis use a frameless system that incorporates ExacTrac, an image-guided patient positioning system

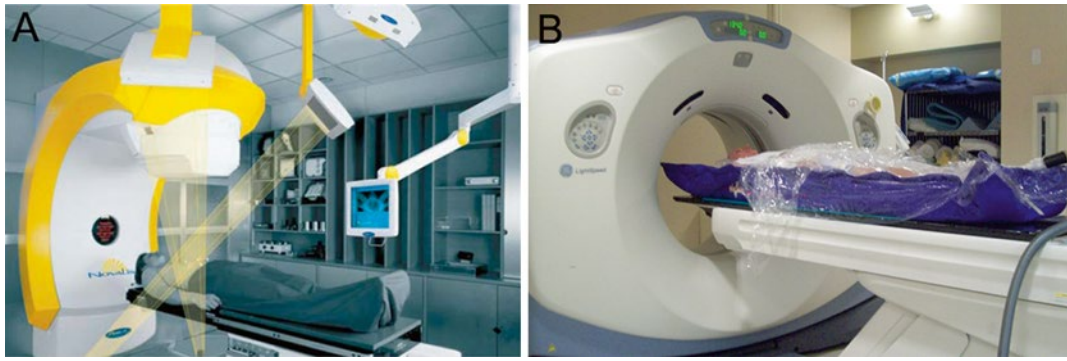

Fig. 20.4 (**a**) Photograph showing the NOVALIS system, which captures oblique images by the on-board imagers. Comparison of the images at the time of treatment is made to radiographs digitally reconstructed from the initial simulation CT. Next, robotic couch shifts are performed, and orthogonal images are again obtained. Shifts are made until there is <1-mm difference between the image sets (Image is courtesy of Brainlab AG, Feldkirchen, Germany). (**b**) Photograph showing how the patient is immobilized in a Bodyfix vacuum bag with a plastic fixation sheet

(Fig. 20.4a). If the spinal lesion is in the cervical spine, the patient will lie on a headrest while a thermoplastic mask is conformed to the patient's head and neck. The mask will keep the patient's head and neck immobilized during simulation and treatment. If the spinal lesion is in the thoracic or lumbar spine, a vacuum bag, such as from BodyFix, is used for immobilization (Fig. 20.4b). The vacuum bag is conformed to the patient's body while in the supine position with the arms down. When the vacuum seal has reached the appropriate pressure, markers will be placed in the vacuum bag in the area of interest. The plastic fixation sheet is then rolled out and sealed to the vacuum bag, and air is then vacuumed out. The lasers in the room serve as guides, and marks are then applied to the vacuum bag for accurate set-up positioning on subsequent treatments. A CT scan is then obtained at ≤2.5–3 mm (1.25 mm used at our institution) slice thickness throughout the area of interest; intravenous contrast should be administered if there is concern for epidural extension. The images are verified for completeness.

Dose/Planning/Dosimetry Considerations

From the CT scan, the physician will delineate areas of interest, including the target volume and critical structures such as the spinal cord, kidneys, liver, heart, ribs, and lungs. MR sequences should be fused to the CT studies. The benefit of contouring from the MRI is more accurate delineation of the soft tissues. Target tumor volumes are chosen by the physician and are based on the amount of involvement. If the metastasis involves a section of the vertebral body, the target volume may be limited to the vertebral body and both pedicles. If only the posterior elements are involved, the spinous processes and bilateral lamina alone can be targeted. When metastatic lesions are more extensive and involve the pedicles, inclusion of both anterior and posterior elements of the spine should be considered. Epidural and/or paraspinal soft tissue components of the tumor should be included in the gross tumor volume. Once the gross tumor volume is delineated, additional margin is not added for a clinical target volume (e.g., potential microscopic disease extension) or a planning target volume (e.g., set-up errors or motion). However, to reach dose coverage constraints of the target, the beam aperture margin may extend to 3 mm beyond the target volume. Using the BrainLab planning system, spinal lesions are treated using intensity-modulated radiation therapy (IMRT). This technology allows radiation dose to better conform to the shape of the tumor volume such that minimal dose is delivered to critical structures. This is especially useful because of potential invaginations of the thecal sac from the tumor.

In a typical IMRT spinal SRS plan using the Novalis system, our institution utilizes 13 coplanar fields to achieve the dose constraints. Each field is separated by approximately 20°. When the gantry is at the proper position, the multileaf collimator moves the leaves in a series of positions while the beam is on; this IMRT technique is called sliding window. Depending on the circumstances, volume of disease, and OARs of concern, the treating radiation oncologist may prescribe the spinal lesion to 14–18 Gy in one fraction for a patient that has not been previously irradiated. Recent literature has shown improved progression-free survival (PFS) in radioresistant tumors such as renal cell carcinoma when spinal lesions are treated to 24 Gy in one fraction (Zelefsky et al., 2012). The literature also describes fractionation schemes for spinal SRS, including 30 Gy in five fractions or 27 Gy in three fractions (Ryu et al., 2010; Garg et al., 2011). Dosing and fractionation are customized for patients who have been previously irradiated. If more than one fraction is delivered, the treatments should be scheduled no closer than every other day. As per prior publications and RTOG 0631, the prescribed radiosurgery dose should cover >90 % of the target volume (Fig. 20.5). The spinal cord dose constraint is 10 Gy to no more than 10 % of the partial spinal cord volume, for which the superior and inferior extent is defined as 5–6 mm above and below the target volume. In addition, no more than 0.35 ml of the spinal cord should receive over 10 Gy (or 0.03 ml for 14 Gy). No more than 105 % of the prescription dose should extend beyond the high-dose spillage region (defined as 1 cm beyond the gross total volume). Timmerman (2008) has described other dose constraints.

Treatment/Image Guidance

At the time of treatment, the patient is set up in the BodyFix immobilization system as at the time of simulation. On at least the first day of treatment, the patient will usually undergo a CT scan, and the physician will verify that the location of the target volume has not substantially changed. This scan is called a "control CT scan." The patient is then transported in the vacuum bag to the treatment room and onto the couch. Using the room lasers, the patient will moved to the coordinates as designated during simulation. The reference star is affixed to the couch, and the ExacTrac system identifies the star's four markers using infrared cameras to determine the exact location of the couch. The on-board imagers acquire orthogonal radiographs, which are fused to the digitally reconstructed radiographs from the initial simulation CT scan. After comparison of the images, shifts are automatically made by the system to correct the patient's position. Shifts are made until the potential differences between the images are <1 mm. Once this is achieved and patient positioning is verified by the attending physician, the treatment can begin.

Results of Spinal Radiosurgery

Metastatic Tumors of the Spine

No prospective randomized trials to date have evaluated the efficacy of spinal SRS versus traditional 3D-CRT for metastatic tumors, but other published reports show that treatment of lesions with SRS results in excellent local control and pain reduction, with a limited toxicity profile. In an early Phase I/II clinical study, patients were treated with five 6-Gy fractions or three 9-Gy fractions (Chang et al., 2007). At a median follow-up period of 21.3 months, tumor progression was noted in 17 of 74 treated tumors (23 %). The 1-year freedom from tumor progression was 84 %. There were no cases of grade 3 or 4 neurologic toxicity. The authors attributed the high rate of tumor progression in 23 % to underdosing of the epidural space to limit spinal cord dose and a failure of the radiation field to capture the posterior spinal elements. Because of this study, it was thought that single-fraction schemas might reduce the possibility of tumor progression. In a study of 49 patients with 61 spinal metastases who were treated with 10–16 Gy in one fraction, patients developed pain relief as quickly as 24 h, with a median time to relief of 14 days (Ryu et al., 2008). Complete pain relief was accomplished in 46 % and partial relief in 19 %, with an overall pain control rate of 84 % at 1 year. The

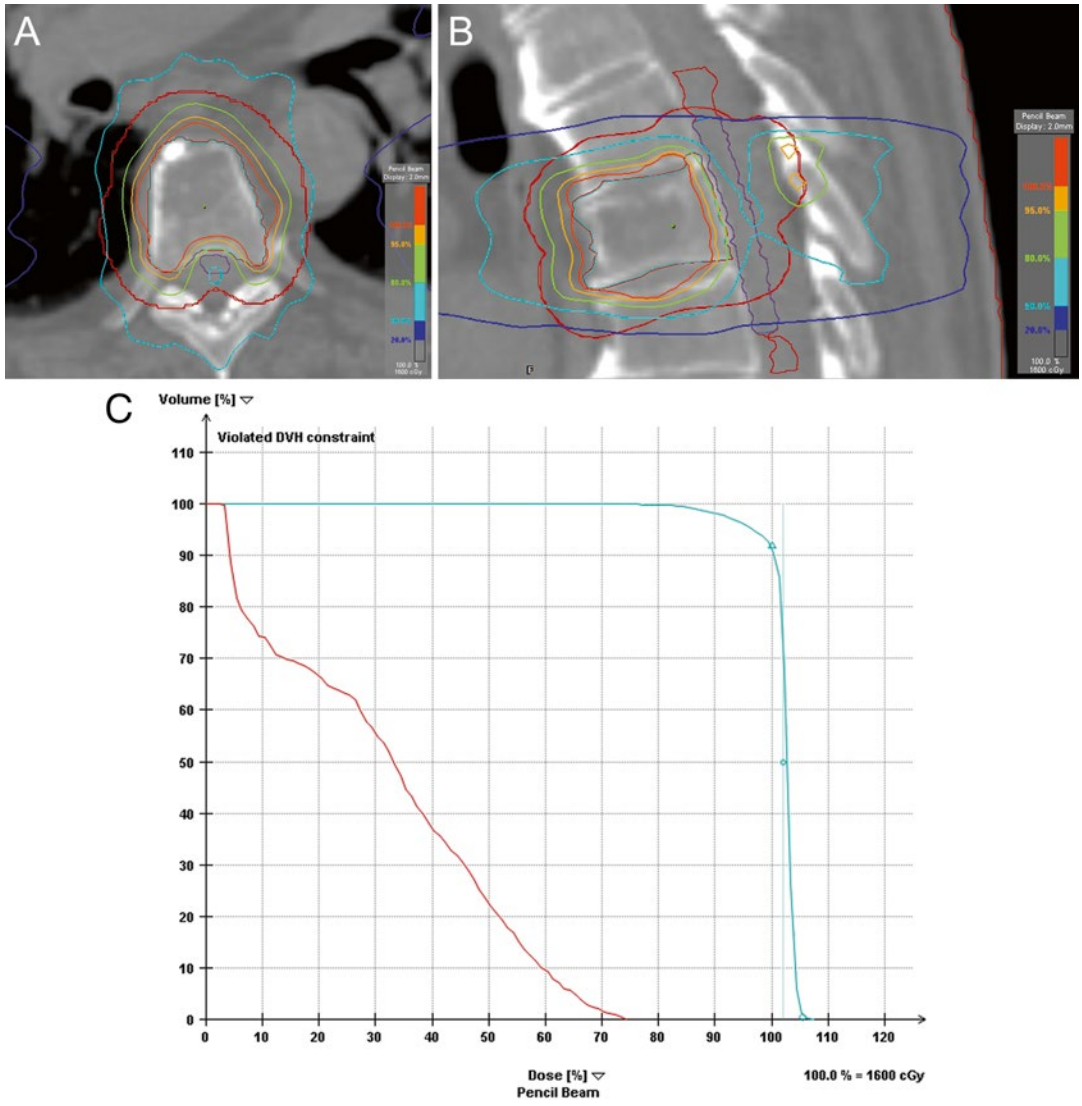

Fig. 20.5 Axial (**a**) and sagittal (**b**) isodose lines on a 13 co-planar field IMRT plan of a patient being treated for a single spinal metastasis. (**c**) The dose volume histogram (DVH) of the target volume is in cyan. In this plan, 95.3 % of the target volume is receiving the prescribed dose of 16 Gy, which is greater than the dosimetric goal of at least >90 % of the target volume receiving the prescribed dose. The DVH of the spinal cord is in *red*. The maximum partial cord dose, defined as the cord extending from 5–6 mm above to 5–6 mm below the target volume, is 539 cGy, well below the defined constraint of 1,000 cGy

median duration of pain relief was 13.3 months. There was a nonsignificant increase in pain control for patients treated with a radiation dose ≥14 Gy. Toxicity contributing to neurologic signs or symptoms was not observed at up to 30 months. On the basis of the findings from this study, fractionation schemata that deliver at least 14 Gy in one fraction are favored. In one of the largest series of patients, 500 lesions received a mean dose of 20 Gy in a single fraction (Gerszten et al., 2007). At a median follow-up of 21 months, pain was controlled in 86 % of patients, and local control by imaging was 88 %. There was no neurologic toxicity associated with treatment.

Primary Tumors of the Spine

Several studies have evaluated the efficacy of spinal SRS in primary tumors of the spine. In a study of 200 patients, 49 patients had benign or malignant primary spinal tumors (Gagnon et al., 2009). The most common primary histologies were sarcoma (n = 19) and chordoma (n = 12). In all patients, the lesions were treated to a mean dose of 26.4 Gy in three fractions. Patients who were on narcotic analgesics were able to stop their use 46 % of the time. In a series of 73 cases of benign intradural tumors including neurofibromas, schwannomas, and meningiomas, the lesions were treated with SRS to a mean dose of 21.64 Gy for purposes of definitive treatment, for tumor progression, or as adjuvant therapy (Gerszten et al., 2008). Radiographic tumor control was demonstrated in all cases, and pain improvement was demonstrated in 73 % of patients. Few series have documented the use of spinal SRS in primary sarcomas. In a series of 24 patients, however, Levine et al. (2009) treated primary sarcoma and metastatic sarcoma lesions to a median of 30 Gy in three fractions prescribed to the 80 % isodose line. For the seven patients with primary spinal sarcomas treated definitively with SRS alone, at a mean follow-up of 33 months, two had complete tumor regression, three had partial regression, and two had recurrences. In this series, an additional seven patients had primary sarcomas treated adjuvantly with radiation. At the latest follow-up, two of these seven individuals had a local recurrence. Thus, there are indications that SRS offers several benefits in the treatment of primary spinal lesions.

Spinal Cord Decompression

Spinal SRS for MESCC may benefit nonoperative candidates. Many patients with MESCC are poor candidates for surgery because of their poor performance status and/or extensive metastatic disease. Because of a need for a less-invasive treatment for such patients, Ryu et al. (2010) treated 62 patients with MESCC in a single fraction to 14–20 Gy. The spinal cord dose constraint allowed up to 10 % of the partial cord volume to receive >10 Gy. After a median follow-up period of 11.5 months, epidural tumor response was noted in 80 % of patients, with a mean reduction in tumor volume of 65 %. In addition, 94 % of patients remained neurologically intact, and 81 % had neurological function improvement Because of the success of this study, spinal SRS is considered to be a viable option in nonoperative candidates.

Radioresistant Tumors

Tumors historically considered radioresistant, such as melanoma and renal cell carcinoma, have been irradiated using SRS with similar results to those obtained in non-radioresistant tumors. Patients that are treated with 3D-CRT may be more likely to have recurrence of their lesion than patients who have been treated with spinal SRS. At MD Anderson, a cohort of 48 patients with 55 spinal metastases from renal cell carcinoma were treated either to 24 Gy in one fraction, 27 Gy in three fractions, or 30 Gy in five fractions, with a median dose of 30 Gy (Nguyen et al., 2010). The 1-year PFS in the spine was 82 % without any grade 3 or 4 neurologic toxicity. In addition, 52 % of patients were free of pain 12 months after their initial treatment. Subgroup analyses of dose or fractionation scheme were not conducted. In a series of 105 spinal lesions from metastatic renal cell carcinoma that were treated either to 24 Gy in a single fraction (n = 45), less than 24 Gy in a single fraction (n = 14), or 20–30 Gy in 3–5 fractions (n = 46), the 3-year local PFS was 44 % (Zelefsky et al., 2012). Single-fraction regimens that treated to 24 Gy showed significantly improved local PFS at 3 years (88 %) compared with regimens that treated to <24 Gy in a single fraction (21 %) or multi-fraction regimens (17 %) ($p < 0.001$). Patients with radioresistant tumors may benefit from high-dose, single-fraction regimens. In a retrospective review of 28 patients with 36 spinal metastatic melanomas that were treated to a dose of 17.5–25 Gy in a single fraction (mean dose 21.7 Gy), pain was improved in 96 % of patients (Gerszten et al., 2005). In four patients who were treated for radiographic tumor progression, tumor control was shown in three of

the cases. No radiation associated toxicity was noted at a median of 13 months.

Reirradiation

Spinal SRS has been increasingly used to treat recurrences after previous radiotherapy because of its ability to deliver conformal doses while sparing critical structures. Avoiding radiation toxicity while obtaining renewed tumor control in these patients is critical. In patients who had to undergo re-irradiation to either 30 Gy in five fractions or 27 Gy in three fractions, the 1-year local control rate was 76 % (Garg et al., 2011). Pain relief was significantly reduced at 1 month, 3 months, and 6 months. Two patients suffered from Grade 3 lumbar plexopathy, which was attributed to SRS, but they were able to remain mobile. In a series of 37 reirradiated tumors, patients who received a median dose of 24 Gy in three fractions had a 1-year PFS of 96 % (Sahgal et al., 2009). Choi et al. (2010) reported on a series of 42 patients with 52 lesions previously irradiated to 40 Gy who were treated with SRS after recurrence to a median dose of 20 Gy in 1–5 fractions (median of 2). A local control of 73 % at 1 year was achieved, and pain relief was experienced in 65 % of patients. One patient experienced Grade 4 neurotoxicity 6 months after SRS, with a maximum dose to the cord at 19.25 Gy (SSED of 14.2 Gy_3). In a study of 60 patients retreated to the spine to a dose of 24–30 Gy_2 in 3–5 fractions, the median PFS was 9 months. Overall, 93 % of patients had stable or improved disease (Mahadevan et al., 2011). Using a mathematical model based on reirradiated patients who developed myelopathy, Sahgal et al. (2012) concluded that when spinal SRS is given 5 months after 3D-CRT, the total maximum thecal sac dose to avoid myelopathy is 70 $Gy_{2/2}$. The recommended reirradiation thecal sac SRS maximum dose is ≤20–25 $Gy_{2/2}$ and should be limited to ≤50 % of the combined total maximal thecal sac dose.

Myelopathy

The side effect profile of spinal SRS is highly dependent on the location of the lesion. In all cases, the risk of radiation-induced myelopathy from SRS should be evaluated. One of the highest SRS doses used was in a retrospective study of 19 patients treated for hemangioblastomas of the spinal cord. In this series, lesions were treated to a median SFBED of either 20 Gy_3 or 18–25 Gy_3 in 2–3 fractions (Daly et al., 2011). This series has one of the highest reported single-fraction maximal doses at a median D_{max} of 22.7 Gy_3. In the fractionated cohort, the SFBED for the spinal cord D_{max} was 14.1 Gy_3. Two patients experienced Grade 1 sensory deficits and 1 patient experienced a Grade 2 left-sided foot drop 5 months after treatment. In one of the largest series of patients, Gibbs et al. (2009) described 1,075 patients treated by SRS with a total dose ranging between 12.5 and 25 Gy_3 in up to five fractions. The authors attempted to limit the maximal spinal cord dose to 8 Gy_3, but the range varied from 3.6 to 29.9 Gy_3. Six patients developed myelopathy at a mean time of 6.3 months. The maximal dose to the spinal cord in these patients ranged from 8.5 to 29.9 Gy_3, or a maximum BED to the spinal cord dose ranging from 32.6 to 140.6 Gy_3. Three of the six patients had improved neurologic symptoms after treatment. Using a case–control approach, Sahgal et al. (2012) determined that patients who had been treated with spinal SRS and developed myelopathy received a higher BED than patients who did not develop myelopathy. In particular, the mean maximum BED was 66.3 $Gy_{2/2}$ in patients who developed myelopathy and 36.4 $Gy_{2/2}$ in patients who did not develop myelopathy. In patients who have been reirradiated, it appears that that multiple-fraction SRS is favored over single-fraction SRS to decrease the chance of late effects and to maximize the therapeutic ratio (Garg et al., 2011).

Follow-Up After Spinal Radiosurgery

Follow-up after SRS should occur every 3–4 months. At the time of visit, a complete neurologic and musculoskeletal assessment should be completed. Follow-up MR imaging scans may be obtained on an as-needed basis. A contrast-enhanced study is most helpful, especially if epidural disease was of concern prior to treatment.

In a study by Hwang et al. (2012), MR findings were reported retrospectively in 44 patients every 3 months after treatment. The post-treatment lesion volumes decreased in 41 % of lesions and increased in 10 % of lesions. Patients with a decrease in tumor volume most commonly had increased T2 signal intensity with intermixed dark signal intensity. Patients with increases in tumor volume had either no significant change in T2 signal or a hypointense signal intensity. It is prudent to follow patients closely after treatment, as patients with myelopathy typically develop the associated symptoms approximately 6–12 months after spinal SRS (Gibbs et al., 2009; Daly et al., 2011; Sahgal et al., 2012). Close follow-up and intervention may assist in alleviating myelopathic symptoms. In a large cohort of patients who were treated with spinal SRS, 6 of 1,075 patients developed radiation-induced myelopathy (Gibbs et al., 2009). On MR imaging, radiographic findings showed edema in the spinal cord, which correlated with T2-weighted hyperintensity. Once symptoms began, intervention consisted of corticosteroids for all patients, as well as vitamin E, pentoxifylline, hyperbaric oxygen, gabapentin, and/or physical therapy. Intervention resulted in improved symptoms in three patients and stable symptoms in two patients, but symptoms progressed in one patient. In patients with clinical improvement, MR imaging revealed decreased spinal cord edema. Radiation-induced myelopathy is a rare occurrence after spinal SRS; however, close follow-up and intervention may stabilize or improve neurologic function.

Future Studies

RTOG 0631 is a Phase II/III study to (1) determine the feasibility of treatment spinal metastases with image-guided SRS and (2) determine whether there is better pain control with image-guided SRS than with conventional 3D-CRT. This study randomizes patients with 1–3 regions of painful (defined as Numerical Rating Pain Scale scores ≥5) spinal metastases with a maximal regional involvement of two contiguous vertebral bodies to spinal SRS at a dose of 16 or 18 Gy or to 3D-CRT at a dose of 8 Gy in a single fraction. The protocol was activated in 2009 and has completed enrollment of 43 patients into the phase II component. It is now accruing towards its goal of 240 patients on the phase III component.

References

Anker CJ, Shrieve DC (2009) Basic principles of radiobiology applied to radiosurgery and radiotherapy of benign skull base tumors. Otolaryngol Clin North Am 42:601–621

ASTRO (2011) ACR–ASTRO practice guideline for the performance of stereotactic radiosurgery, pp 1–9. http://www.acr.org/~/media/F80A2737FF0F4753B6ABABA73E15D757.pdf

Bilsky MH, Laufer I, Fourney DR, Groff M, Schmidt MH, Varga PP, Vrionis FD, Yamada Y, Gerszten PC, Kuklo TR (2010) Reliability analysis of the epidural spinal cord compression scale. J Neurosurg Spine 13:324–328

Chang EL, Shiu AS, Mendel E, Mathews LA, Mahajan A, Allen PK, Weinberg JS, Brown BW, Wang XS, Woo SY, Cleeland C, Maor MH, Rhines LD (2007) Phase I/II study of stereotactic body radiotherapy for spinal metastasis and its pattern of failure. J Neurosurg Spine 7:151–160

Choi CY, Adler JR, Gibbs IC, Chang SD, Jackson PS, Minn AY, Lieberson RE, Soltys SG (2010) Stereotactic radiosurgery for treatment of spinal metastases recurring in close proximity to previously irradiated spinal cord. Int J Radiat Oncol Biol Phys 78:499–506

Cole JS, Patchell RA (2008) Metastatic epidural spinal cord compression. Lancet Neurol 7:459–466

Daly ME, Choi CY, Gibbs IC, Adler JR Jr, Chang SD, Lieberson RE, Soltys SG (2011) Tolerance of the spinal cord to stereotactic radiosurgery: insights from hemangioblastomas. Int J Radiat Oncol Biol Phys 80:213–220

Fourney DR, Frangou EM, Ryken TC, Dipaola CP, Shaffrey CI, Berven SH, Bilsky MH, Harrop JS, Fehlings MG, Boriani S, Chou D, Schmidt MH, Polly DW, Biagini R, Burch S, Dekutoski MB, Ganju A, Gerszten PC, Gokaslan ZL, Groff MW, Liebsch NJ, Mendel E, Okuno SH, Patel S, Rhines LD, Rose PS, Sciubba DM, Sundaresan N, Tomita K, Varga PP, Vialle LR, Vrionis FD, Yamada Y, Fisher CG (2011) Spinal instability neoplastic score: an analysis of reliability and validity from the spine oncology study group. J Clin Oncol 29:3072–3077

Gagnon GJ, Nasr NM, Liao JJ, Molzahn I, Marsh D, McRae D, Henderson FC Sr (2009) Treatment of spinal tumors using cyberknife fractionated stereotactic radiosurgery: pain and quality-of-life assessment after treatment in 200 patients. Neurosurgery 64:297–306

Garg AK, Wang XS, Shiu AS, Allen P, Yang J, McAleer MF, Azeem S, Rhines LD, Chang EL (2011) Prospective evaluation of spinal reirradiation by using stereotactic body radiation therapy: The University of Texas MD Anderson Cancer Center experience. Cancer 117:3509–3516

Gerszten PC, Burton SA, Quinn AE, Agarwala SS, Kirkwood JM (2005) Radiosurgery for the treatment of spinal melanoma metastases. Stereotact Funct Neurosurg 83:213–221

Gerszten PC, Burton SA, Ozhasoglu C, Welch WC (2007) Radiosurgery for spinal metastases: clinical experience in 500 cases from a single institution. Spine (Phila Pa 1976) 32:193–199

Gerszten PC, Burton SA, Ozhasoglu C, McCue KJ, Quinn AE (2008) Radiosurgery for benign intradural spinal tumors. Neurosurgery 62:887–895

Gibbs IC, Patil C, Gerszten PC, Adler JR Jr, Burton SA (2009) Delayed radiation-induced myelopathy after spinal radiosurgery. Neurosurgery 64:A67–A72

Grosu AL, Andratschke N, Nieder C, Molls M (2002) Retreatment of the spinal cord with palliative radiotherapy. Int J Radiat Oncol Biol Phys 52:1288–1292

Hamilton AJ, Lulu BA, Fosmire H, Stea B, Cassady JR (1995) Preliminary clinical experience with linear accelerator-based spinal stereotactic radiosurgery. Neurosurgery 36:311–319

Hwang YJ, Sohn MJ, Lee BH, Kim SY, Seo JW, Han YH, Lee JY, Cha SJ, Kim YH (2012) Radiosurgery for metastatic spinal tumors: follow-up MR findings. AJNR Am J Neuroradiol 33:382–387

Levine AM, Coleman C, Horasek S (2009) Stereotactic radiosurgery for the treatment of primary sarcomas and sarcoma metastases of the spine. Neurosurgery 64:A54–A59

Lohr F, Debus J, Frank C, Herfarth K, Pastyr O, Rhein B, Bahner ML, Schlegel W, Wannenmacher M (1999) Noninvasive patient fixation for extracranial stereotactic radiotherapy. Int J Radiat Oncol Biol Phys 45:521–527

Mahadevan A, Floyd S, Wong E, Jeyapalan S, Groff M, Kasper E (2011) Stereotactic body radiotherapy reirradiation for recurrent epidural spinal metastases. Int J Radiat Oncol Biol Phys 81:1500–1505

Moulding HD, Elder JB, Lis E, Lovelock DM, Zhang Z, Yamada Y, Bilsky MH (2010) Local disease control after decompressive surgery and adjuvant high-dose single-fraction radiosurgery for spine metastases. J Neurosurg Spine 13:87–93

Nguyen QN, Shiu AS, Rhines LD, Wang H, Allen PK, Wang XS, Chang EL (2010) Management of spinal metastases from renal cell carcinoma using stereotactic body radiotherapy. Int J Radiat Oncol Biol Phys 76:1185–1192

Nieder C, Grosu AL, Andratschke NH, Molls M (2006) Update of human spinal cord reirradiation tolerance based on additional data from 38 patients. Int J Radiat Oncol Biol Phys 66:1446–1449

Park C, Papiez L, Zhang S, Story M, Timmerman RD (2008) Universal survival curve and single fraction equivalent dose: useful tools in understanding potency of ablative radiotherapy. Int J Radiat Oncol Biol Phys 70:847–852

Patchell RA, Tibbs PA, Regine WF, Payne R, Saris S, Kryscio RJ, Mohiuddin M, Young B (2005) Direct decompressive surgical resection in the treatment of spinal cord compression caused by metastatic cancer: a randomised trial. Lancet 366:643–648

Petteys R, Sciubba D, Gokaslan Z (2009) Surgical management of metastatic spine disease. Semin Spine Surg 21:86–92

Ropper AE, Cahill KS, Hanna JW, McCarthy EF, Gokaslan ZL, Chi JH (2012) Primary vertebral tumors: a review of epidemiologic, histological and imaging findings, part II: locally aggressive and malignant tumors. Neurosurgery 70:211–219

Ryu S, Jin R, Jin JY, Chen Q, Rock J, Anderson J, Movsas B (2008) Pain control by image-guided radiosurgery for solitary spinal metastasis. J Pain Symptom Manage 35:292–298

Ryu S, Rock J, Jain R, Lu M, Anderson J, Jin JY, Rosenblum M, Movsas B, Kim JH (2010) Radiosurgical decompression of metastatic epidural compression. Cancer 116:2250–2257

Sahgal A, Ames C, Chou D, Ma L, Huang K, Xu W, Chin C, Weinberg V, Chuang C, Weinstein P, Larson DA (2009) Stereotactic body radiotherapy is effective salvage therapy for patients with prior radiation of spinal metastases. Int J Radiat Oncol Biol Phys 74: 723–731

Sahgal A, Ma L, Weinberg V, Gibbs IC, Chao S, Chang UK, Werner-Wasik M, Angelov L, Chang EL, Sohn MJ, Soltys SG, Letourneau D, Ryu S, Gerszten PC, Fowler J, Wong CS, Larson DA (2012) Reirradiation human spinal cord tolerance for stereotactic body radiotherapy. Int J Radiat Oncol Biol Phys 82:107–116

Sciubba DM, Gokaslan ZL (2006) Diagnosis and management of metastatic spine disease. Surg Oncol 15: 141–151

Timmerman RD (2008) An overview of hypofractionation and introduction to this issue of seminars in radiation oncology. Semin Radiat Oncol 18:215–222

Yarnold J (1999) 8 Gy single fraction radiotherapy for the treatment of metastatic skeletal pain: randomised comparison with a multifraction schedule over 12 months of patient follow-up. Bone Pain Trial Working Party. Radiother Oncol 52:111–121

Zelefsky MJ, Greco C, Motzer R, Magsanoc JM, Pei X, Lovelock M, Mechalakos J, Zatcky J, Fuks Z, Yamada Y (2012) Tumor control outcomes after hypofractionated and single-dose stereotactic image-guided intensity-modulated radiotherapy for extracranial metastases from renal cell carcinoma. Int J Radiat Oncol Biol Phys 82:1744–1748

Etiology and Outcomes of Pediatric Spinal Cord Tumors

21

Susan Biffl

Contents

Abstract

Spinal cord tumors are a rare entity in the pediatric population. Pediatric oncology patients may develop spinal cord compression from tumors in the extradural, intradural extramedullary or intramedullary space. There are a variety of genetic syndromes that have a predisposition for spinal cord tumors, most notably Neurofibromatosis Type 2. Most spinal cord tumors tend to be slow growing with insidious presentation. Common symptoms may consist of pain, weakness, sensory changes, sphincter dysfunction and spinal deformity. The pattern of involvement depends upon tumor location in the cord. Because symptoms are often vague, slowly progressive and difficult to assess in young children, there is often a significant delay between symptom onset and diagnosis.

The most important predictors of overall survival (OS) and progression free survival (PFS) are the histologic grade and the degree of resection or treatment response. OS and PFS are often very good for most tumor types as low-grade histology predominates. The best predictor of neurologic outcome in virtually any tumor type is the degree and duration of neurologic impairment prior to treatment. Neurologic deficit and progressive spinal deformity are common. Overall function tends to improve over time with a combination of neurologic recovery and learning compensatory skills. Rehabilitation is an important

S. Biffl (✉)
Children's Hospital Colorado Rehabilitation Medicine, 13123 E. 16th Avenue, B285, Aurora, CO 80045-7106, USA
e-mail: susan.biffl@childrenscolorado.org

M.A. Hayat (ed.), *Tumors of the Central Nervous System, Volume 11*,
DOI 10.1007/978-94-007-7037-9_21,

part of the patient's care to support maximum function and quality of life. The importance of maintaining functional independence and begins in the early stages and continues as long as there is neurologic deficit. Long-term morbidities as well as risk of tumor recurrence necessitates long term follow up both for screening and support.

Introduction

Spinal cord tumors make up 4–10 % of all central nervous system tumors in children as reported by Nadkarni and Rekate (1999) and 2 % of all childhood tumors reported by Wilne and Walker (2010). Incidence in the general population is 0.26 per 100,000 person years reported by Benesch et al. (2010). This rarity contributes to a pattern of delay in diagnosis as most signs and symptoms of spinal cord tumors have many more common etiologies. It also confounds research, due to difficulty massing enough patients to study. Many studies are small case series, data may be gathered over many years during which treatment patterns may change and studies often combine multiple types of tumors and may also combine adult and pediatric data.

Pediatric spinal cord tumors may occur in three primary anatomic compartmental locations. Extradural extramedullary tumors arise from local extension of other primary neoplasms often through the neuroforamen. Intradural extramedullary tumors are located within the subarachnoid space and primarily metastatic from a primary brain tumor spread by the CSF. Meningiomas and nerve sheath tumors also occur in this space. Intramedullary tumors are within the spinal cord parenchyma and are commonly low grade gliomas. 25–40 % of spinal cord tumors in children are intramedullary.

Histology and treatment response are the strongest predictors of over all survival (OS) and progression-free survival (PFS). OS and PFS of spinal cord tumors are similar to supratentorial tumors with similar histology and degree of treatment response, though morbidity is different due to their location in the spinal cord. High grade histology is a poor prognostic factor in OS and PFS as is incomplete resection or treatment response. The two most common morbidities associated with spinal cord tumors are neurologic deficit and spinal deformity. The strongest predictive factor of neurologic outcome in virtually any spinal cord tumor is the degree and duration of neurologic abnormality prior to treatment. Spinal deformity is often related to age at the time of treatment and the type of intervention necessary. In this chapter we will discuss presenting symptoms of spinal cord tumors, principles of treatment, some of the most common tumors occurring in the three compartments described, genetic syndromes predisposing patients to spinal cord tumors, long term outcomes and rehabilitation support as it impacts the long term quality of life.

Presenting Symptoms

Presenting symptoms are generally due to mass effect on surrounding tissues and may include neurologic impairment from spinal cord compression (SCC), progressive spinal deformity, either scoliosis or torticollis. Patients may also present with signs and symptoms of hydrocephalus which occurs at a higher rate in the pediatric as opposed to the adult patient population. Certain tumors also present with systemic symptoms of fever, weight loss and fatigue, and if this represents a metastatic process, other tumor sites may be symptomatic as well.

Symptoms of spinal cord tumors are commonly due to mass effect of tumor and possibly cystic or hemorrhagic elements, on the cord itself causing SCC. In the setting of intraforaminal extension of a paraspinal tumor, the neurologic insult is due to direct compression as well as impaired blood flow of local venous plexuses resulting in impairment of the spinal cord circulation resulting in infarction and irreversible neurologic insult. Location in the cord, both the level and which tracts are effected, determines which symptoms are present. Sensory symptoms may include impairment of perception of pain, temperature, touch and proprioception. Motor impairments

may present as weakness, spasticity or sphincter dysfunction. All functions located below the lesion are at risk. High cervical tumors risk involvement of cranial nerves, upper, and lower extremities, trunk and bowel and bladder. The lower in the cord the tumor is located the fewer functions are at risk. In the lumbar area, lower extremity function and bowel and bladder function may be involved. Involvement of the cord causes upper motor neuron signs with increased tone and reflexes, whereas involvement of the conus, cauda or peripheral nervous system result in lower motor neuron signs with decreased tone and reflexes. A patient may have both SCC or other central nervous system involvement and peripheral nerve involvement in which case both upper and lower motor neuron signs may be present. Incomplete patterns of impairment predominate as complete interruption of the cord is uncommon. Intramedullary tumors also commonly span multiple segments and may be asymmetric and infiltrative especially in the setting of astrocytoma.

Histology has a greater influence on the chronology of symptom development. Low grade slow growing tumors are the most common intramedullary tumors and symptoms often present insidiously often over months to years. However, if hemorrhage or vascular insult are present, or if there is a high grade histology or malignant pattern of growth, there will likely be a more abrupt presentation. Peritumoral cysts may be present in as many as 60 % of intramedullary tumors and can cause significant neurologic impairment. Neurologic symptoms related to cysts are often significantly improved following resection as reported by McGirt et al. (2008a). Extramedullary tumors are often more aggressive and SCC comes on more rapidly. They are also more commonly associated with systemic symptoms of weight loss, fatigue, fever, etc.

Recognizing spinal cord tumors is complicated by many factors. In general the most common presenting symptoms all have far more common etiologies than spinal cord tumor. Many pediatric spinal cord tumor patients are nonverbal infants and toddlers in whom an accurate and highly sensitive neurologic examination is very difficult. Ideally patients can communicate regarding sensory symptoms and follow directions to assess motor and sensory function. In children much of the evaluation is observational. Symptoms are also often vague and present insidiously so patients have learned to adapt to them. Often a constellation of symptoms must be present before the concern for a mass occupying lesion is considered. This delay in recognition and thus treatment can threaten treatment efforts and neurologic recovery.

The most important predictor of neurologic outcome in all causes of oncologic myelopathy is known to be the degree and duration of neurologic compromise at the start of treatment. This has led to improved vigilance for signs and symptoms of spinal involvement. In a large retrospective study reported by Findlay (1984) of adult and pediatric spinal cord injury patients from 1963 to 1982, 32 % of patients with neoplastic spinal cord involvement were ambulatory at the start of treatment. Husband (1998) had similar results. However, Rades et al. (2011) showed 62 % of patients being ambulatory at the start of treatment.

In children with paravertebral malignant tumors causing SCC, Gunes et al. (2009) reported presenting symptoms of pain in 64 %, motor dysfunction in 43 %, sphincter dysfunction in 36 % and sensory deficits in 7 %. Similar patterns of involvement have also been shown in other SCC types. Median interval from symptom onset to diagnosis in paravertebral malignant tumors has been reported as 7 weeks by Gunes et al. (2009). Wide ranges of delay from symptom onset to diagnosis have been reported for intradural low grade tumors from 0.1 to 84 months reported by Scheinemann et al. (2009) with median intervals commonly reported as 9–10 months reported by Constantini et al. (1996).

The most common presenting symptom in all groups is pain. This may be generalized back pain, radicular pain if nerve root compression is a factor or may be referred pain, commonly abdominal pain. The pain is commonly worse at night when vascular congestion may become a factor in the supine position. Sensory change can also present as pain due to dysesthesia or hyperesthesia often in a radicular pattern perceived as pain. Assessing intermittent diffuse

pain in very young children especially with a non-verbal infant or toddler is extremely difficult. There are a myriad of causes for infant fussiness and sleep disturbance in an infant or young child. The fact that it is persistent, and more common in supine may raise suspicion and prompt more thorough evaluation.

Weakness or abnormal tone may be seen as a subtle gait disturbance, delay in achieving developmental milestones or developmental regression. Again in a young child or toddler there are a number of possible and more common etiologies for these concerns. The cause may lie anywhere in the neuromuscular system from the central nervous system to the muscle. Any of these etiologies are concerning and should prompt thorough investigation which includes evaluation of spinal cord function.

Sensory change may present as numbness or dysesthesias or loss of proprioception. The latter may present with balance difficulty or ataxia. As weakness, sensory change and particularly balance problems or ataxia can also be symptoms of brain tumor it is important to image the entire neuroaxis in investigation of these complaints. While evaluation of possibly subtle sensory change is difficult in an adult, it is extremely challenging in an infant or young child. However, serial examination and a thorough history of may bring it to light.

Loss of bowel and bladder control are not common presenting signs of spinal cord tumors, though they may be present in 23 % of patients presenting with intramedullary tumor reported by Wilson et al. (2007). An exception to this is myxopapillary ependymoma which occurs almost exclusively in the conus and filum terminale and sphincter dysfunction is a common presenting sign. In most cases, as sphincteric dysfunction commonly presents later and in combination with other symptoms, it often signals more advanced disease. Change in bowel or bladder function are difficult to ascertain in a child who has not yet been potty trained. However, new onset of constipation, abdominal discomfort or frequent urinary tract infections due to retention would be a sign of loss of bowel and bladder function. Evidence of neurogenic bowel or bladder should always prompt evaluation of spinal cord function.

One-third of patients with spinal cord tumor may present with spinal deformity including torticollis if cervical or scoliosis if thoracic or lumbar. Though congenital muscular torticollis is relatively benign and not terribly uncommon in infants, a new onset or progressive torticollis are unusual symptoms. Central nervous system process including spinal cord mass, infection and trauma are part of the differential diagnosis for this concern. Scoliosis in adolescents is also not uncommon, however, scoliosis occurring outside of that age range or with other accompanying symptoms of pain and weakness or sphincter dysfunction is unusual. Also a thoracic curve with the apex toward the left is concerning as a rightward curve is most common in idiopathic scoliosis. Patients presenting with progressive scoliosis without associated symptoms of SCC often experience a longer delay from symptoms to diagnosis mean of 26 months in LGG reported by Scheinemann et al. (2009).

Hydrocephalus presents with signs and symptoms of increased intracranial pressure such as vomiting early am headache, irritability and lethargy as well as cranial nerve abnormalities and papilledema. These symptoms may present abruptly or insidiously and intermittently and some may be misconstrued as viral or behavioral issues. The risk for hydrocephalus or brain tumor should be considered with almost any identified spinal cord tumor.

Work up of any suspected spinal cord tumor should include MRI with and without contrast of the entire neuroaxis. Plain films can be useful for tracking progressive spinal deformity. Biopsy, either of the spinal cord tumor, bone marrow or other remote tumor, additional imaging and labs are dependent upon the tumor type suspected. Due to the significant association of spinal cord tumor with several genetic syndromes, a thorough exam and family history should be performed to look for any evidence of these conditions.

In addition to the previously mentioned factors confounding the diagnostic process, there are other processes some of which are more common in the oncology population that can present similarly to spinal cord tumors. Epidural abscess can present with signs and symptoms of SCC as well

as systemic symptoms and may occur more commonly in an immunocompromised patient or after surgical intervention for the central nervous system or spine. Radiation myelopathy presents with ascending numbness and upper motor neuron findings 9–15 months after radiotherapy in the area of the spinal cord. There is often a hemicord location presumably due to a vascular lesion with Brown-Sequard symptoms. Spinal cord cavernous hemangiomas can also cause SCC. Spontaneous or traumatic epidural hematomas occurring on anticoagulant therapy which is more commonly used in hypercoaguable oncology patients also causes SCC.

Intramedullary Spinal Cord Tumors

Intramedullary spinal cord tumors are a rare entity comprising 4–10 % of all CNS tumors and 35 % of intraspinal tumors in children and 20 % of intraspinal tumors in adults. Pathology is most commonly astrocytomas in children, most commonly ependymomas in adults. We will focus here on low-grade gliomas (LGG) including astrocytomas, and ependymomas.

LGG predominate as a group in pediatric patients with intramedullary tumors and include astrocytomas, mixed gliomas, gangliomas, oligodendromas and other low grade glial tumors. Gangliomas comprise 30 % of tumors <3 years. High grade tumors are found in only 10–15 % of patients with gliomas and carry a poor prognosis with most patients dying of progressive disease within 6 months of diagnosis. 40–70 % of childhood intramedullary tumors are astrocytomas commonly fibrillary or juvenile pilocytic astrocytomas, 12–30 % are ependymomas, 4 % developmental tumors 27 % ganglioma, 12 % miscellaneous. Location along cord among intramedullary tumors varies with a general cervical predominance and often tumors span multiple segments. Associated peritumoral cysts filled with fluid produced by the tumors are common and can cause symptoms due to mass effect. When these cysts are decompressed during resection, there is often a significant and immediate postop improvement in neurologic status.

Spinal cord LGG are similar to intracranial LGG of similar histologic grade. Location in the spinal cord is uncommon for low grade gliomas (LGG). Spinal cord low grade gliomas constitute <5 % of all low grade gliomas. There is an age peak at 2 years with more than 1/3 of patients receiving a diagnosis before age 5, similar to intracranial LGG. Clinical behavior was also similar to intracranial LGG with younger patients showing a higher rate of recurrence. Most subtypes are treated with surgical resection. Gross total resection (GTR) is the goal and is more achievable in well-defined tumors with a midline location. Unfortunately astrocytomas are more likely to be infiltrative and asymmetrically located, however GTR is still possible in many situations. Scheinemann et al. (2009) reported patients with LGG who undergo GTR have a dramatically better 5 years PFS reported as of 88 +/−13 %, with a 5 years PFS of 34–57 % for other therapies including partial resection. OS low grade gliomas w/ varying rates of resection and radiation were 66–70 % at 5 years, 55–73 % at 10 years and 67 % at 20 years and with GTR, OS can be as high as 100 % at 8 years follow up. Low grade astrocytomas do respond to vincristine and carboplatin or focal radiation and these options may be used when GTR is not possible. Malignant gliomas do not have as favorable response to resection and GTR is often not possible due to aggressive tumor growth pattern. Radical surgical resection may still be possible for malignant astrocytoma though it may not have an effect on overall survival. There are, however, reports of long term >12 years survival in spinal cord Glioblastoma multiforme following resection.

Spinal ependymomas are second most common spinal cord tumor in children. They arise from ependymal cells lining the central canal and from the cells in the ventriculus terminalis in the filum terminale. They are generally centrally located and well- circumscribed. They can be divided into intramedullary and myxopapillary ependymomas. 13 % of pediatric ependymomas occur in the spine as compared with 75 % of adult ependymomas. Spinal ependymomas tend to occur in older children as would be expected

with the shifting predominance of ependymomas in adulthood.

Intramedullary ependymomas have a very favorable OS and PFS with complete resection. OS at 5 years has been reported as of 50–100 % and 50–70 % at 10 years with varying degrees of resection. PFS at 5 years was 75–84 % with GTR, 57.1 % with<GTR. PFS at 10 and 20 years reported as 50 and 46 % with longer time to progression with greater degree of resection. As these tend to be well-demarcated lesions, GTR rates have ranged from 50 to 100 %. In studies combining pediatric and adult data, there was a 19 % recurrence rate with the vast majority of these patients experiencing incomplete resection. Larger tumors >6 cm have a greater chance of being infiltrative and a lesser chance of PFS 58 % as opposed to smaller tumors with PFS of 92 %. No clear role for adjuvant radiation or chemotherapy has been found in intramedullary ependymomas after GTR. Tumor recurrences may occur years post treatment necessitating long term follow up.

Myxopapillary Ependymoma (MEPN) is a slow growing tumor that is generally confined to the conus medullaris-cauda equina-filum terminale region of the spinal cord. As a result, bowel and bladder dysfunction is a more common presenting symptom than in other spinal cord tumors. MEPN constitutes 13 % of all ependymomas in children and adults. Age at diagnosis ranges from 6 to 82 years. OS in combined adult and pediatric studies was reported as 85–93 % and PFS at 5 years of 68 %. In children, OS 96.6 % at 5 years and 90 % 10 years. PFS at 5 years with varying treatment was 72.3 %, 84.4 % with GTR, 57.1 % with<GTR. Ten years PFS for children was 70 % with varying treatment. In adults OS 60–80 % PFS 40–50 % at 10 years w/ predominance of Grade I–II tumors. Though as stated previously, PFS and OS may be better in children, MEPN in children is more likely to have local recurrence and tumor dissemination. Bagley et al. (2009) reported 64 % of pediatric patients with MEPN had disseminated disease as opposed to 32 % reported in adults. Benesch et al. (2010) reported a high relapse incidence of 4/6 patients.

MEPN is considered to be biologically different from other ependymal neoplasms. Molecular biology studies have shown evidence that molecular signature differs depending upon location as does clinical behavior. Molecular studies suggest adult and pediatric tumors differ, which may present new opportunities for targeted therapies. There is a clear association with NF2 and higher incidence in that population. Standard treatment is aggressive surgical resection with a goal of GTR, which is often curative. Encapsulated lesions have a better postoperative outcome both with regard to survival and neurologic outcome. The role of adjuvant therapy is unresolved in the setting of incomplete resection or recurrence. Relapse or recurrence can occur years after treatment and long-term surveillance is mandatory.

Intradural Extramedullary Spinal Cord Tumors

Two types of tumors commonly occurring in the intradural extramedullary space will be highlighted here; meningiomas, and nerve sheath tumors, specifically neurofibromas, schwannomas and malignant nerve sheath tumors. Both meningiomas and nerve sheath tumors are commonly associated with NF2 and neurofibromas are specifically associated with NF1 though they also occur sporadically.

Meningiomas arise from arachnoid cells anywhere along the neuroaxis, Typically slow growing invasive, they may remodel bone. Usual treatment is surgical resection. They comprise 1/3 of all primary brain and CNS tumors in adult data and 1–4 % of pediatric CNS tumors. There is a higher incidence in those with NF2 or radiation exposure from prior treatment. Risk is higher in patients treated at a younger age with radiotherapy, but often does not present for many years with incidence rising for 30 years post initial diagnosis. Half of NF2 patients will develop meningiomas, often multiple meningiomas. There is an increasing incidence with age, necessitating lifelong surveillance in this population. GTR has been associated with a higher PFS and OS rate childhood and adolescent meningiomas.

Upfront radiotherapy did not show a clear benefit. Both PFS and OS rates were worse for NF patients.

Nerve sheath tumors (Constantini et al., 1996) are derived from Schwann cells and perineural cells of the peripheral nervous system. 65 % of NST are schwannomas and 5 % are malignant nerve sheath tumors (MNST) with most of the remainder being neurofibromas. They account for 25 % of tumors in the intramedullary extradural space. This is where the vast majority of nerve sheath tumors occur, though extension into the extradural or intramedullary space is possible and rarely they may occur primarily in either of those locations. They may occur sporadically or as a manifestation of NF1 (neurofibromas) or NF2 (schwannomas).

Schwannomas are predominantly made of Schwann cells, arise from recognizable nerves and are relatively circumscribed from those nerves. Neurofibromas are comprised of Schwann, perineurial and fibroblastic cells and are more intermingled with the axons of their associated nerves. Both Schwannomas and neurofibromas are slow growing and slow to become symptomatic. MNST may occur sporadically or as dedifferentiated neurofibromas and are fast growing with necrosis and high mitotic index as a feature and produce rapidly progressive symptoms. Presentation is similar to other SCT with symptoms dependent upon location of the tumor. Interestingly, radicular symptoms are uncommon, even in the setting of nerve root involvement of the tumor.

Surgical resection, GTR when possible, can be curative in neurofibromas and schwannomas, especially those occurring sporadically. Chemotherapy and radiotherapy are generally reserved for aggressive incompletely resected tumors though supporting evidence for their use is limited. OS is quite good for sporadic NST, somewhat less so for those associated with NF1 and 2. MNST require a more aggressive approach and even with resection, which is often more difficult, carry a worse prognosis with most patients with MNST having an OS of <1 year from diagnosis. Resection can often be done while preserving motor function, though sensory loss is common. Myelopathic symptoms commonly resolve with relief of SCC as with other SCT. Due to the slow growing nature of schwannomas and neurofibromas, the timing and extent of surgical resection may be more driven by the need to preserve function than to eradicate the tumor, especially in the setting of NF1 or 2.

Extradural Spinal Cord Tumors

Extradural tumors causing SCC and neurologic deficit in the pediatric population are commonly from intraforaminal extension of paravertebral tumors representing primary or metastatic disease. SCC from extradural tumors occurs more commonly in relapse as opposed to primary presentation. Neurologic symptoms of SCC from extradural tumors are related to the level of the cord involved with a similar constellation of symptoms consistent with other causes of SCC. There is a higher rate of advanced disease in this group, likely related to the fact that these tumors have a higher rate of being metastatic rather than primary tumors. The speed of onset neurologic symptoms is often more abrupt, as rapidly dividing tumors such as Neuroblastoma, Ewing's sarcoma, PNET and Lymphomas are often the paravertebral tumors involved. These types of tumors are also more likely to present with systemic signs and symptoms of fever, weight loss, lymphadenopathy and lethargy compared with intradural tumors.

Treatment is dependent upon tumor type and histologic grade and may consist of chemotherapy, radiation or surgical resection or a combination thereof. Biopsy as well as imaging will help guide diagnosis and therapy. Tissue may be obtained from needle biopsy, bone marrow or during tumor resection for decompression. Chemotherapy and radiation are more common in extradural as opposed to intradural tumors. Though there are a variety of tumor types that may be involved, we will focus on three of the most common; Ewing's sarcoma, Lymphoma and Neuroblastoma.

Ewing's Sarcoma (ES) is a small round cell tumor that can arise from bone or soft tissue. It is the second most common malignant primary

bone tumor in children and adolescents. PNET is a more differentiated peripheral primitive neuroectodermal tumor in the same spectrum. ES may involve the cord via paravertebral extension or in primary ES of the spine. Primary ES of the spine much more commonly causes SCC. Kramer et al. (1989) reported on 162 patients with soft tissue sarcomas including ES, 10 presented with SCC. Primary ES of the spine accounts for 5 % of all primary sites. ES has a generally good prognosis with OS reported as 50–80 % with multi-agent chemotherapy, surgery and radiation. Five years PFS reported as 28–72 %. In neurologically stable patients in whom ES is suspected, a large bore needle biopsy can confirm the diagnosis and allow chemotherapy to start promptly. This may shrink the tumor and allow more conservative surgery. Preservation of spinal integrity with minimally invasive procedures is important in this population as post laminectomy kyphoscoliosis has been reported in 40–75 % of patients reported by Indelicato et al. (2010).

In Non-Hodgkins lymphoma (NHL) the most common cause of spinal cord involvement is from epidural cord compression from interforaminal extension without bony involvement as opposed to other solid tumors that invade the vertebral body and encroach on the spinal cord anteriorly. SCC occurs in 0.1–6.5 % of NHL patients as a presenting sign of initial diagnosis or relapse reported by Norden et al. (2011). NHL is radiosensitive and unlikely to be cured by surgical resection. Patients will also require systemic chemotherapy. While patients with advanced disease presenting with SCC have a poor prognosis with median OS after diagnosis of SCC of 6 months, those who present with SCC as an initial presenting symptoms have a better survival rate.

Neuroblastoma is a neoplasm of neural crest origin that populate the sympathetic ganglia and inner adrenal gland. It is the most common extracranial solid tumor of childhood. 50 % of all neuroblastoma patients present with localized tumor and have a good prognosis. Plantaz et al. (1996) reported PFS as excellent at 90 % as is OS reported as 97 %. Intraspinal intraforaminal extension (dumbbell tumor) occurs in 7–15 % of cases and has a 1–7% incidence of causing SCC as reported by Angelini et al. (2011). Dumbell neuroblastoma is the most common malignant cause of SCC in children. The most common involved spinal level was thoracic as expected with the normal pattern of tumor location in neuroblastoma. Neuroblastoma tends to occur in the <3 years population and may be present at birth. As we have noted, spinal deformity is more common when tumor and treatment occur at a younger age to a developing spine. Also, delay in diagnosis is common as neurologic abnormality can be harder to discern.

Treatment is dependent upon presentation, specifically degree of neurologic deficit, speed of progression of deficit and histology. As always, preservation of spinal integrity is preferable and as neuroblastoma is often quite chemo sensitive, laminectomy may be avoidable. Chemotherapy may effectively rapidly shrink the tumor and provide decompression, however laminectomy may be necessary to preserve neurologic function if neurologic deficit is significant and rapidly progressive. Unfortunately, there isn't necessarily consensus on how severe or how rapidly the presentation must be to prompt emergent surgical decompression and evidence is not conclusive. In most studies, patients treated with chemotherapy had a lower incidence of post treatment progressive deformity and laminectomy was not consistently associated with a higher degree of neurologic recovery. Many factors related to treatment bias would be evident here as patients with more significant neurologic deficit and thus a likely worse outcome, would be more likely to undergo laminectomy. Scoliosis is also more common in patients with neurologic deficit. In most cases, neurosurgical decompression was reserved for patients with rapidly progressive neurologic deficit, within 72 h of presentation or over 12 h under observation or while undergoing chemotherapy. De Bernardi et al. (2001) reported patients who had laminectomy for the previously mentioned criteria, 83 % had neurologic improvement though 44 % of surviving patients had late sequelae. This was mainly spinal deformity 31 % which was more common with laminectomy or radiotherapy. Sphincteric dysfunction also occurred in 28 % of these patients following treatment regardless of intervention.

Genetic Syndromes Associated with Spinal Cord Tumors

Several genetic syndromes are associated with CNS tumor predisposition such as Tuberous sclerosis, Turcot syndrome and Li Fraumeni syndrome with a predisposition for astrocytoma, and Von Hippel-Lindau disease with predisposition for hemangioblastoma. The syndrome most commonly associated with spinal cord tumors is Neurofibromatosis specifically type 2.

Neurofibromatosis Type 2 (NF2) is a rare autosomal dominant phenotypically variable genetic disorder with mutations in chromosome 22q12 involved with production of "merlin" or "schwannomin" considered a tumor suppressor. NF2 is considered a tumor predisposition syndrome. It is associated with numerous central nervous system tumors. Vestibular schwannomas, often bilateral, are a defining feature though cranial nerve and spinal nerve schwannomas, intracranial and spinal meningiomas, ependymomas and intrinsic spinal cord tumors are also common. Spinal tumors are commonly slow growing and multiple tumors are common. Most common are extramedullary schwannomas. Evans (2009) reported intramedullary tumors occur in 5–33 % of NF2 patients and 75 % of these are slow growing ependymomas. Schwannomas in NF2 patients undergo malignant transformation rarely, if ever. Dow et al. (2005) found larger tumors (>5 mm) are more likely to continue to grow whereas smaller tumors may remain static. Multiple tumors are often present and tumor types are heterogenous in location, both intra and extramedullary and by level in the cord. Intramedullary tumors have been characterized as being centrally located in the cord, have intense enhancement and multiple tumors are common. Neuroimaging of NF2 pediatric and adult patients has revealed spinal tumors in 67–90 % though symptomatic lesions are present in <30 %. Tumors become more common with age typical presentation with symptomatic tumor occurs at 20 years also reported by Dow et al. (2005).

Radiation therapy is contraindicated in NF2 especially in childhood as it may induce, accelerate or transform tumors. It is generally felt that surgical intervention for asymptomatic tumors in NF is likely to result in neurologic impairment at an earlier stage than it would have occurred without intervention and is not recommended. It is controversial whether to operate on tumors when advanced neurologic deterioration is already present. Patients with NF2 are less likely to experience neurological improvement than patients without the disorder. Thus surgical intervention may be indicated in patients with new neurologic deficit and expanding lesions. Extramedullary lesions notably meningiomas are more often considered amenable to surgical intervention and are more likely to exhibit rapid growth. In a study of 87 patients with spinal neuromas, comparing patients with NF1, NF2 and without NF, gross total resection significantly decreased recurrence risk in patients without NF2. Non-NF2 patients had recurrence rates of 10.7 % at 5 years and 28.2 % at 10 and 15 years. In NF2 patients, 5 year recurrence rate was 39.2 % and virtually 100 % at 9 years reported by Klekamp and Samii (1998).

NF2 patients are often best served by centers offering specialized multidisciplinary NF care and require regular clinical and radiologic surveillance to identify tumors which may require intervention in a timely fashion. Due to the high incidence of spinal tumors in patients with NF2, identification of a spinal tumor should prompt clinical evaluation for NF2 as well as imaging of the entire neuroaxis.

NF1 is an autosomal dominant disorder linked to a defect on Chromosome 17 in the neurofibrin gene, predisposing patients to peripheral and central neurofibromas. Tumors of the spinal canal are not a regular feature with approximately 2 % of patients with NF1 exhibiting symptomatic spinal tumors. Some studies suggested a higher incidence of LGG but this has not been consistently noted. Spinal nerve root tumors in NF1 are typically neurofibromas rather than schwannomas as are seen in NF2. Both types of tumors have been considered together under the category of "neurinomas" and are thought to comprise 25 % of all spinal tumor as reported by Seppala et al. (1995). Spinal neurofibromas are thought to comprise 3 % of all spinal tumors and though they can occur sporadically, are much more common in NF1. Presentation is similar in patients

with and without NF1, thus any patient presenting with a spinal neurofibroma should be screened for NF1. Patients with NF1 are at higher risk of developing a second tumor and ongoing surveillance is indicated.

Assessment of Functional Outcomes

In all causes of SCC, the neurologic deficit is dependent upon the location of the tumor in the cord and the degree it compromises the cord. Thus accurate assessment of spinal cord function can help localize the tumor and the degree of compromise of neurologic elements. This is important for initial evaluation as well as for assessment of post-operative function, and in follow up to monitor for tumor recurrence. From a rehabilitation perspective, understanding of spinal cord function guides prognosis for functional ability and need for support. In most scoring systems, there is some aspect of the exam that requires communication or following directions so these exams are always more difficult in infants and young children.

A variety of tools are used to make these assessments both from an overall functional perspective and to assess specific spinal cord function. In the spinal cord injury literature and clinical practice the ASIA or American Spinal Cord Injury Assessment is used to assess motor and sensory function at each spinal cord level to localize the involved levels. Motor function is scored on a six point scale. 0/5 is no contraction, 1/5 trace contraction, 2/5 partial antigravity motion, 3/5 full antigravity motion, 4/5 full antigravity able to take partial resistance and 5/5 being normal, anti-gravity and able to take full resistance. The injury is further classified according to completeness which requires a rectal exam to assess function at the most sacral level. Sacral cord function must be intact for the lesion to be considered incomplete. If the patient is currently or imminently neutropenic, this part of the exam is not possible and thus the timing of the exam should be considered in this context. The lesion is graded from A which is a complete lesion with absent sacral function and in a traumatic injury has the worst prognosis for recovery to E which is normal function. The assessment is modified in the setting of an infant or toddler who cannot follow specific motor commands or respond to sensory questioning. A modified ASIA has appeared in the spinal cord tumor literature with a Grade 1 mild hypoesthesia with walking disability for legs or difficulty raising arms overhead for arms. Grade 2 moderate hypoesthesia with inability to walk and make movements against gravity or raise hands above head; Grade 3 severe hypoesthesia with paraplegia with no elicitable deep tendon reflexes or muscle movements.

The ASIA classification system is not used as commonly in the spinal cord tumor literature and the modified McCormick Scale is more standard here. This scale assesses more global functional impairment.

McCormick Functional Scale

Grade I	Neurologically intact; may have minimal dysesthesia; normal gait
Grade II	Mild motor or sensory deficit; patient maintains functional independence
Grade III	Moderate deficit; limitation of function, independent w/a external aid
Grade IV	Severe motor or sensory deficit, limit of function w/a dependent patient
Grade V	Paraplegic or quadriplegic, even if there is flickering movement

In many studies using the McCormick scale overall function tends to improve over time, possibly with a combination of neurologic recovery and learning compensatory skills as many studies follow function with the modified McCormick scale which would reflect both of these phenomena. However, deterioration of function in the absence of new tumor growth or progressive scoliosis is unusual and thus a decline in the Modified McCormick scale would likely pick this up.

Neurologic Post-operative Course

Patients presenting with minimal to no neurologic impairment generally have less than a 1 % risk of postoperative paralysis reported by Jallo et al. (2003). The degree and duration of pre

treatment impairment is most strongly correlated with post operative impairment. It is common for patients to have an initial post-operative neurologic decline that is often transient at least in severity with improvements seen in weeks to months.

Intramedullary tumors with cystic elements have a higher likelihood of postoperative neurologic improvement as do those with a less infiltrative pattern. Preoperative steroids are considered standard of care to improved post-surgical outcome. Adjuvant radio and chemotherapy is generally reserved for malignant or inoperable intramedullary tumors.

Post-operative Progressive Spinal Deformity

Scoliosis can result in cosmetic and functional deficit including compromised seating, head and extremity control and pain. In severe cases, SCC can occur. Neuromuscular scoliosis is often progressive and may require surgical stabilization. Post-operative progressive spinal deformity is known common sequela of treatment for SCT occurring in 16–100 % of cases in children though in only 6–10 % of adults as cited in McGirt et al. (2008b). Age reflective of spinal maturity is a factor, with 36 % of patients under 15 years and 6 % in 15–24 years experiencing progressive deformity in a pediatric study by Yasuoka et al. (1982). Jallo et al. (2003) found that 35 % of pediatric SCT patients required stabilization procedures for progressive deformity. The pediatric spine has several unique aspects that are thought to predispose patients to these complications. Facet joints are more horizontally oriented, ligaments are more extensible, bone itself has more plasticity, stabilizing musculature is less well developed and the spine is still in the process of growth.

Patients with greater motor impairments are also at high risk for progression due to the combination of decreased stabilizing forces and muscular imbalances resulting from incomplete injury. Damage to anterior horn cells or nerve roots supplying paraspinal musculature can cause weakness and instability. Location of the tumor also plays a role with a higher risk with tumors in the mobile thoracolumbar junction likely reflecting the relative stability of the disrupted segment as reported by Yeh et al. (2001). There are also issues related to the tumor that can lead to scoliosis. Asymmetrical tumor growth or cystic elements can cause deforming forces and bony erosion is also possible, decreasing structural stability noted by Houten and Weiner (2000).

Treatment itself can contribute to progressive spinal deformity. Surgery, chemotherapy and radiation all contribute to risk of post treatment spinal deformity and these risks must be weighed along with preservation of neurologic function and the best chance of disease control or eradication. Biopsy prior to resection, especially in extrameullary SCTs either by tissue sample of the SCT or if metastatic, another tumor site, or bone marrow may be used to determine histology and aid in planning the extent and timing of resection, chemotherapy and or radiation. This can prevent seeding which may occur with some tumors during resection.

If radiation is necessary in the area of the surgical site there is a significantly higher wound complication rate of 20–30 %. Radiated bone has lower fusion rate and is of poor quality. Radiation stops bone growth predisposing the spine to deformity. Chemotherapy also impairs healing and carries a higher rate of wound complications, though these factors resolve post treatment as opposed to radiation concerns that persist.

Surgical approach is determined by tumor size, location, stage and degree of resection desired. Laminectomy may be necessary to provide adequate exposure, but does compromise structural stability. More than 3–4 levels of laminectomy carries a higher risk of deformity. Preservation of facet joints promotes stability. In one series 30 % of pediatric patients who underwent laminectomy later required fusion as opposed to 5 % with laminoplasty as reported by McGirt et al. (2008a, b). This study also identified preoperative scoliosis, involvement of the thoracolumbar junction, age <13 years and multiple surgeries as risk factors for development of progressive spinal deformity. Stabilization at the

time of resection may be possible and in certain settings, beneficial. In general, preservation of the maximal amount of stability while allowing the most complete resection is considered best practice.

Routine follow up of all patients with SCT to detect progressive scoliosis is of great importance and should occur more frequently during growth and promptly with any clinical concern for curve progression. A progressive curve can signal a need for stabilization and can also be a sign of tumor relapse. In the setting of a progressive curve, early stabilization is advantageous to avoid fixed deformity and avoid more invasive, complicated and risky procedures. In the setting of tumor recurrence, prior resection may almost double the risk of progressive deformity. As with other patient populations with neuromuscular scoliosis, bracing may promote function by stabilizing the trunk to facilitate head and upper extremity control, but has not been shown to alter the course of curve progression as reported by Yasuoka et al. (1982) and is rarely well tolerated.

Rehabilitative Care

Many patients with spinal cord tumors will present with some degree of neurologic impairment and any process involving the spinal cord raises concern for functional impairment. Thus it is important that Rehabilitative care starts in the early stages of diagnosis and treatment. A Rehabilitation Physician also known as a Physiatrist can assist as part of the care team in assessing neurologic deficits, supporting recovery and regaining functional skills as well as counseling patients and families about functional possibilities in the face of present or possible neurologic deficits. The patient's functional potential based upon neurologic and developmental level, with emphasis on potential for skill achievement and eventual independence should be discussed with the patient and family. Mobility and self-care are important topics and this discussion should include options for social continence with a neurogenic bowel and bladder if this is an issue. It is often reassuring to address these issues directly as patients and families are often unaware of the skills the child can gain and thinking about future independent function can provide a positive perspective.

An additional concern in pediatric rehabilitation is not only regaining skills lost due to the neurologic insult but also assisting in attaining new developmental skills as they grow to support their best developmental progress regardless of neurologic deficit. For this reason, rehabilitative care will continue at varying intensity throughout development and into adulthood at varying intensity according to functional needs.

Members of the rehabilitation team may include physical, occupational and speech therapists as well as orthotists, specialized equipment vendors and rehabilitation nursing. Each of the therapy disciplines may play a role in supporting recovery. Physical therapists can address mobility and gross motor skills. Occupational therapists support gaining skills necessary for activities of daily living, which are often more compromised with upper extremity involvement. Speech therapists address communication including voicing, feeding and swallowing, which may be impaired with higher-level lesions.

Spinal cord tumor can cause impairment of any spinal level below the lesion. Thus in the cervical spine may involve upper extremity function, trunk and lower extremity control as well as bowel and bladder function. Thoracic tumor can involve trunk, lower extremity and bowel and bladder. Lumbosacral tumor can effect lower extremity and bowel and bladder function. Depending upon the completeness of the injury the patient may require total assistance for care to minor impairments and as many tumors result in more incomplete lesions, functional outcomes vary widely. Even in the setting of a complete lesion, a patient with cervical impairment below C5 should be able to propel a manual chair and have some independence with transfers, thoracic level lesions should be able to propel a manual chair, transfer and do their own bowel and bladder management. In lumbar lesions they should have the previously mentioned abilities and also may have ability to ambulate with or without bracing. Promoting functional independence is of great importance and can be more difficult in

the setting of a significant illness but needs to be prioritized and planned for even if progress is delayed due to treatment related issues.

Once deficits in functional abilities are identified, factors influencing these deficits such as debilitation, sensory deficit, abnormal tone, contracture and neurogenic bowel and bladder are identified and can be addressed. Rehabilitation medicine can treat issues such as spasticity, neuropathic pain and assist in neurogenic bowel and bladder management. They can also prescribe appropriate orthotics, adaptive equipment and overseeing therapy programs to promote function. We will discuss a few of the interventions for some of the common problems that may face a child with persistent neurologic deficit, specifically; mobility impairment, spasticity management and neurogenic bowel and bladder management.

Supporting the patient's most functionally independent mobility may involve therapies to increase strength, endurance, range of motion and learning new movement patterns and compensatory strategies. Custom orthotics may be used to provide stability and maintain alignment and range. Adaptive equipment in the form of mobility aides such as crutches, wheelchairs or bath equipment can increase the patient's functional independence and participation in daily life. Activities of daily living also include play and sports participation which are possible at any level of injury and need to be supported.

Spasticity results from a lack of descending control and modulation by the central nervous system and is common in spinal cord injury. Need for intervention for spasticity is determined by impact on comfort, mobility or flexibility. Spasticity can be managed with therapeutic handling and positioning using techniques that therapists can teach patients and families. Medications with systemic effects such as baclofen, dantrium, tizanadine or diazepam may be used for tone effecting large parts of the body. Choice of medication is guided by efficacy and side effects. The most common limiting side effects are often sedation or weakness. When spasticity is more localized, focal tone management is possible with botulinum toxin or phenol injections for motor point blocks. This can provide focal control of spasticity for 3–6 months periods without systemic side effects. In many cases of significant tone, a combination of interventions may be most helpful.

Neurogenic bowel and bladder can present as a total loss to a continuum of impairment of control and sensation of voiding and stooling. They can present as upper motor neuron or spastic or lower motor neuron or flaccid impairment. In either case the goal is preservation of bowel and renal health and promoting social continence.

Regular bladder emptying often with clean intermittent catheterization, is critical for long term renal health in the setting of upper motor neuron bladder dysfunction to avoid pressure injury to the bladder and kidney, to decrease risk of urinary tract infection due to urinary retention and also prevent overflow incontinence. Sometimes medications are used to manage bladder spasticity and detrusor dyssynergia. The Mitrofanoff is a surgical option, which allows catheterization through a stoma in the umbilicus, which can be helpful in the setting of limited dexterity and or mobility and trunk control.

Bowel management consists of promoting normal gastrointestinal motility and predictable emptying. Ideally, a patient with absolutely no voluntary control can be regulated such that involuntary bowel movements occur <1–2x/year. There are aspects of oncology treatment that complicate this process and often, functional control isn't achieved until after treatment. Many chemotherapy regimens can result in neutropenia or chronic diarrhea. Predictable emptying in the setting of chronic diarrhea is difficult to achieve and neutropenia limits bowel management options as digital rectal stimulation and suppositories, both commonly used to predictably empty the bowels are not possible. With prolonged chronic diarrhea and skin breakdown, a colostomy may be a helpful option and may be a temporary measure. Another surgical option for long term bowel management is the ACE or anterograde continence enema in which the colon is connected to a stoma in the abdominal wall and enemas are performed to empty to bowel at regular in a more physiologic direction and without the need for digital rectal stimulation which can be difficult to

perform with impaired hand dexterity or limited mobility, especially trunk control. However as the rate of recovery of bowel and bladder function is reasonably high and the time course often lags behind motor and sensory recovery, surgical management options need to be carefully considered.

Quality of Life

While survival is often the first question on patients and family's minds, overall quality of life is of great importance. Health related quality of life (HRQOL) is a multi-dimensional concept including physical, social, cognitive, and emotional functioning. Because it is primarily subjective, it is difficult to quantitate in the way the survival statistics can be. Subjective perception is however, of great importance in assessing quality of life as two individuals with similar medical and functional outcomes may report very different quality of life. HRQOL has been studied in a variety of patient types including pediatric central nervous system tumors, childhood spinal cord injury and even specifically in pediatric spinal cord tumors.

Mostow et al. (1991) reported that among children with CNS tumors, those with cognitive deficits had greater functional limitations and more impaired quality of life than those with motor deficits. Children with spinal cord tumors are less likely to experience cognitive decline though it is possible especially if hydrocephalus was a complication.

In children with spinal cord injury, Garma et al. (2011) reported that HRQOL was found to be more dependent upon psychological functioning specifically depression and anxiety, than upon injury related variables. Levels of anxiety and depression in children with spinal cord injury have been reported as not statistically different from their peers. Anderson et al. (2009) reported that anxiety is somewhat higher in patients with a shorter duration of injury and depression more common in those with less functional independence. Thus, maximizing functional independence and providing support during periods of transition is of great importance.

Poretti et al. (2008) reported on Quality of Life of 28 children with spinal cord tumor of varying tumor types and locations enrolled over 30 years. Median age at diagnosis was 3.2 years and mean follow up time was 8.5 years. Ten year OS was 96 % and PFS rate 84 %. Neurologic complications persisted in 50 % including paraparesis, monoparesis and neurogenic bowel and bladder, 35 % had scoliosis and 50 % had pain. All patients did well in regular school and those who were old enough all found employment in their field of choice. Limitations in activities of daily living did correlate with neurologic impairment. Psychosocial issues were not common and were similar to those noted in studies of other childhood cancer survivors. Though overall health related quality of life was reported as slightly lower in patients with spinal cord tumor compared with healthy peers it was not statistically significant. Of note, similar to other studies, parents report a somewhat more impaired quality of life for their children than their children do for themselves. This highlights the need to support parents as they may be having more difficulty with their child's functional limitations. It is also a hopeful message regarding long term quality of life for survivors.

In conclusion, generally, survival rates, functional outcomes and quality of life are quite favorable in most children with spinal cord tumors, though persistent neurologic and orthopedic impairments are common. A multidisciplinary approach to treating the primary disease as well as supporting the best functional outcome despite possible neurologic deficit is critical in providing the best care for these children and their families.

References

Anderson CJ, Kelly EH, Klaas SJ, Russell H, Daharsh E, Vogel LC (2009) Anxiety and depression in children and adolescents with spinal cord injuries. Dev Med Child Neurol 51:826–832

Angelini P, Plantaz D, De Bernardi B, Passagia JG, Rubie H, Pastore G (2011) Late sequelae of symptomatic epidural compression in children with localized neuroblastoma. Pediatr Blood Cancer 57:473–480

Bagley CA, Wilson S, Kothbauer KF, Bookland MJ, Epstein F, Jallo GI (2009) Long term outcomes following

surgical resection of myxopapillary ependymomas. Neurosurg Rev 32:321–334, discussion 34

Benesch M, Weber-Mzell D, Gerber NU, von Hoff K, Deinlein F, Krauss J, Warmuth-Metz M, Kortmann RD, Pietsch T, Driever PH, Quehenberger F, Urban C, Rutkowski S (2010) Ependymoma of the spinal cord in children and adolescents: a retrospective series from the HIT database. J Neurosurg Pediatr 6:137–144

Constantini S, Houten J, Miller D, Freed D, Ozek M, Rorke L, Allen J, Epstein F (1996) Intramedullary spinal cord tumors in children under the age of 3 years. J Neurosurg 85:1036–1043

De Bernardi B, Pianca C, Pistamiglio P, Veneselli E, Viscardi E, Pession A, Alvisi P, Carli M, Donfrancesco A, Casale F, Giuliano M, di Montezemolo L, Di Cataldo A, Lo Curto M, Bagnulo S, Schumacher R, Tamburini A, Garaventa A, Clemente L, Bruzzi P (2001) Neuroblastoma with symptomatic spinal cord compression at diagnosis: treatment and results with 76 cases. J Clin Oncol 19:183–190, Official Journal of the American Society of Clinical Oncology

Dow G, Biggs N, Evans G, Gillespie J, Ramsden R, King A (2005) Spinal tumors in neurofibromatosis type 2. Is emerging knowledge of genotype predictive of natural history? J Neurosurg Spine 2:574–579

Evans DG (2009) Neurofibromatosis 2 [Bilateral acoustic neurofibromatosis, central neurofibromatosis, NF2, neurofibromatosis type II]. Genet Med 11:599–610, Official Journal of the American College of Medical Genetics

Findlay GF (1984) Adverse effects of the management of malignant spinal cord compression. J Neurol Neurosurg Psychiatry 47:761–768

Garma SI, Kelly EH, Daharsh EZ, Vogel LC (2011) Health-related quality of life after pediatric spinal cord injury. J Pediatr Psychol 36:226–236

Gunes D, Uysal K, Cetinkaya H, Tekin H, Yuceer N, Sarialioglu F, Olgun N (2009) Paravertebral malignant tumors of childhood: analysis of 28 pediatric patients. Child's Nerv Syst: ChNS 25:63–69, Official Journal of the International Society for Pediatric Neurosurgery

Houten JK, Weiner HL (2000) Pediatric intramedullary spinal cord tumors: special considerations. J Neurooncol 47:225–230

Husband DJ (1998) Malignant spinal cord compression: prospective study of delays in referral and treatment. BMJ 317:18–21

Indelicato DJ, Keole SR, Shahlaee AH, Morris C, Gibbs C Jr, Scarborough M, Pincus D, Marcus R Jr (2010) Spinal and paraspinal Ewing tumors. Int J Radiat Oncol Biol Phys 76:1463–1471

Jallo GI, Freed D, Epstein F (2003) Intramedullary spinal cord tumors in children. Child's Nerv Syst: ChNS 19:641–649, Official Journal of the International Society for Pediatric Neurosurgery

Klekamp J, Samii M (1998) Surgery of spinal nerve sheath tumors with special reference to neurofibromatosis. Neurosurgery 42:279–289, discussion 89–90

Kramer ED, Lewis D, Raney B, Womer R, Packer RJ (1989) Neurologic complications in children with soft tissue and osseous sarcoma. Cancer 64:2600–2603

McGirt MJ, Chaichana KL, Atiba A, Attenello F, Woodworth GF, Jallo GI (2008a) Neurological outcome after resection of intramedullary spinal cord tumors in children. Child's Nerv Syst: ChNS 24:93–97, Official Journal of the International Society for Pediatric Neurosurgery

McGirt MJ, Chaichana KL, Atiba A, Bydon A, Witham T, Yao K, Jallo G (2008b) Incidence of spinal deformity after resection of intramedullary spinal cord tumors in children who underwent laminectomy compared with laminoplasty. J Neurosurg Pediatr 1:57–62

Mostow EN, Byrne J, Connelly RR, Mulvihill JJ (1991) Quality of life in long-term survivors of CNS tumors of childhood and adolescence. J Clin Oncol 9:592–599, Official Journal of the American Society of Clinical Oncology

Nadkarni TD, Rekate HL (1999) Pediatric intramedullary spinal cord tumors. Critical review of the literature. Child's Nerv Syst: ChNS 15:17–28, Official Journal of the International Society for Pediatric Neurosurgery

Norden AD, Drappatz J, Wen PY, Claus EB (2011) Survival among patients with primary central nervous system lymphoma, 1973–2004. J Neurooncol 101:487–493

Plantaz D, Rubie H, Michon J, Mechinaud F, Coze C, Chastagner P, Frappaz D, Gigaud M, Passagia J, Hartmann O (1996) The treatment of neuroblastoma with intraspinal extension with chemotherapy followed by surgical removal of residual disease. A prospective study of 42 patients–results of the NBL 90 Study of the French Society of Pediatric Oncology. Cancer 78:311–319

Poretti A, Zehnder D, Boltshauser E, Grotzer MA (2008) Long-term complications and quality of life in children with intraspinal tumors. Pediatr Blood Cancer 50:844–848

Rades D, Douglas S, Huttenlocher S, Rudat V, Veninga T, Stalpers L, Basic H, Karstens J, Hoskin P, Adamietz I, Schild S (2011) Validation of a score predicting post-treatment ambulatory status after radiotherapy for metastatic spinal cord compression. Int J Radiat Oncol Biol Phys 79:1503–1506

Scheinemann K, Bartels U, Huang A, Hawkins C, Kulkarni A, Bouffet E, Tabori U (2009) Survival and functional outcome of childhood spinal cord low-grade gliomas. J Neurosurg Pediatr 4:254–261, Clinical article

Seppala MT, Haltia MJ, Sankila RJ, Jaaskelainen JE, Heiskanen O (1995) Long-term outcome after removal of spinal neurofibroma. J Neurosurg 82:572–577

Wilne S, Walker D (2010) Spine and spinal cord tumours in children: a diagnostic and therapeutic challenge to healthcare systems. Arch Dis Child Educ Pract Ed 95:47–54

Wilson PE, Oleszek JL, Clayton GH (2007) Pediatric spinal cord tumors and masses. J Spinal Cord Med 30(Suppl 1):S15–S20

Yasuoka S, Peterson HA, MacCarty CS (1982) Incidence of spinal column deformity after multilevel laminectomy in children and adults. J Neurosurg 57:441–445

Yeh JS, Sgouros S, Walsh AR, Hockley AD (2001) Spinal sagittal malalignment following surgery for primary intramedullary tumours in children. Pediatr Neurosurg 35:318–324

Part V

Meningioma

Selection of Elderly Meningioma Patients for Surgery Using a Clinical-Radiological Grading System as a Predictor of Outcome

22

Manuela Caroli, Andrea Di Cristofori, Francesca Lucarella, Leonardo Zottarelli, Barbara Zarino, and Samis Zella

Contents

Abstract

Based on a retrospective study, in a previous report we developed a grading system, called 'Clinical Radiological Grading System' (CRGS), in order to standardise surgical indications in patients older than 70 years affected by intracranial meningiomas. Various prognostic factors were taken into consideration: clinical conditions, comorbidities, neurological status, size and size of the lesion and peritumoral edema. We then performed a prospective cross-sectional study including 90 consecutively recruited patients (from 1990 to 2000), 70 years of age or older, affected by meningiomas in whom the decision whether to operate was based on the CRGS score. Our findings showed that patients with a score lower than 10 had a poor prognosis regardless of surgical treatment, those with a score between 10 and 12 had a prognosis positively influenced by surgery, and those with a score higher than 12 had a good prognosis regardless of surgical treatment. A further validation of our scale has been made in a second prospective study, which is discussed in the present chapter. We also

M. Caroli (✉) • A. Di Cristofori (✉) • F. Lucarella
L. Zottarelli • B. Zarino • S. Zella
Neurosurgery Unit, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, via F. co Sforza 35, 20122 Milano, Italy
e-mail: andrea.dicristofori@gmail.com; man.caroli@tin.it

M.A. Hayat (ed.), *Tumors of the Central Nervous System, Volume 11*,
DOI 10.1007/978-94-007-7037-9_22, © Springer Science+Business Media Dordrecht 2014

analyzed similar studies performed by other authors and compare our grading system to alternative scores which have been created afterwards.

Introduction

The incidence of intracranial meningioma is between 1 and 2.8 per 100.000 inhabitants per year in the general population and 8.5 per 100.000 among elderly people. Given the increases in the average human life span, partially due to improved life conditions, indications for the surgical treatment of intracranial meningiomas have been broadened to include its use as a valid therapeutic option in the elderly population as a guarantee of longer survival and improved quality of life. The recent literature reports the effectiveness of surgical treatment even in patients older than 80 years of age (D'Andrea et al., 2005; Sacko et al., 2007). Based on a first retrospective study (Arienta et al., 1990), we developed a scored grading system, named Clinical Radiological Grading System (CRGS), which is composed of different subset items including the size and the location of the tumor, the presence of peritumoral edema, the patient's neurological status, the preoperative KPS score and the presence of concomitant diseases. According to this scale, when applied retrospectively to operated and unoperated subjects, patients with a total score lower than 10 had a bad prognosis even if surgically treated, whereas patients with a score higher than 12 had a very good prognosis regardless of whether they received surgical treatment. Patients with a score between 10 and 12 had a better prognosis if surgically treated. To confirm whether the CRGS scale was a good prediction of outcome, we performed a prospective cross-sectional study by including 90 consecutively recruited patients over 70 in whom the surgical indication was based on the CRGC score and the conclusions of the study supported the assertion that the CRGS was a practical and valuable grading system for use in the selection of elderly meningioma patients for surgery.

Further validation of the study has been made in the surgical series analyzed in the present chapter. Taking into consideration and comparing our system with other experiences by different authors that applied our grading or proposed alternative evaluating system, we decided to improve our grading, adding a specific neuropsycological assessment, analyzed in a specific chapter by the neuropsycologist. Considering the previous experiences where CRGS was retrospectively (Arienta et al., 1990) and prospectively (Caroli et al., 2005) applied, in this paper we present our updated case study of patients over 70 years with intracranial meningioma.

Clinical Radiological Grading System

Taking into account the various factors which can negatively affect the prognosis of the patients (size, location, neurological condition, initial Karnofsky performance status, edema, concomitant diseases) we have created a scored grading system which is summarized in the Table 22.1. The size of the meningioma was subdivided into three categories: small (<4 cm), medium (4–6 cm) and large (>6 cm). The location was considered critical when the tumor was attached to a venous sinus or close to major cerebral vessels, cranial nerves or the brain stem and eloquent areas. The definition of a critical location actually is made by a combination of radiological and neuroimaging tools: CT scanning, MR imaging, angiography and MR angiography with visualization of the venous sinus. Edema was considered moderate if it is only found to be perilesional and severe if there was a shift of midline structures. Neurological deficits were determined to be unrecoverable if they were stabilized and complete (for example, hemiplegia, amaurosis, or hearing loss) and recoverable if there was a progressive impairment of a neurological function (for example, hemiparesis, worsening of visual acuity, or hypacusia). The best score was attributed to patient without neurological deficit or with only seizures. Concomitant diseases are usually systemic diseases that potentially increase the anesthesiological risk to the patient and interfere with post-operative course; example are diabetes, cardiovascular diseases, respiratory

Table 22.1 Clinical radiological grading system (CRGS)

	1 point	2 points	3 points
Factors			
Size of lesion	>6 cm	4–6 cm	<4 cm
Neurological conditions	Unrecoverable	Progressive	No deficits
KPS score	< or = 50	60–80	90–100
Critical location	Highly	Moderately	Not critical
Peritumoral edema	Severe	Moderate	Absent
Concomitant disease(s)	Decompensated	Compensated	Absent

diseases. We defined diseases compensated when they were controlled by medical therapy and decompensated when they were uncontrolled despite medical therapy.

Patients and Methods

Patients

Between 2000 and 2006, a total of 68 patients old patients with supratentorial were evaluated in our database.

Inclusion criteria of database search were: age at diagnosis ≥70 years and histologically confirmed Meningioma according to the World Health Organization (WHO) [meningiothelial meningioma (WHO Grade 1), atypical meningioma (WHO Grade II) or anaplastic meningioma (WHO Grade III)], treated with open surgery and available clinical and radiological follow-up data within the first 6 months after surgery. The preoperative CRGS Score was ≥10 in all our patients.

Diagnosis and tumor grade was histologically confirmed in all cases. Patients with lack of histopathological confirmation or with CRGS Score <10 were excluded.

The following clinical data were determined for each patient: age at the time of operation, gender, KPS, CRGS Score, comorbidities, tumour localization, tumour size, extent of resection through a post-operative cerebral MRI obtained 72 h after surgery, type and rate of complications.

Surgical adverse events after treatment data were collected for each patient.

Endpoints of this study were to evaluate, after the surgical treatment, the KPS, the clinical and neurological status, the mortality rate within the within the first 3 months after surgery, the need of rehabilitation, and the rate of surgical complications.

Surgical Techniques

All patients were operated on in a MRI setting.

Patients underwent open resection with partial or complete removal of the contrast enhancing tumor as demonstrated by early postoperative MRI.

Postoperatively, all patients were treated with 8 mg/day steroid therapy for the first 3 days after surgery, then the doses was arranged depending on the presence of perifocal edema, mass effect, and clinical status.

Contrast enhanced MRI was performed within 72 h of intervention in order to determine the extent of resection.

Clinical Follow-Up

Patient were clinically evaluated pre-operatively, post-operatively, before discharge and then every 3 months. A neurological assessment was performed. The incidence of peri-operative morbidity was assessed within the first 3 months after surgery in all cases. Symptomatic edema was defined as an acute increase in edema surrounding the resection cavity in the first 3 months that could

not be attributed to early tumor progression and that required aggressive corticosteroid therapy.

MRI Follow-Up

All MRI studies included Fluid Attenuated Inversion Recovery, T2-weighted and T1-weighted before and after administration of Gadolinium contrast material. MRI was performed within 72 h from surgery to evaluate extent of removal. Degree of resection was retrospectively classified from postoperative MRIs as macroscopical complete total resection (no residual nodular enhancement on MRI) or as subtotal resection (residual nodular enhancement on MRI). Pre and postoperative MRI reports documented by an attending neuroradiologist were re-evaluated.

Analysis

A formal statistical analysis were conducted to determine the results.

In order to calculate the statistical significance, the Chi Squared Test has been used or, when necessary due to sample size, the Fisher's Exact Test. As a significance limit, a value of $p<0.05$ has been adopted.

Results

Our series consists of 56 patients with intracranial meningiomas, surgically treated at our Institute between 2000 and 2006. Of the 56 patients, 25 were males and 31 were females. Median age was 74; age range was 70–86 year-old. Most patients had a single meningioma, only five patients presented with multiple lesions.

The most common anatomical location was represented by the cerebral convexity (21 cases), followed by the parasagittal area (13 cases). Other areas involved were the falx cerebri (6), the small sphenoidal wing (5), the middle cranial fossa (3), the ponto-cerebellar angle (3), the tentorium border (2), the tuberculum sellae (1), the olfactory groove (1), intraventricular (1).

Considering the Clinical Radiological Grading System (CRGS), we observed a range score between 9 and 18. Median CRGS score was 12.5. Lesions were classified by size, location and peri-lesional edema. Lesions were divided by size superior than 6 cm, between 4 and 6 cm or smaller than 4 cm. Sixteen patients of our series belonged to the first group, 18 patients had intermediate lesion' size and the remaining 22 patients were in the last group. Location was sub-divided into brain areas considered to be at high risk (for example motor areas, speech areas) to which the majority of our patients belonged (29). Medium risk locations (such as occipital region, periventricular regions) were involved in 23 cases; while just a few patients (4) had tumors involving low risk areas (for instance postcentral area, right hemisphere frontal region).

Edema was classified, considering its extension, in severe, moderate or absent. Most of the patients (24) presented with a severe edema, 19 patients with moderate edema and 13 patients had none.

The other parameters part of this score take into account the clinical conditions of the patients at presentation, including their neurological status and KPS score and their comorbidities.

The neurological status could vary from irreversible deficits to progressive and reversible deficits or no deficits at all (presence of seizures being included in this group). In our series, no patients presented with irreversible deficits, the majority of them having progressive/reversible deficits (41). Only 15 patients belonged to the last group.

We observed a KPS score minor to 50 in only 4 patients, between 60 and 80 in 18 patients and between 90 and 100 in 34 patients. Comorbidities were divided into decompensated diseases, compensated ones and absence of comorbidities. Only a few patients suffered from decompensated diseases, while the majority of them (32) had well compensated comorbidities. Eighteen patients had no clinically relevant comorbidities. One or several complications were noticed in 11 patients (19.6 %). All the complications were observed in patients having a CRGS < 13 (range 10–13). Fourteen patients needed rehabilitation

treatments after discharge (25 %). All the 14 patients were scored between 10 and 14. In our series of patients, mortality at 1 month was 3.5 % (2 patients); mortality at 3 months was 7 % (4 patients). One-year mortality was 14 % (8 patients). In particular, patients with CRGS < 13 had a 3-months mortality of 13.8 %, against a 0 % mortality in patients with CRGS > 13. In a similar way, 1-year mortality was 24.13 % for patients with CRGS < 13 and 3.84 % for patients with CRGS > 13. At 1-year follow up we analyzed the quality of life (QOL) of the 48 remaining patients, by calculating the KPS. Median KPS score was 83. Sixteen patients with pre-operative KPS < 90 (range 60–80) showed a significant increase of KPS after surgery. Thirty-two patients having an initial KPS of 90–100 worsened their KPS score after surgical treatment, though this change was not significant in terms of QOL.

Discussion

In the literature, many different scales have been proposed to assess the risk of surgical procedure in elderly patients with meningiomas. Particularly, only few have been validated based on retrospective and subsequent prospective studies. Our experience started in 1990 with a retrospective analysis of 46 patients over 70 years of age or older of which 34 underwent surgical exeresis and 12 did not undergo surgery (Arienta et al., 1990, 1992). First results showed 12 % of perioperative mortality rate increasing to 20 % at 3 months follow-up. Diabetes and peritumoral edema were the most important prognostic factors. Moreover, KPS and presence of heart failure were other important predicting factors. This probably was related with the reduction of bedtime period and anesthesia length (Stéphan et al., 2001).

Based on our first retrospective study, we developed a clinical radiological grading score (CRGS) to orientate surgical decision making in elderly meningioma patients and to explore prognostic factors of survival. To confirm whether this grading was a good predictor of outcome, we applied CRGS prospectically in 90 consecutive recruited patients, in which surgical indication has been decided on the basis of the score. In this series, CRGS ranged from 9 to 16 and perioperative mortality was reduced to 6.7 % while 1 year mortality rate was 15.6 %. However, CRGS and female sex were strongly related with surgical outcome in patients with CRGS higher than 10 (Caroli et al., 2005). According to this validation, we now submit to surgery only patients with CRGS higher or equal to 10. Surgery in patients with CRGS lower than 10 is related only with emergency conditions. Our score underwent a further validation by Schul and colleagues in a different surgical series (Schul et al., 2012). They retrospectively reviewed 165 patients aged 65 or older that underwent an exeresis for intracranial meningioma and they found only two statistical predicting factor related with patient's clinical outcome: ASA score and concomitant diseases (Schul et al., 2012). They compared the CRGS and the SKALE score by Sacko et al. (2007). Limitations of this study was due to its retrospective character because in the institution involved in the study, patients had been selected for surgery independently of a grading score. Moreover, the series was younger than Caroli's and Sacko's. That cohort of patients was aged between 65 and 87, with an average age of 72 that is not comparable to our series or to Sacko's casistic, which included patients aged 80 years or older (Sacko et al., 2007).

When we compare CRGS and SKALE score we can observe that tumor location, KPS and edema are common factors taken into consideration in both scores even if there are few conceptual differences in the definition of the "tumor location". On the other hand, the authors of the SKALE score do not consider "concomitant diseases" as a single risk factor, but they adopted the ASA as a predictive score assessing the anesthesiological risk.

Moreover, sex is considered an important factor in the SKALE score while we do not consider it a relevant factor in deciding which patient have to be surgically treated. Influence of sex in postoperative outcome is related with the natural history of patients in the elderly. Selecting patients aged 80 or over, the life expectancy decrease and

being a female it is known to be a positive factor because life expectancy in aged females is longer than in men. Thus, in authors' opinion, in selecting patients aged 70 or older, sex does not play an important role in deciding which patient has to be submitted to surgery. Role of ASA score is very important to manage surgical patients but it doesn't relate and doesn't impact on post-operative outcome. In fact, in our opinion ASA score is important to decide if a patient can be surgically treated, especially for those aged more than 80, but is not related with post-operative outcome or quality of life and it cannot relate with 3 months or 1 year follow-up.

Other scores taking into account ASA score as a predicting factor of surgical outcome are the CLASS score (Lee and Sade, 2009) and the geriatric score system (GSS) by Cohen-Inbar et al. (2010). The first one, is only a surgical indicator for post-operative morbidity which takes into account two different features influencing surgical outcome: risk factors and beneficial factors. Risk factors included patient's age, co-morbidities and tumor's location. Beneficial factors are considered size and neurologic signs and symptoms. Particularly, tumor size is considered a beneficial factor because the bigger the tumor and the worse neurologically the patient appears, the better the score is. Neurological signs and symptoms relate to mass effect or epilepsy that can be relieved by tumor debulking. On the other hand, patients aged 71 or older are considered at high risk for surgery. Co-morbidities have been considered using the ASA score, like many other authors did. Tumor location have been divided according three different subgroups: low risk group including tumor at the convexity and at the lateral skull base; medium risk group including olfactory groove, planum sphenoidale, tentorial (lateral/paramedian), parasagittal, intraventricular, cerebellopontine angle, falcine, posterior/lateral foramen magnum as well as para-sigmoid and para-transverse sinus locations; high risk group locations included clinoidal, cavernous sinus, tuberculum sellae, tentorial (medial/incisural), ventral petrous, petroclival and anterior/antero-lateral foramen magnum (Lee and Sade, 2009).

The GSS by Cohen-Inbar et al. is quite similar to our score but it differs in the list of comorbidities. Only diabetes mellitus, arterial hypertension and pulmonary diseases are considered as risk factors. Other conditions that can influence surgical outcome such as chronic liver diseases or kidney diseases are excluded. Infact, the Charlson Comorbidity Score, which as been adopted by Grossman et al. (2011) as a predictor of outcome in elderly patients with meningioma, included all these comorbidities. Moreover, in the GSS meningioma's locations are well subdivided based on complications related to the surgical site considered. This classification can be questionable because not all institutions have the same surgical expertise (Cohen-Inbar et al., 2010). This score has been validated on a following paper 1 year after. A cohort of 120 patients aged 65 years or older submitted to surgery and selected using the GSS was studied (Cohen-Inbar et al., 2011). Authors showed a correlation between GSS and outcome; patients with preoperative GSS equal or higher than 16 had a better 5 years outcome in terms of KPS, GCS and Barthel index. Moreover, this group of patients had reduced hospitalization time and better overall survival.

Relevant Factors Considered in the Literature

All the rating scales reported above have been composed by radiological and clinical parameters. Edema, size and location are the most important radiological item taken into account; while clinical parameters are: age, ASA score and/or chronic disease, neurological status and KPS (Caroli et al., 2005; Sacko et al., 2007; Cohen-Inbar et al., 2010; Schul et al., 2012; Lee and Sade, 2009; Arienta et al., 1990).

Age is not always considered a risk factor for meningioma surgery. It is reported in our experiences (Arienta et al., 1990; Caroli et al., 2005) and by other authors assessing that meningioma surgery is feasible in the elderly and the outcomes were similar to those of younger people (Black et al., 1998). Other authors consider age an important

factor with differences between younger and elderly patients (Bateman et al., 2005; Patil et al., 2010). Particularly, Patil in his study assessed that age greater than 70 was associated with a threefold increase in the odds of perioperative mortality (Patil et al., 2010) and Bateman showed that elderly patients were three times more likely to die during their hospital stay than younger people.

KPS has been utilized in the majority of the studies as an important index to evaluate the preoperative functional conditions. A low KPS is generally considered a worse prognostic factor, but it is not an independent item, since intracranial meningiomas likely correlate with neurological status and therefore the real KPS score could be reduced. In our previous paper and in the second validation (2000–2006) of our prognostic score (CRGS) we observed an improvement in KPS scores in patients with a baseline score equal or lower than 70 and no change or only a mild worsening (without affecting the quality of life) in patients with a higher score. This fact is probably related with the important mass effect of meningiomas in patients with KPS lower than 70. This observation has been made by Lee and Sade that consider size as a beneficial factor (Lee and Sade, 2009). Moreover also Schul et al. (2012) underlined that there was an improvement in mean KPS postoperatively in patients with preoperative KPS equal or lower than 80 and a mild worsening in patients with preoperative KPS equal or higher than 90 (Schul et al., 2012).

The presence of perilesional edema is an important factor and it has been assessed by different works. Cohen-Inbar et al. (2010), measured post-surgical outcome using 5 years Barthel index. In their work peritumoral edema upon admission showed a direct correlation with the Barthel index at 5 years follow-up: the more severe the edema, the lower is Barthel 5-year score (Cohen-Inbar et al., 2010). Also In our experience peritumoral edema is considered a prognostic factor. Severe edema relates with worse post-operative and, conversely, lack of peritumoral edema and concomitant diseases is likely to provide the strongest contribution to survival following surgery and to 1 year survival (Caroli et al., 2005). Different authors confirmed our experience in prospective and retrospective analysis. Sacko et al. (2007) established that the presence of severe peritumoral edema was associated with a higher risk of postoperative mortality and morbidity than in patients with moderate or no edema. In the paper of Schul et al. (2012), who retrospectively applied CRGS and a SKALE, the presence of edema showed a significant contribution only in univariate analysis, but it was deleted as a predictor in multivariate regression (Schul et al., 2012).

Size of meningioma is commonly associated to surgical outcome since it is related with surgical time, intra-operative and post-operative hemorrhagic risk and with extent of resection. In our retrospective study (Arienta et al., 1990) we correlated the size and the location of the tumor to the duration of the surgery that indirectly affected mortality, because the longer the surgery the higher the mortality score, and therefore tumor size was considered to be a risk factor and was introduced in the scored system. Nevertheless, in the prospective validation study we found no statistical influence on size of lesion and post-operative outcome (Caroli et al., 2005). These considerations are debated in the literature because data often contrast with common clinical experience. Other authors considered tumor size to be a risk factor. Particularly, in the work by Sacko and colleagues, size tumor related with post-operative morbidity (Sacko et al., 2007). According to Cohen-Inbar, tumor size concomitant to venous sinusoidal resection together influence the Barthel Index 5 years after (Cohen-Inbar et al., 2010). On the other hand, Lee and Sade consider meningiomas size a positive prognostic factor indicating the potential benefit from tumor gross total resection (Lee and Sade, 2009).

Location of the tumor is important and impact on post-operative outcome. As a matter of fact, tumor location is taken into account in many studies in the literature dealing with meningioma surgery in the elderly (Arienta et al., 1990; Caroli et al., 2005; Patil et al., 2010; Lee and Sade, 2009; Cohen-Inbar et al., 2011; Sacko et al., 2007). Unfortunately, the definition of critical region is highly subjective and changes between the

different authors. The classification of critical site is quite similar in CRGS and SKALE: cranial base, eloquent area and near the large vessels. In fact, resection of skull base meningiomas is considered to be risky for complication; while resection on eloquent area can relate with post-operative deficits impacting on post-operative outcome. Particularly, Sacko found correlation between tumor location and mortality during the follow-up period. On the other hand, Cohen-Inbar in his score (GSS) define falcine, parasagittal and foramen magnum meningiomas as critical located tumors; while posterior fossa or tentorial meningiomas are considered in medium risk regions and the other sites, including skull bases meningiomas, are surprisingly considered to be placed in low risk regions (Cohen-Inbar et al., 2010). This classification is not reflected in any other study. In fact, Patil states that patients with infratentorial tumor location are associated with a twofold increase in the odds of perioperative death (Patil et al., 2010). The same considerations are made by Cornu et al. (1990) and Sacko et al. (2007).

Clinical conditions, meaning both general and neurological status are important items influencing the impact on post-operative course and on the total bedtime, which is related with different medical complications. Functionally dependent or partially dependent patients were 2.8 times more likely to die than patients who were preoperatively independent. The parameter "neurological deficit" in included in CRGS and in GSS, but not in SKALE score. In the Charlson Comorbidities Score, neurological impairment is included in the scale, but it is not an independent parameter (Grossman et al., 2011). In our opinion the evaluation of neurological status is mandatory, since if a patient shows unrecoverable deficits, we should answer the question: can ensure an improvement in the patient against the risk run by the intervention? And, finally, we have to consider that the general status, the neurological function and the KPS score contribute to define the quality of life of the patient. Only GSS included in its score the Barthel index, which is a parameter investigating the quality of life. On the other hand in none of the studies, the patient's cognitive status was taken into account as an independent parameter.

Rational for Surgical Treatment in the Elderly Patients

Rationale for surgical treatment of intracranial meningiomas is based on clinical and radiological findings. First of all, in our opinion, asymptomatic patients without signs of mass effect have to be followed-up without any treatment. On the contrary, patients with radiological mass effect or symptoms referring to the meningioma, need to be treated. The decision to surgical treat meningiomas has to be considered on the factors reported above and on the medical general condition of a patient, without taking into account age and sex. Particularly, patients with a poor KPS or with chronic uncompensated disease may not benefit from any surgical procedure. The CRGS, we proposed resembles this rationale and can be considered a global predictor for assessing the surgical outcome of elderly patients submitted to surgery. On the other hand, we don't exclude compromised patients from surgery but in those cases the choice have to be made with a precise indication.

We suggest to submit to surgery only patients with CRGS more than 10. Particularly, in the second validation of our score, we observed a favorable outcome in patients with CRGS higher or equal to 13. We also noted a perioperative mortality of 13.8 % in patient with CRGS lower than 13; while patients with CRGS higher or equal to 13 had no perioperative mortality. A 1 year mortality was observed to be 24.13 % in patients with CRGS lower than 13; while the other group had a 1 year mortality of 3.84 %. Our data seem to be similar to those found in literature. A summary of data reported in literature are shown in Table 22.2.

In our opinion, patients with CRGS under 10 can undergo to surgical procedure only if the meningioma is responsible to a decrease of KPS influencing the global result calculating the CRGS. In this cases, post-surgical outcome probably can be characterized by an increase of KPS.

Table 22.2 Comparison of mortality rates across different studies in the literature

Author	Age	Number of patients	30-day mortality	Perioperative morbidity	3-months mortality
Papo (1983)	>65	29	55 %	n. r.	n. r.
Jan et al. (1986)	>70	35	n. r.	n. r.	13 %
Awad et al. (1989)	>70	25	n. r.	52 %	6.7 %
Cornu et al. (1990)	>65	96	16 %	43 %	23 %
Arienta et al. (1990)	>70	34	12 %	44 %	20 %
Umansky et al. (1992)	>70	37	5.4 %	40.5 %	n. r.
Maurice-Wiliams and Kitchen (1992)	>65	46	2.2 %	30 %	n. r.
McGrail and Ojemann (1994)	>70	56	3.6 %	11.3 %	n. r.
Nishizaki et al. (1994)	>70	78	13 %	n. p.	n. r.
Mastronardi et al. (1995)	>80	17	29 %	11.8 %	29 %
Proust et al. (1997)	>70	39	n. r.	n. r.	7.6 %
Black et al. (1998)	>65	57	1.8 %	17.6 %	1.8 %
Lieu and Howng (1998)	>65	36	11.1 %	47.2 %	16.7 %
Buhl et al. (2000)	>70	66	7.6 %	n. r.	n. r.
D'Andrea et al. (2005)	>80	37	n. r.	2.7 %	13.5 %
Caroli et al. (2005)	>70	90	6.7 %	n. r.	7.8 %
Sacko et al. (2007)	>80	74	0 %	9.4 %	1.4 %
Cohen-Inbar et al. (2010)	>65	250	n. r.	n. r.	8.4 %
Patil et al. (2010)	>70	258	12 %	n. r.	n. r.
Cohen-Inbar et al. (2011)	>65	120	n. r.	n. r.	5.8 %
Schul et al. (2012)	>65	164	3.7 %	21 %	3 %
Grossman et al. (2011)	>65	5,717	n. r.	n. r.	n. r.
Our series	>70	56	n. r.	19.6 %	7.2 %
		Total pts	**Average 30-day mortality**	**Perioperative morbidity**	**3-months mortality**
		7,417	19.57 %	38.00 %	17.60 %

n. r. not reported

Neuropsychological Assessment of Elderly Patients with Intracranial Meningioma

Introduction

Neuropsychology is an applied science interested in the behavioural expression of brain dysfunction and the correlation between site of lesion and subsequent cognitive deficit. The neuropsychologist usually describe the cognitive functioning of the patient through the administration of standardized cognitive tests.

Since the US Food and Drug Administration designated improved neuro-cognitive function or delay in neuro-cognitive decline as acceptable end points in clinical trials in 1998, cognition has been demonstrated to be an independent predictor of survival in patients with central nervous system (CNS) tumors. Actually neuropsychological evaluation has demonstrated extreme value in several neurological disorders, including brain tumours (Papagno et al., 2012). A variety of alteration in mental functioning and personality can be observed with neuropsychological tests in patients with intracranial neoplasms. Identifying personality and neuropsychological changes may lead, for example, to better therapeutic interventions to improve outcome, better quality of life for the patient and better care by relatives. Furthermore, cognitive deterioration has been shown to be an early indicator of tumour progression, sometimes before it is detectable on imaging studies (Meyers and Brown, 2006). Despite the fact that the outcome is measured by size of lesion, location,

edema, neurological and physical condition, and concomitant disease (Caroli et al., 2005), this parameters do not inform about cognitive and functional situation of the patients. Indeed the simple ability to execute the activities of daily living, like washing, dressing, moving and eating, not indicate the patient's cognitive status. Cognitive status plays a very important role in the overall well-being and quality of life of patient: cognitive impairments, more than physical disability, has important implication for quality of life. For these reasons neuropsychological tests of cognitive functions have become increasingly important in clinical and pharmacological trials to quantify the effects of tumours, surgery and therapy (pharmacotherapy, chemotherapy and radiotherapy). Finally, after treatments like surgery and therapy the cognitive follow-up can guides the rehabilitation programs, in particular for the elderly population.

Neuropsychological Assessment

Characteristic and Criticality

Parameters such as survival and impairment of neurological function have traditionally been used to evaluate the outcome after brain tumour surgery. Today, advanced technology has resulted in a considerable decrease of severe neurological deficits observed in the past after meningioma surgery (Curry et al., 2005). According to recommendations of current outcomes research programs, cognitive functions and quality of life (QoL) variables needs to be integrated to comprehensively evaluate surgical procedures (Giovagnoli et al., 1996). Furthermore, parameters like tumour control, short- and long-term neurotoxicity, and rates of neurocognitive decline are all outcomes that may vary among different treatment regimes and subsequently inform treatment decisions (Meyers and Brown, 2006).

The World Health Organization (WHO – International Classification of Impairments, Disabilities, and Handicaps, 1998) proposes an evaluation model for elderly patients that includes the assessment of (1) cognitive impairment, (2) disability, and (3) quality of life.

Neuropsychological assessment can be divided into two macro-parts: a qualitative and a quantitative.

Qualitative part is composed by: (a) clinical interview with the patient; (b) observation of the subject; and (c) medical history with family/caregiver. The quantitative part of neuropsychological evaluation is composed by: (a) scales for assessing the functional status of the patient; (b) scales for assessing the quality of life; (c) scales for assessing the affective state; (d) brief global cognitive tests; (e) test-specific of cognitive abilities.

In general, there are a numbers of difficulties in building cognitive batteries for brain tumour clinical trials (Lageman et al., 2010), and in particular for the elderly patient because it collides with the need for brevity, sensibility, simplicity and completeness. Brevity is important to limit the demand on patients' stamina and allow time for measurement of other outcomes. Generally in the selection of batteries for clinical trials researchers try to sample from multiple cognitive domains and also try to select tests sensitive to generalized dysfunction. The objective is to detect potential focal changes due to tumour effect, and detect general dysfunction that might be due to medication or other factors. The other necessary features of cognitive assessment of elderly patients are the sensibility to cognitive changes, the simplicity in order to the majority of patients complete it, and the completeness in order to be sensitive to focal effects of tumour.

In the majority of clinical trials the assessments of brain dysfunction and cognitive impairment in brain tumour, when included, have been limited to brief screenings for global cognitive function, such as the Mini Mental State Examination (MMSE). However, the MMSE was developed as a screening tool for dementia and is insensitive to mild cognitive impairments or focal lesions. The MMSE does not have well-established sensitivity or specificity, it does not measure many of the functions known to be impaired in brain tumour patients, and it does not have validated alternative forms for repeated testing. The use of such an insensitive tool might mean that patients with true

disability resulting from cognitive impairments would not be identified and offered appropriate interventions (Lezak et al., 2004).

A good neuropsychological test battery usually consists of validated, standardized, reliable and normed measures that help the neuropsychologists to quantify cognitive changes resulted from brain injury like tumours. Neuropsychological exam furnish a comprehensive evaluation of cognitive domains potentially associated with different brain substrates.

To date few data are available concerning the assessment and the outcome of surgical removal of intracranial meningioma in elderly patients (Tucha et al., 2001). The selection of appropriate tests for clinical trials is complicated further by the range of tumour locations and possible associated cognitive symptoms. The following will examine the neuropsychological tests commonly used in neuropsychological evaluation of elderly patients with meningioma, and a proposal to insert the neuropsychological evaluation in a CRGS.

Cognitive and Quality of Life (QoL) Assessment of Elderly Patients with Meningioma

The cognitive assessment of elderly patients with intracranial meningioma, who undergo surgical removal of the lesion, includes tests that are performed by all patients and a tests depending on the lesion location. All tests are selected according to essential psychometric properties such as objectivity, reliability, validity, and responsiveness. All tests are from the most frequently used psychometric instruments in their cognitive area in Italian-speaking countries. Results of all tests are calculated in relation to normative population values: raw scores are adjusted for age, education end sex.

To evaluate the effect of meningioma, surgery and treatments on cognitive functioning is necessary to submit patients to neuropsychological evaluation few day before surgery, in the week post-surgery, and then at 3–6 months as follow-up:

(a) pre-operatory evaluation: allow the neuropsychologist to evaluate the effect of meningioma on cognitive functioning;
(b) post-operative evaluation: allow the neuropsychologist to evaluate the effect of surgery;
(c) follow-up evaluation: allow the neuropsychologist to evaluate recoveries/loss of functions.

The neuropsychological assessment of elderly patients with intracranial meningioma must include the investigation of: orientation, attention, executive functions, memory and working memory, and language.

Orientation

Temporal orientation is assessed by asking the patient the day of the month, month, year, day of the week and season; spatial orientation is assessed by asking the patient if he knows the place, plan, city, region and the state in which it resides; finally, personal orientation is evaluated asking the date and place of birth.

Attention

The attention includes a series of different mechanisms and behaviours. The attention is a set of processes that modulate the ability of individuals to act and interact in the world, by maintaining a state of activation, through the selection of sensory information and control and monitoring of thoughts and actions.

Attention and concentration are critical for higher level neuropsychological functioning, deficits in attention and concentration are often the bases for reported deficits among brain-injured patients in learning and memory, communication, reading, writing and executive functions. In general we can divide the attention in: alertness, sustained attention, selective attention and divided attention. The neuropsychological tests most commonly used in psychometric assessment of elderly patients are:

– for the alert the most widely used is the record of reaction time;
– sustained attention is measured by asking patients to perform simple and monotonous

tasks that required to maintain over time accuracy of response and speed execution (for example the Simple Vigilance Test (SVT) and Continuous Performance Test (CPT));
- selective attention is usually assessed by cancellation task in which the patient has to perform a visual search of target-stimulus among distracters (for example the Visual Search test and the Stroop test);
- divided attention is assessed by tasks in witch the patient must do two things at once – dual task (for example the Trail Making Test and Paced Auditory Serial Addition Task).

Executive Functions

The anterior frontal areas have a crucial role in the regulation of cognition and behaviour. The prefrontal areas are complex from the standpoint of structural and functional, and can be divided into the lateral surface, orbital and medial. Executive functions tests' may be divided with reference to the predominant executive component:
- dorsolateral prefrontal cortex control the ability to making plan, strategic decision, cognitive flexibility, problem solving and divided attention. These abilities can be evaluated in elderly patients with, for example, Tower of London test, verbal fluency, cognitive estimates, Trail Making test, etc.
- orbitfrontal cortex control, in particular, the ability to make decisions and to regulate the behaviour. These abilities can be evaluated with task like Gambiling test.
- medial cortex (anterior cingulated cortex) control the ability to inhibit automatic or impulsive responses; tests that are most commonly used to assess these abilities are the test of motor learning inverted (go – no-go) and the Stroop test.

Memory

Memory is the ability to store information to draw upon when needed and includes two processes: learning and memory. The learning process is composed by different phases: encoding, consolidation, storage and subsequent recovery. The learning may be intentional or incidental. Memory is not a unitary function and can be divided into short- and long-term memory; the short-term memory may be divided into verbal and visuo-spatial component; the long-term memory may be divided into explicit or declarative memory and implicit or procedural memory. Explicit memory can be further divided into two components: episodic and semantic.
- verbal short-term memory is composed by phonological recording and articulatory rehearsal loop; test most commonly used is called span (of digits or disyllabic words);
- visuo-spatial short-term memory can be assessed by memory tasks for positions (like Corsi span test), or with memory for matrices test;
- verbal learning can be assessed by words list learning tests and short story;
- visuo-spatial learning can be assessed with Corsi learning test, supra-span learning, delayed reproduction of complex figure (Rey Complex Figure test – RCFT, or Modified Taylor Complex Figure test – MTCF), and learning a route in a maze.

Working Memory

The working memory is the system which actively holds information in the mind and allow to do verbal and visuo-spatial tasks, and make the information available for further processing. Working memory can be assessed with goal-oriented active monitoring tasks, or with manipulation of information or behaviours tasks, or the speed of memory retrieval process like the digit span forward and backward.

Language

Language can be assessed with naming tasks (verbal fluency on phonemic and semantic cue and picture naming of objects and of actions), lexical/phrases comprehension tasks, repetition tasks, reading and writing tasks.

Quality of Life

For decades the effectiveness of a treatment in oncology was evaluated in terms of quantity of survival. In recent years it has become increasingly important the quality dimension – Quality of Life (QoL)- perceived by the patient. The World Health Organization defines QoL "perception that individuals have of their position in life, in the context of culture and value systems in which they live and in relation to their goals, expectations, lifestyle and interests." In particular, in oncology the concept of QoL is important for the drama of the event, the traumatic impact of the diagnosis, the effects of surgical treatment, chemo-and radiotherapy and the impact that the disease has on the psychological spheres, emotional, social and family.

The quality of life of elderly patients with meningioma can be assessed by general instruments such as the SF-36 or specific tools for the cancer patient as the EORTC Quality of Life Questionnaire Core 30 (QLQ-C30), the Rotterdam Symptom Checklist (RSCL), the Functional Living Index Cancer (FLIC), and the Functional Assessment of Cancer Therapy scale (FACT). While for generic quality of life questionnaires norm values for the general population are often available, disease-specific questionnaires mainly focus on reference values for specific disease groups.

- The SF-36 (Ware and Sherbourne, 1992) is composed of 36 items, organized into eight multi-item scales assessing physical functioning, role limitation caused by physical health problems, bodily pain, general health, vitality, social functioning, role limitation caused by emotion problems, and mental health. Raw scores are converted linearly to scales of 0–100, with higher scores representing better levels of functioning.
- The QLQ-C30 (Fayers and Bottomley, 2002) is a 30-item questionnaire that incorporates nine multi-item scales and reflect the multidimensionality of the quality of life construct: five functional scales (physical, role, cognitive, emotional, and social); three symptom scales (fatigue, pain, and nausea and vomiting); and a global health and quality-of-life scale. The remaining single items assess additional symptoms commonly reported by cancer patients (dyspnea, appetite loss, sleep disturbance, constipation, and diarrhea), as well as the perceived financial impact of the disease and treatment.

Clinical Radiological Grading System (CRGS) and Cognitive Assessment

The Clinical Radiological Grading System (CRGS) was developed to standardize the indication for surgery in elderly patients with meningiomas. The dimensions considered in CRGS are: size of lesion, location, edema, neurological and physical condition, and concomitant disease (Caroli et al., 2005). Despite the growing interest in quality of life (QoL) as an outcome measure in clinical trials, little is know about the health-related quality of life (HRQoL) and cognitive functioning pre- and post-surgical of patients with meningioma.

In general, patients with meningiomas show deficits in executive functioning more marked than in health controls (Waagemans et al., 2011), many studies have also demonstrated the influence of age on progressive cognitive deterioration (Krupp et al., 2009). Some studies have identified, in particular, significant deficits in specific domains such as psychomotor speed, verbal memory, working memory and the ability to consolidate information. Some recent studies emphasize the significant effect of psycho-physical limitations on the QoL of patients with meningioma, with or without involvement of the general health and psycho-emotional (Waagemans et al., 2011). The association between cognitive deficits and reduced quality of life found in many studies suggests that cognitive deficits may represent a further point of vulnerability for this patient population.

The objective of the integration between CRGS and neuropsychological assessment is to perform a prospective-longitudinal study of quality of life (QoL) and cognitive functions in elderly patients with meningioma studied with CRGS. With this assessment is possible to:

1. detect the presence of cognitive deficits in elderly patients with meningioma;
2. assess the quality of life in elderly patients with meningioma and the influence of possible cognitive deficits on it;
3. perform a prospective study of cognitive function and quality of life of patients with meningioma.

In conclusion the Clinical Radiological Grading System (CRGS) is a tool developed to standardize the indications for surgery in elderly patients with meningiomas. The support of the cognitive assessment and QoL at CRGS is configured as a possible step towards the perfection of an instrument already validated and widely used in neurosurgery, as well as a step towards improvement in the assessment and taking care of the elderly patient with meningioma.

The strengths of neuropsychological assessment are:

1. quantify the effects of tumours, surgery and therapy;
2. provide accurate information to guide rehabilitation programs;
3. correlate cognitive and quality of life data with clinical outcomes and clinical instruments like CRGS.

Conclusions

The CRGS was the first attempt to standardize surgical indication in elderly meningioma patients and after several prospective validations we can support the assertion that it is a practical and valuable grading system for use in the selection for surgery and it should be improved by the contribution of the neuropsychological evaluation. Ongoing efforts by clinicians in search of new rating scales (as we can see in several papers) show that the simple evaluation of general medical conditions is not enough to judge properly. Only a combination of several factors enables us to set a balanced surgical indication and we think that it is the rating scales as a whole that, despite their limitations, provide guidance for treatment choice. It is reasonable to underline that even if general medical status is the most important predictive factor for mortality, the rating scales are useful tools also for predicting the quality of life. There is a substantial agreement in all the proposed score (CRGS, SKALE, GSS, Charlson Score) regarding the most important items that should be evaluated in the decision making for surgery, despite the differences among the systems and we think that every scientific contribution will help to stimulate a discussion on an issue that appears to be more and more topical in neurosurgical practice.

References

Arienta C, Caroli M, Crotti F, Villani R (1990) Treatment of intracranial meningiomas in patients over 70 years old. Acta Neurochir (Wien) 107:47–55

Arienta C, Caroli M, Balbi S (1992) Intracranial meningiomas in patients over 70 years old follow-up in operated and unoperated cases. Aging Clin Exp Res 4:29–33

Awad IA, Kalfas I, Hahn JF, Little JR (1989) Intracranial meningiomas in the aged: surgical outcome in the era of computed tomography. Neurosurgery 24(4): 557–560

Bateman BT, Pile-Spellman J, Gutin PH, Berman MF (2005) Meningioma resection in the elderly: nationwide inpatient sample, 1998–2002. Neurosurgery 57(5):866–872

Black P, Kathiresan S, Chung W (1998) Meningioma surgery in the elderly: a case–control study assessing morbidity and mortality. Acta Neurochir (Wien) 140:1013–1101

Buhl R, Hasan A, Behnke A, Mehdorn HM (2000) Results in the operative treatment of elderly patients with intracranial meningioma. Neurosurg Rev 23(1):25–29

Caroli M, Locatelli M, Prada F, Beretta F, Martinelli-Boneschi F, Campanella R, Arienta C (2005) Surgery for intracranial meningiomas in the elderly: a clinical-radiological grading system as a predictor of outcome. J Neurosurg 102(2):290–294

Cohen-Inbar O, Soustiel JF, Zaaroor M (2010) Meningiomas in the elderly, the surgical benefit and a new scoring system. Acta Neurochir (Wien) 152(1): 87–97

Cohen-Inbar O, Sviri GE, Soustiel JF, Zaaroor M (2011) The Geriatric Scoring System (GSS) in meningioma patients – validation. Acta Neurochir (Wien) 153(7):1501–1508

Cornu P, Chatellier G, Dagreou F, Clemenceau S, Foncin JF, Rivierez M, Philippon J (1990) Intracranial meningiomas in elderly patients. Postoperative morbidity and mortality. Factors predictive of outcome. Acta Neurochir 102:98–102

Curry WT, McDermott MW, Carter BS, Barker FG II (2005) Craniotomy for meningioma in the United

States between 1988 and 2000: decreasing rate of mortality and the effect of provider caseload. J Neurosurg 102:977–986

D'Andrea G, Roperto R, Caroli E, Crispo F, Ferrante L (2005) Thirty-seven cases of intracranial meningiomas in the ninth decade of life: our experience and review of the literature. Neurosurgery 56(5):956–961

Fayers P, Bottomley A (2002) Quality of life research within the EORTC – the EORTC QLQ C30. Eur J Cancer 38:S125–S133

Giovagnoli AR, Tamburini M, Boiardi A (1996) Quality of life in brain tumor patients. J Neurooncol 30:71–80

Grossman R, Mukherjee D, Chang DC, Bennett R, Brem H, Olivi A, Quiñones-Hinojosa A (2011) Preoperative charlson comorbidity score predicts postoperative outcomes among older intracranial meningioma patients. World Neurosurg 75(2):279–285

Jan M, Bazézé V, Saudeau D, Autret A, Bertrand P, Gouaze A (1986) Outcome of intracranial meningioma in adults. Retrospective study of a medicosurgical series of 161 meningiomas. Neurochirurgie 32(2):129–134, French

Krupp W, Klein C, Koschny R, Holland H, Seifert V, Meixensberger J (2009) Assessment of neuropsychological parameters and quality of life to evaluate outcome in patients with surgically treated supratentorial meningiomas. Neurosurgery 64:40–47

Lageman SK, Cerhan JH, Locke DEC, Anderson SK, Wu W, Brown PD (2010) Comparing neuropsychological tasks to optimize brief cognitive batteries for brain tumour clinical trials. J Neurooncol 96:271–276

Lee JH, Sade B (2009) The novel "CLASS" algorithmic scale for patient selection in meningioma surgery. In: Lee JH (ed) Meningiomas: diagnosis, treatment, and outcome. Springer, London, pp 217–223

Lezak MD, Howieson DB, Loring DW (2004) Neuropsychological assessment, 4th edn. Oxford University Press, New York

Lieu AS, Howng SL (1998) Surgical treatment of intracranial meningiomas in geriatric patients. Kaohsiung J Med Sci 14(8):498–503

Mastronardi L, Ferrante L, Qasho R, Ferrari V, Tatarelli R, Fortuna A (1995) Intracranial meningiomas in the 9th decade of life: a retrospective study of 17 surgical cases. Neurosurgery 36(2):270–274

Maurice-Williams RS, Kitchen ND (1992) Intracranial tumours in the elderly: the effect of age on the outcome of first time surgery for meningiomas. Br J Neurosurg 6:131–131e137

McGrail KM, Ojemann RG (1994) The surgical management of benign intracranial meningiomas and acoustic neuromas in patients 70 years of age and older. Surg Neurol 42:2–7

Meyers CA, Brown PD (2006) Role and relevance of neurocognitive assessment in clinical trials of patients with CNS tumors. J Clin Oncol 24:1305–1309

Nishizaki T, Kamiryo T, Fujisawa H, Ohshita N, Ishihara H, Ito H, Aoki H (1994) Prognostic implications of meningiomas in the elderly (over 70 years old) in the era of magnetic resonance imaging. Acta Neurochir (Wien) 126:59–62

Papagno C, Casarotti A, Comi A, Gallucci M, Riva M, Bello L (2012) Measuring clinical outcomes in neuro-oncology. A battery to evaluate low-grade gliomas (LGG). J Neurooncol 108:269–275

Papo I (1983) Intracranial meningiomas in the elderly in the CT scan era. Acta Neurochir (Wien) 67:195–204

Patil CG, Veeravagu A, Lad SP, Boakye M (2010) Craniotomy for resection of meningioma in the elderly: a multicentre, prospective analysis from the national surgical quality improvement program. J Neurol Neurosurg Psychiatry 81(5):502–505

Proust F, Verdure L, Toussaint P, Bellow F, Callonec F, Menard JF, Fréger P (1997) Intracranial meningioma in the elderly. Postoperative mortality, morbidity and quality of life in a series of 39 patients over 70 years of age. Neurochirurgie 43(1):15–20, French

Sacko O, Sesay M, Roux FE, Riem T, Grenier B, Liguoro D, Loiseau H (2007) Intracranial meningioma surgery in the ninth decade of life. Neurosurgery 61(5): 950–954

Schul DB, Wolf S, Krammer MJ, Landscheidt JF, Tomasino A, Lumenta CB (2012) Meningioma surgery in the elderly: outcome and validation of 2 proposed grading score systems. Neurosurgery 70(3):555–565

Stéphan F, Cheffi A, Bonnet F (2001) Nosocomial infections and outcome of critically ill elderly patients after surgery. Anesthesiology 94(3):407–414

Tucha O, Smely C, Lange KW (2001) Effects of surgery on cognitive functioning of elderly patients with intracranial meningioma. Br J Neurosurg 15:184–188

Umansky F, Ashkenazi E, Gertel M, Shalit MN (1992) Surgical outcome in an elderly population with intracranial meningioma. J Neurol Neurosurg Psychiatry 55(6):481–485

Waagemans ML, van Nieuwenhuizen D, Dijkstra M, Wumkes M, Dirven CF, Leenstra S, Reijneveld JC, Klein M, Stalpers LJA (2011) Long-term impact of cognitive deficits and epilepsy on quality of life in patients with low-grade meningiomas. Neurosurgery 69:72–79

Ware JE Jr, Sherbourne CD (1992) The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. Med Care 30(6):473–483

Cranial Meningioma in Neurofibromatosis Type 2 Patients: Role of Mutations

23

Miriam J. Smith and D. Gareth R. Evans

Contents

Abstract

Meningiomas are the most common form of primary intracranial tumour in adults and are associated with the neurogenetic syndrome neurofibromatosis type 2 (NF2). Somatic mutations of the *NF2* gene are found in the majority of both sporadic and NF2-associated meningiomas. With comprehensive genetic testing germline mutations can be identified in approximately 93 % of NF2 patients. The type and location of these mutations have both been shown to determine the risk of meningioma in these patients. It is also possible that sporadic and NF2 disease-associated meningiomas arise as a result of different pathological mechanisms.

Introduction

Meningiomas account for approximately one third of all primary brain tumours in the general population (CBTRUS, 2012). Meningiomas are rare in children and the risk of developing a meningioma increases with age. There is also an apparent gender bias for developing a sporadic meningioma, with women two to three times as likely to develop a meningioma as men. Most meningiomas (~90 %) are intracranial, benign and asymptomatic. A post mortem study has shown that asymptomatic meningiomas can be found in up to 2.8 % of apparently healthy individuals (Nakasu et al., 1987). In symptomatic meningioma patients,

M.J. Smith (✉) • D.G.R. Evans
Department of Genetic Medicine, St. Mary's Hospital, Manchester Academic Health Sciences Center, University of Manchester, Oxford Road, Manchester M13 9WL, UK
e-mail: miriam.smith@manchester.ac.uk

M.A. Hayat (ed.), *Tumors of the Central Nervous System, Volume 11*,
DOI 10.1007/978-94-007-7037-9_23,

clinical symptoms vary, depending on the location of the tumour, and are generally caused by displacement or compression. These symptoms may include headache, migraine and seizures. Surgery is the principal form of treatment, although many meningioma patients may be managed by observation alone.

While the majority of meningiomas occur sporadically, they are also closely associated with the neurogenetic tumour suppressor syndrome, neurofibromatosis type 2 (NF2). Within the context of NF2, they are the second most common type of tumour, after the schwannoma. While NF2 disease is relatively rare, occurring in 1:25,000-1:40,000 births (Evans et al., 1992, 2010), patients affected with NF2 have a hugely increased risk of developing a meningioma compared to the general population, with approximately 50–75 % of NF2 patients developing at least one meningioma during their lifetime.

Somatic mutations of the *NF2* gene are found in the majority of meningiomas, normally involving loss of all or part of chromosome 22, and constitutional mutations can be found in greater than 90 % of patients with NF2 disease through comprehensive genetic testing. The position of these germline mutations within the *NF2* gene has been shown to correlate with the risk of meningioma development (Smith et al., 2011). Several other genes have also been implicated in the development and progression of meningiomas. In this review we will summarise the effects of mutations linked to the occurrence of meningiomas in NF2 disease.

Occurrence of Sporadic and NF2 Disease-Associated Meningiomas

There are several histological subtypes of meningioma. The three major subtypes are meningothelial, transitional and fibroblastic meningiomas. The different subtypes tend to occur in distinct locations within the brain. A study of the correlation between meningioma histologic subtype and cranial location showed that meningothelial meningiomas are frequently found in the anterior region of the skull base, particularly the olfactory groove and sphenoid ridge, while fibroblastic meningiomas were more common in the posterior of the brain and transitional meningiomas tended to be found in the convexity (Kros et al., 2001).

Approximately 60 % of sporadic meningiomas show loss of heterozygosity of chromosome 22 and 30–60 % also have a specific point mutation within the *NF2* gene (Wellenreuther et al., 1995; Lekanne Deprez et al. 1994). This *NF2* involvement is biased towards the fibroblastic and transitional histological subtypes, while meningothelial meningiomas involve *NF2* far less frequently (Wada et al., 2004). On this basis, it has been suggested that a distinct molecular pathway is involved in the pathology of meningothelial meningiomas. However, a comparison of histological subtypes of meningioma occurring sporadically and in NF2 disease showed that, although the proliferation potential of NF2 disease-associated meningiomas was higher than those of sporadic tumours, the distribution of subtypes was similar (Antinheimo et al., 2000).

In adults, sporadic meningiomas seem to occur more frequently in women than men (CBTRUS, 2012), with a reported 3:1 ratio, although this bias is not seen in the paediatric population and a slightly higher incidence in males has been reported in populations below the age of 20 years (Perry and Dehner, 2003). It has been suggested that sex hormone receptors my account for this gender bias, although there is much conflicting data on this (Martuza et al., 1985; Adams et al., 1990; Koper et al., 1990; Korhonen et al., 2006). For meningiomas occurring in NF2 disease, several small studies supported a gender bias towards females (Evans et al., 1995), although a larger cohort showed that any gender bias in adults was not statistically significant (Smith et al., 2011). However, below the age of 20, the gender bias seemed to be reversed, giving younger males with NF2 a higher risk of developing a meningioma.

Intracranial meningiomas occur in approximately 50 % of patients with NF2 disease in cross-sectional studies. It has been suggested that spinal meningiomas may also be present in up to 30–50 % of NF2 patients (Mautner et al., 1996; Goutagny and Kalamarides, 2010). However, it is difficult to determine an accurate number as many

spinal meningiomas are asymptomatic, only ever found incidentally and are therefore underreported. While bilateral vestibular schwannomas are the hallmark tumour of NF2 disease, some patients may present with meningioma disease alone and many NF2 patients develop meningiomas before a vestibular schwannoma (Evans, 2009), making it important to test for germline *NF2* mutations in these patients. The rarity of meningiomas in children also means that undiagnosed NF2 disease should be suspected when meningiomas appear during childhood (Evans et al., 1999).

The *NF2* Gene and Its Protein Product, Merlin

The *NF2* gene covers approximately 100 kilobases of DNA on the long arm of chromosome 22. It contains 17 exons, 15 of which are constituent exons and are present in each of the two NF2 isoforms. Exons 16 and 17 are mutually exclusive. Exon 17 is found in isoform 1 and exon 16 is found in isoform 2. *NF2* encodes a cytoskeletal protein called Merlin (aka Schwannomin), which is a band 4.1 cytoskeletal protein family member, involved in several signalling pathways that regulate cell growth, proliferation and movement. The protein can be divided into three major domains: the N-terminal region, which includes a FERM (band 4.1, ezrin, radixin, moesin homology domains) domain, an α-helical domain whose conformation is dependent on its phosphorylation status, and a C-terminal domain containing an actin binding domain. The N-terminal FERM domain can be further divided into three subdomains, each of which contains binding sites for protein interactors, including actin, NHERF and CD44. FERM1 has a ubiquitin-like structure, FERM2 has an acyl CoA binding protein-like structure and FERM3 has a structure similar to phosphotyrosine binding protein (PTB), pleckstrin homology domain (PH), or Enabled/VASP Homology 1 (EVH1).

When dephosphorylated, the α-helical region folds to bring the N- and C-terminal domains into close proximity. In its folded conformation Merlin is inhibited from binding actin. When the α-helical region is phosphorylated, it unfolds, revealing the actin binding domain. Both the phosphorylated and dephosphorylated forms of Merlin are involved in a wide range of cellular functions via interactions with a variety of binding partners. Each of these interactions requires a specific conformation of the merlin protein. Several reports have suggested that mutation of the *NF2* gene results in loss of the merlin protein product. However, genotype-phenotype studies showing that different types or locations of mutations determine disease severity suggest that some mutant proteins may be expressed, at least transiently (Baser et al., 2005; Kluwe et al., 1998; Smith et al., 2011).

Spectrum and Location of *NF2* Mutations

Roughly half of all NF2 patients harbour an inherited *NF2* mutation, while the other half are sporadic, resulting from a *de novo* mutation. Approximately 30 % of sporadic NF2 patients have a somatic mosaic mutation, conferring a low risk of passing on the mutation to future generations. These patients also generally present with a milder disease phenotype. A mosaic *NF2* mutation is the cause of some cases of multiple meningiomas in adult patients who have no other indications of NF2 disease (Evans et al., 2005). Identification of an identical mutation in more than one tumour is suggestive of mosaic NF2, although in the case of patients with only multiple meningiomas it may be difficult to distinguish NF2 mosaicism from clonal spread of a single tumour (Larson et al., 1995), unless the mutation is seen at a low level in blood.

The spectrum of germline mutations found in NF2 patients reported to date shows that the majority of these mutations are truncating point mutations (nonsense or frameshift). Truncating mutations are generally thought to lead to nonsense mediated decay, resulting in loss of the protein product. There are fewer patients with missense (non-truncating) mutations and these patients tend to present with a milder clinical

phenotype. Patients with constitutional *NF2* whole gene deletions generally present with a mild phenotype more similar to the non-truncating than the truncating mutations (Lopez-Correa et al., 2000; Zucman-Rossi et al., 1998; Watson et al., 1993), perhaps suggesting that truncated proteins are expressed transiently and interfere with normal merlin function, while complete loss of the protein has a lesser effect (Lopez-Correa et al., 2000). Individuals with non-truncating mutations (missense or splice-site mutations) have a significantly lower prevalence of cranial meningiomas than those with truncating mutations (nonsense or frameshift mutations).

The location of mutations within the *NF2* gene is also important. It has been noted that mutations are not found in *NF2* exons 14 and 15 in sporadic meningiomas (Ahronowitz et al., 2007; Baser, 2006) and very few in NF2 disease (Smith et al., 2011). The risk of meningioma in NF2 patients with a known germline *NF2* mutation correlates with the position of the mutation within the *NF2* gene (Baser et al., 2005; Kluwe et al., 1998; Smith et al., 2011). Patients with mutations occurring within earlier exons are more likely to developing at least one meningioma during their lifetime. In particular, mutations occurring within the first two FERM domains, lead to a significantly higher risk of meningiomas than mutations occurring in exons 14 or 15. It is still possible for an NF2 patient with a germline mutation in exon 14 or 15 to develop an intracranial meningioma, but they are much less common and have an age of onset up to 10 years later than patients with mutations in earlier exons. The positional effect can be seen for both truncating and non-truncating mutations and in both mosaic and non-mosaic patients.

In addition to the generally decreasing risk of meningiomas from mutations occurring towards the 3′ end of the gene, there are also minor peaks in risk resulting from mutations occurring in exons coding for amino acid residues near the junctions between functional protein domains. The positional effect is difficult to understand if all of the mutations lead to nonsense mediated decay and somatic loss of the wild type allele results in complete biallelic inactivation. Rather, it suggests that at least some mutant proteins (both truncating and non-truncating) are expressed, even if only transiently and that the protein domain junctions are particularly important for the correct folding or functioning of merlin. Mutant mRNA transcripts with missense mutations have been found in NF2 disease-associated schwannoma and meningioma tumours, albeit less stable than wild type transcripts, indicating that loss occurs at the level of protein degradation (Yang et al., 2011).

Other Genetic and Epigenetic Factors

While the most common somatic mutations found in meningiomas involve chromosomal loss of regions of chromosome 22 q including the *NF2* locus studies have investigated other chromosomal loci which may be involved in meningioma formation and progression. Multiple somatically acquired chromosomal losses and gains have been identified across the genome by comparative genomic hybridisation (CGH) of benign sporadic meningiomas, although no consistent patterns have been found (Weber et al., 1997).

Several individual genes have also been investigated. The *DAL-1/EPB41L3* gene, located on chromosome 18, which codes for another member of the band 4.1 protein family, has been found to show reduced expression in up to 71 % of sporadic meningiomas (Gutmann et al., 2000), although corresponding gene mutations are uncommon (Martinez-Glez et al., 2005) and have not been reported in cases of multiple meningioma disease (Heinrich et al., 2003). In addition, chromosomal losses involving *DAL-1/EPB41L3* are generally found in tumours in conjunction with loss of the *NF2* locus and are more commonly associated with higher grade meningiomas, indicating that loss of this gene may be involved in tumour progression, rather than initiation (Nunes et al., 2005). Other genes thought to be involved in meningioma progression include *CDKN2A*, *CDKN2B*, *CDKN2C*, *TP73*, *RAD54L* and *ALPL*. These genes tend to be found in higher grade meningiomas and appear to be unrelated to inherited predisposition to meningioma.

A mutation in the chromatin remodelling gene, *SMARCB1*, was found to cause both schwannomatosis and meningiomatosis in members of a single multi-generational family (Christiaans et al., 2010). Meningiomas are only found in around 5 % of schwannomatosis patients and the reason for their occurrence in particular families is unknown. Screening of both germline and somatic mutations in larger cohorts has not found *SMARCB1* to be a major cause of meningioma disease (Schmitz et al., 2001; Hadfield et al., 2010; Rieske et al., 2003).

Since loss of merlin expression seems to occur in a larger number of meningiomas than the number with identified *NF2* mutations, it has been postulated that epigenetic regulation may play a role in NF2-related meningiomagenesis. However, while one study found that the *NF2* gene may be hypermethylated in up to 26 % of meningiomas (Lomas et al., 2005), subsequent studies did not support this theory (van Tilborg et al., 2006; Hansson et al., 2007).

References

Adams EF, Schrell UM, Fahlbusch R, Thierauf P (1990) Hormonal dependency of cerebral meningiomas. Part 2: In vitro effect of steroids, bromocriptine, and epidermal growth factor on growth of meningiomas. J Neurosurg 73(5):750–755. doi:10.3171/jns.1990.73.5.0750

Ahronowitz I, Xin W, Kiely R, Sims K, MacCollin M, Nunes FP (2007) Mutational spectrum of the NF2 gene: a meta-analysis of 12 years of research and diagnostic laboratory findings. Hum Mutat 28(1):1–12. doi:10.1002/humu.20393

Antinheimo J, Sankila R, Carpen O, Pukkala E, Sainio M, Jaaskelainen J (2000) Population-based analysis of sporadic and type 2 neurofibromatosis-associated meningiomas and schwannomas. Neurology 54(1):71–76

Baser ME (2006) The distribution of constitutional and somatic mutations in the neurofibromatosis 2 gene. Hum Mutat 27(4):297–306. doi:10.1002/humu.20317

Baser ME, Kuramoto L, Woods R, Joe H, Friedman JM, Wallace AJ, Ramsden RT, Olschwang S, Bijlsma E, Kalamarides M, Papi L, Kato R, Carroll J, Lazaro C, Joncourt F, Parry DM, Rouleau GA, Evans DG (2005) The location of constitutional neurofibromatosis 2 (NF2) splice site mutations is associated with the severity of NF2. J Med Genet 42(7):540–546. doi:10.1136/jmg.2004.029504, 42/7/540 [pii]

CBTRUS (2012) CBTRUS statistical report: primary brain and central nervous system tumors diagnosed in the United States in 2004–2008. Central Brain Tumor Registry of the United States, Hinsdale

Christiaans I, Kenter SB, Brink HC, van Os TA, Baas F, van den Munckhof P, Kidd AM, Hulsebos TJ (2010) Germline SMARCB1 mutation and somatic NF2 mutations in familial multiple meningiomas. J Med Genet 48(2):93–97. doi:10.1136/jmg.2010.082420, jmg.2010.082420 [pii]

Evans DG (2009) Neurofibromatosis type 2 (NF2): a clinical and molecular review. Orphanet J Rare Dis 4:16

Evans DG, Huson SM, Donnai D, Neary W, Blair V, Teare D, Newton V, Strachan T, Ramsden R, Harris R (1992) A genetic study of type 2 neurofibromatosis in the United Kingdom. I. Prevalence, mutation rate, fitness, and confirmation of maternal transmission effect on severity. J Med Genet 29(12):841–846

Evans DG, Blair V, Strachan T, Lye RH, Ramsden RT (1995) Variation of expression of the gene for type 2 neurofibromatosis: absence of a gender effect on vestibular schwannomas, but confirmation of a preponderance of meningiomas in females. J Laryngol Otol 109(9):830–835

Evans DG, Birch JM, Ramsden RT (1999) Paediatric presentation of type 2 neurofibromatosis. Arch Dis Child 81(6):496–499

Evans DG, Watson C, King A, Wallace AJ, Baser ME (2005) Multiple meningiomas: differential involvement of the NF2 gene in children and adults. J Med Genet 42(1):45–48. doi:10.1136/jmg.2004.023705, 42/1/45 [pii]

Evans DG, Howard E, Giblin C, Clancy T, Spencer H, Huson SM, Lalloo F (2010) Birth incidence and prevalence of tumor-prone syndromes: estimates from a UK family genetic register service. Am J Med Genet 152A(2):327–332. doi:10.1002/ajmg.a.33139

Goutagny S, Kalamarides M (2010) Meningiomas and neurofibromatosis. J NeuroOncol 99(3):341–347. doi:10.1007/s11060-010-0339-x

Gutmann DH, Donahoe J, Perry A, Lemke N, Gorse K, Kittiniyom K, Rempel SA, Gutierrez JA, Newsham IF (2000) Loss of DAL-1, a protein 4.1-related tumor suppressor, is an important early event in the pathogenesis of meningiomas. Hum Mol Genet 9(10):1495–1500

Hadfield KD, Smith MJ, Trump D, Newman WG, Evans DG (2010) SMARCB1 mutations are not a common cause of multiple meningiomas. J Med Genet 47(8):567–568. doi:10.1136/jmg.2009.075721, jmg.2009.075721 [pii]

Hansson CM, Buckley PG, Grigelioniene G, Piotrowski A, Hellstrom AR, Mantripragada K, Jarbo C, Mathiesen T, Dumanski JP (2007) Comprehensive genetic and epigenetic analysis of sporadic meningioma for macro-mutations on 22q and micro-mutations within the NF2 locus. BMC Genomics 8:16

Heinrich B, Hartmann C, Stemmer-Rachamimov AO, Louis DN, MacCollin M (2003) Multiple meningiomas: investigating the molecular basis of sporadic

and familial forms. Int J Cancer 103(4):483–488. doi:10.1002/ijc.10840

Kluwe L, MacCollin M, Tatagiba M, Thomas S, Hazim W, Haase W, Mautner VF (1998) Phenotypic variability associated with 14 splice-site mutations in the NF2 gene. Am J Med Genet 77(3):228–233

Koper JW, Foekens JA, Braakman R, Lamberts SW (1990) Effects of progesterone on the response to epidermal growth factor and other growth factors in cultured human meningioma cells. Cancer Res 50(9): 2604–2607

Korhonen K, Salminen T, Raitanen J, Auvinen A, Isola J, Haapasalo H (2006) Female predominance in meningiomas can not be explained by differences in progesterone, estrogen, or androgen receptor expression. J Neuro-Oncol 80(1):1–7. doi:10.1007/s11060-006-9146-9

Kros J, de Greve K, van Tilborg A, Hop W, Pieterman H, Avezaat C, Lekanne Dit Deprez R, Zwarthoff E (2001) NF2 status of meningiomas is associated with tumour localization and histology. J Pathol 194(3):367–372. doi:10.1002/path.909, [pii] 10.1002/path.909

Larson JJ, Tew JM Jr, Simon M, Menon AG (1995) Evidence for clonal spread in the development of multiple meningiomas. J Neurosurg 83(4):705–709. doi:10.3171/jns.1995.83.4.0705

Lekanne Deprez RH, Bianchi AB, Groen NA, Seizinger BR, Hagemeijer A, van Drunen E, Bootsma D, Koper JW, Avezaat CJ, Kley N et al (1994) Frequent NF2 gene transcript mutations in sporadic meningiomas and vestibular schwannomas. Am J Hum Genet 54(6): 1022–1029

Lomas J, Bello MJ, Arjona D, Alonso ME, Martinez-Glez V, Lopez-Marin I, Aminoso C, de Campos JM, Isla A, Vaquero J, Rey JA (2005) Genetic and epigenetic alteration of the NF2 gene in sporadic meningiomas. Genes Chromosomes Cancer 42(3):314–319

Lopez-Correa C, Zucman-Rossi J, Brems H, Thomas G, Legius E (2000) NF2 gene deletion in a family with a mild phenotype. J Med Genet 37(1):75–77

Martinez-Glez V, Bello MJ, Franco-Hernandez C, De Campos JM, Isla A, Vaquero J, Rey JA (2005) Mutational analysis of the DAL-1/4.1B tumour-suppressor gene locus in meningiomas. Int J Mol Med 16(4): 771–774

Martuza RL, Miller DC, MacLaughlin DT (1985) Estrogen and progestin binding by cytosolic and nuclear fractions of human meningiomas. J Neurosurg 62(5): 750–756. doi:10.3171/jns.1985.62.5.0750

Mautner VF, Lindenau M, Baser ME, Hazim W, Tatagiba M, Haase W, Samii M, Wais R, Pulst SM (1996) The neuroimaging and clinical spectrum of neurofibromatosis 2. Neurosurgery 38(5):880–885, discussion 885–886

Nakasu S, Hirano A, Shimura T, Llena JF (1987) Incidental meningiomas in autopsy study. Surg Neurol 27(4):319–322

Nunes F, Shen Y, Niida Y, Beauchamp R, Stemmer-Rachamimov AO, Ramesh V, Gusella J, MacCollin M (2005) Inactivation patterns of NF2 and DAL-1/4.1B (EPB41L3) in sporadic meningioma. Cancer Genet Cytogenet 162(2):135–139. doi:10.1016/j.cancergencyto.2005.04.003, S0165-4608(05)00206-2 [pii]

Perry A, Dehner LP (2003) Meningeal tumors of childhood and infancy. An update and literature review. Brain Pathol 13(3):386–408

Rieske P, Zakrzewska M, Piaskowski S, Jaskolski D, Sikorska B, Papierz W, Zakrzewski K, Liberski PP (2003) Molecular heterogeneity of meningioma with INI1 mutation. Mol Pathol 56(5):299–301

Schmitz U, Mueller W, Weber M, Sevenet N, Delattre O, von Deimling A (2001) INI1 mutations in meningiomas at a potential hotspot in exon 9. Br J Cancer 84(2):199–201. doi:10.1054/bjoc.2000.1583, S0007092000915830 [pii]

Smith MJ, Higgs JE, Bowers NL, Halliday D, Paterson J, Gillespie J, Huson SM, Freeman SR, Lloyd S, Rutherford SA, King AT, Wallace AJ, Ramsden RT, Evans DG (2011) Cranial meningiomas in 411 neurofibromatosis type 2 (NF2) patients with proven gene mutations: clear positional effect of mutations, but absence of female severity effect on age at onset. J Med Genet 48(4):261–265. doi:10.1136/jmg.2010.085241, jmg.2010.085241 [pii]

van Tilborg AA, Morolli B, Giphart-Gassler M, de Vries A, van Geenen DA, Lurkin I, Kros JM, Zwarthoff EC (2006) Lack of genetic and epigenetic changes in meningiomas without NF2 loss. J Pathol 208(4):564–573. doi:10.1002/path.1909

Wada K, Maruno M, Suzuki T, Kagawa N, Hashiba T, Fujimoto Y, Hashimoto N, Izumoto S, Yoshimine T (2004) Chromosomal and genetic aberrations differ with meningioma subtype. Brain Tumor Pathol 21(3): 127–133

Watson CJ, Gaunt L, Evans G, Patel K, Harris R, Strachan T (1993) A disease-associated germline deletion maps the type 2 neurofibromatosis (NF2) gene between the Ewing sarcoma region and the leukaemia inhibitory factor locus. Hum Mol Genet 2(6):701–704

Weber RG, Bostrom J, Wolter M, Baudis M, Collins VP, Reifenberger G, Lichter P (1997) Analysis of genomic alterations in benign, atypical, and anaplastic meningiomas: toward a genetic model of meningioma progression. Proc Natl Acad Sci U S A 94(26):14719–14724

Wellenreuther R, Kraus JA, Lenartz D, Menon AG, Schramm J, Louis DN, Ramesh V, Gusella JF, Wiestler OD, von Deimling A (1995) Analysis of the neurofibromatosis 2 gene reveals molecular variants of meningioma. Am J Pathol 146(4):827–832

Yang C, Asthagiri AR, Iyer RR, Lu J, Xu DS, Ksendzovsky A, Brady RO, Zhuang Z, Lonser RR (2011) Missense mutations in the NF2 gene result in the quantitative loss of merlin protein and minimally affect protein intrinsic function. Proc Natl Acad Sci U S A 108(12):4980–4985. doi:10.1073/pnas.1102198108, 1102198108 [pii]

Zucman-Rossi J, Legoix P, Der Sarkissian H, Cheret G, Sor F, Bernardi A, Cazes L, Giraud S, Ollagnon E, Lenoir G, Thomas G (1998) NF2 gene in neurofibromatosis type 2 patients. Hum Mol Genet 7(13):2095–2101

Classification of Meningioma Using Immunogenic Antigens

24

Nicole Ludwig

Contents

Abstract

Diagnosis of meningioma is often an incidental finding. Although the majority of meningioma is clinically benign, a relevant subgroup of them is prone to recur and inherit a poor prognosis. Biological markers for this subgroup or for the early detection of meningioma are not known or not generally accepted. A novel method might improve early detection of meningioma. Autoantibodies generated from the patients' immune system directed against proteins expressed from the meningioma tumours might aid in early detection of meningioma. Because the autoantibody repertoire reflects the expression of the tumour, autoantibodies also might hold the potential to differentiate between the benign meningiomas and the meningiomas with worse prognosis.

Introduction

There is a trend in recent medicine toward a personalized medicine, especially in the field of cancer. In this context the search for biomarkers that can indicate the presence of a cancer, preferably at an early stage, has been widened. A useful biomarker can be a genetic aberration, a specific protein or a metabolic compound, that can be measured in the body fluids of the patient. Ideally, the biomarker does not only detect the cancer, but also predict its behaviour during treatment or the prognosis of the patient. For meningioma, one of

N. Ludwig (✉)
Department of Human Genetics, Medical Faculty, Saarland University, Building 60, Kirrberger Strasse, D-66421 Homburg, Saar, Germany
e-mail: n.ludwig@mx.uni-saarland.de

M.A. Hayat (ed.), *Tumors of the Central Nervous System, Volume 11*,
DOI 10.1007/978-94-007-7037-9_24,

the most common human intracranial tumours, the only known markers are cytogenetic markers in the tumours, that are not suitable for early detection of meningioma. Currently, there are no clinical trials investigating biomarkers specifically in meningioma, and only two biomarker trials in brain cancers including meningioma: the first trial is searching for protein biomarkers in the cerebrospinal fluid of patients suffering from childhood central nervous system tumours including meningioma (NCT00897959) and the second trial trying to correlate VEGF protein levels in blood of meningioma and glioma patients with recurrence, prognosis and treatment response (NCT00985036, http://clinicaltrials.gov/). Autoantibodies generated from the patients immune system against the cancer offer themselves as readily available and stable biomarkers, that can be measured very early in the disease, sometimes years before clinical detection (Chapman et al., 2007). This review will provide an overview on the concept of tumour associated autoantibodies as markers for cancer detection in general, the techniques applied to identify the antigens, antigens in meningioma and the recent developments in detecting meningioma with multi-antigen panels.

Immune System as Early Warning System in Cancer

The body's immune system is constantly looking for structural features that appear foreign, either that is an external intruder like in infection, or a change of the body's own cells like in malignant transformation. The immune reaction against a tumour, although in general lower than in infection, consists of cellular and humoral immune response. The proteins, against which the immune response is directed, are called tumour-associated antigens (TAAs). There is a constant discussion about the features of TAAs that are able to break the immune systems tolerance against self-proteins and allow for induction of an immune response. Among the most frequently discussed possible reasons are (1) mutation, (2) overexpression or expression of foetal proteins in adult tissue, (3) differential folding, (4) differential post-translational modifications, (5) aberrant degradation, or (6) different cellular localization. Many TAAs are *per se* intracellular proteins and are believed to come into contact with the immune system during necrotic, apoptotic or active secretion processes in the tumour cells to be able to induce an immune response.

The most well studied TAA is the tumour suppressor protein p53, that is a multi-functional transcription factor playing a central role in regulating transcription of genes involved in cell cycle control, apoptosis, DNA repair and angiogenesis. Mutations in the TP53 gene are common in many cancer types and are often associated with poor prognosis (Oliveira et al., 2005). The existence of autoantibodies against p53 was first demonstrated in mice (DeLeo et al., 1979), and later also in a number of different cancer types with frequencies ranging from 4 to 30 %. There is a correlation of TP53 mutation and presence of autoantibodies against p53 in serum. Because the antigenic epitopes are located on the C-terminal and N-terminal ends of the protein and not in the central region bearing the most common mutation sites it is assumed, that the induction of the immune response is more likely due to the prolonged half-life and the resulting accumulation of the mutated protein rather than to the structural change by the mutation itself (Soussi, 2000).

A second widely investigated group of antigens are the so-called *Cancer-Testis*-antigens, which are foetal proteins, expressed in adults only in ovary and testis and in several cancers. A well-known example of this group is the NY-ESO-1 antigen, identified to be immunogenic and overexpressed in various cancers including breast cancer, melanoma and prostate cancer (Chen et al., 1997). Proteins, which are degraded by the proteasome due to aberrant translation or folding, may also induce an immune response via presentation of the degraded fragments by MHC-class I molecules (Schubert et al., 2000). Strong glycosylation can also lead to an increased immune response, e.g. in breast cancer patients a stronger response against heavily glycosylated MUC1 has been observed in contrast to nonglycosylated MUC1

(von Mensdorff-Pouilly et al., 2000). Tumour specific degradation of nucleophosmin by granzyme B in liver cancer has been shown to lead to an immunogenic epitope at the granzyme B cleavage site. Furthermore the cellular localization of nucleophosmin is altered in cancer from cytoplasmatic to nuclear (Ulanet et al., 2003).

Several practical considerations make autoantibodies ideal diagnostic markers for the detection of cancers: (1) their presence in the patients blood makes them readily available in a minimal invasive manner, which represents only a small burden for the patients; (2) antibody molecules are stable in the serum with a half-life of over 7 days, so that hourly or daily variations in their concentrations are believed to be minimal, which simplifies sample collection; (3) secondary reagents to detect human antibodies are well tested and cheaply available, with an ELISA as the preferred detection method for antibodies (Anderson and LaBaer, 2005).

Despite these advantages, there are several critical points that have to be addressed when employing autoantibodies as diagnostic markers to detect cancer in an individual: (1) the frequency of autoantibodies against a single TAA rarely exceeds 30 % of the patients of a specific cancer type, resulting in a sensitivity too low for general clinical use, (2) there are numerous TAAs, e.g., p53, that are immunogenic in various cancer types, and therefore are not suitable to detect a specific type of cancer, (3) there are also TAAs that are immunogenic in other diseases, e.g. in autoimmune related diseases, and also in apparently healthy individuals, although mostly at a lower frequency, (4) some autoantibodies detected in an individual might be the result of an underlying non-cancer disease not yet clinically diagnosed or a indication of a past unrelated disease.

Taking into account these critical points, studies on TAAs as diagnostic markers for cancer are increasingly focussed on multiple marker panels. These panels overcome most of the critical points, e.g., the low sensitivity of single markers and the appearance of some TAA also in healthy individuals. Using these panels requires, however, a more sophisticated bioinformatical evaluation of the test results to detect cancer.

The potential of TAAs as cancer markers are fourfold. (1), Early detection of cancer: Autoantibodies against p53 have been demonstrated to predate clinical diagnosis of lung cancer for several years (Trivers et al., 1996) and autoantibodies against a TAA panel have been detected up to 4 years prior mammographic detection of breast cancer (Chapman et al., 2007); (2), Differentiation of cancer grades: Autoantibodies against NY-ESO1 are more frequent in patients with grade III and IV neuroblastoma than in patients with lower grade neuroblastoma or patients in clinical remission (Rodolfo et al., 2003). (3), Monitoring disease progression or treatment response: Autoantibodies against the aberrantly glycosylated MUC1 are associated with a better prognosis in early stage breast cancer (Blixt et al., 2011); (4), Identification of possible targets for immunotherapeutic approaches: A partial peptide of HOM-MEL-40, a melanoma antigen, has been shown to induce CD4+, CD8+ and B cell responses *in vitro* (Neumann et al., 2011), and a phase I/II nonrandomized trial using mRNA-based vaccination strategy induced immunological responses against several TAAs and clinical responses in some patients with renal cell carcinoma (Rittig et al., 2011).

Methods of Detecting Immunogenic Antigens

Several methods have been used for identification of immunogenic antigens, including SEREX, Phage Display, SERPA, and NAPPA, each with specific advantages and downsides. The *serological identification of recombinantly expressed antigens* (SEREX) was first applied 1995 by Sahin et al. It is based on cloning of a cDNA expression library from a patients tumour into a bacteriophage and subsequently recombinant expression of the library in bacteria. The expressed antigens were blotted onto a membrane that is subsequently screened with autologous patients serum. Later, there have been variations of this method, e.g. the use of a foetal tissue library instead of a tumour derived library or the screening of heterologous patient sera. Many investigators

have applied the SEREX method, and the identified antigens are deposited at the *Cancer Immunome Database* (CIDB, http://www2.licr.org/CancerImmunomeDB/).

A second method using a bacteria/phage system to express antigens is the *Phage Display*. Here, the cancer or foetal tissue libraries are expressed as fusion proteins with the phages'capsid protein, so that the antigens are fixed on the phages' surface. After several rounds of immunoprecipitation of the phages with sera of cancer patients and healthy controls thus enriching cancer-associated antigens and depleting normally occurring antigens, the remaining phages can be singularized, sequenced and spotted onto microarray slides for further evaluation (Sioud and Hansen, 2001). Due to the use of the antigens in a microarray format, this method can be used as high-throughput screening system with only small amounts of sera needed for a test, which is the most important advantage over the laborious conventional SEREX method. Since both SEREX and phage display rely on bacterial expression of antigens, therefore the antigens do not have their usual post-translational modifications and even their folding might be different than in the tumour. This might lead to the false identification of autoantibodies or the missing of true autoantibodies.

To circumvent the issue of bacterial expression of antigens, the *serological proteome analysis* (SERPA) has been employed (Klade et al., 2001). In SERPA, tumour cell lysate is separated with two dimensional gel electrophoresis, then blotted onto a membrane and incubated with patient and control sera. Those spots, where binding of patient sera but no binding of control sera is detected, are further analysed with mass spectroscopy to identify the target antigens. Although the method offers the advantage to detect antigens in their native conformation, the method is laborious and not suitable for high-throughput analyses.

The most recent platform that has been used to identify TAAs are self assembling protein microarrays termed *Nucleic Acid Protein Programmable Arrays* (NAPPA) (Ramachandran et al., 2004). The full-length cDNAs of proteins are spotted onto microarrays. Directly before performing of the experiment, the proteins are translated with a cell free reticulocyte lysate and immobilized, thereby circumventing possible degradation of the proteins that result from longer storage and at the same time providing the correct folding and modification.

Although all these four methods are able to identify numerous TAAs, all identified antigens have to be evaluated for their performance in detection cancer in an independent method in an independent set of patient samples and if successful, they have to be transferred into an ELISA format, which is the method of choice for detection of antibodies in a clinical setting.

Immune Response and Antigens in Meningioma

As early as 1972, Levy et al. demonstrated a cellular immune response in three of four meningioma patients. First evidence of IgG antibodies in meningioma tumour tissue as indication of a humoral immune response in meningioma patients was reported by Pees and Seidel (1976) 4 years later. From then it took another two decades until the first autoantigen in meningioma was identified.

The meningioma-expressed antigen 6, MEA6, was identified in a SEREX screening of a meningioma expression library with autologous patient serum (Heckel et al., 1997). Autoantibodies against MEA6 have subsequently been identified in 42 % of meningioma patients, 4 % of glioblastoma patients and 0 % of healthy controls. Furthermore, overexpression of MEA6 was detected in meningioma tumour tissue as a possible mechanism for overcoming tolerance and induction of the immune response (Comtesse et al., 2002). The protein, now called CTAGE5, belongs to a multigene family, the CTAGE family, of antigens, that also are immunogenic in cutaneous T cell lymphoma and melanoma (Eichmuller et al., 2001). Subsequently, the same group identified further meningioma-associated antigens: MGEA5 and its splice variant MGEA5s, that have a high sequence similarity to the hyaluronidase of *C. elegans* were immunogenic in 22 % and 0 % of meningioma patients and healthy controls,

respectively (Heckel et al., 1998). TNKS2, a tankyrase related gene was reactive in 38 % of common-type meningioma patients, but only in 4.2 % of the sera of healthy controls (Monz et al., 2001). The connective tissue growth factor CTGF was also identified in an autologous SEREX screening (Comtesse et al., 1999).

The complex nature of the humoral immune response against meningioma was shown in a subsequent study (Comtesse et al., 2005). One remarkable point in this study is the observation that the number of reactive antigens decreases with increasing tumour grade, from 17 reactive antigens in WHO grade I to only 11 reactive antigens in WHO grade III. This might partly be explained by the transformed nature of WHO III meningiomas resulting in a depletion of antigens as tumour immune escape mechanism. A total of 17 antigens reacted exclusively with meningioma sera, of which the thioredoxin domain containing 16 (TXNDC16, 50 %), the natural killer-tumor recognition sequence (NKTR, 37.5 %) and the SRY (sex determining region Y)-box 2 (SOX2, 29.2 %) antigens are the most frequently reactive. In a subsequent study with an enlarged number of patients and controls the reactivity of NKTR remained at 37 %, while the reactivities of TXNDC16 and SOX2 decreased to 22 % and 24 %, respectively (Keller et al., 2006). While the function of TXNDC16 is still unknown, NKTR plays a role in the function of natural killer cells as component of the tumour recognition complex (Anderson et al., 1993) and SOX2 is a transcription factor involved in cell fate determination and embryonic development. Notably, SOX2 is part of a six-antigen panel that is currently tested for early diagnosis in lung cancer (Boyle et al., 2011).

Additional meningioma-associated antigens have been identified in a study using a similar approach to SEREX. Ludwig et al. used macroarrays with bacterial clones expressing 1827 immunogenic sequences to identify novel antigens, that might improve meningioma detection (Ludwig et al., 2011). Among the most important antigens for the differentiation between meningiomas and controls as measured by their AUC value are the antigens enolase 1 (ENO1), vimentin (VIM), and inhibitor of growth family, member 4 (ING4). Enolase 1, a glycolytic enzyme, is a known antigen in autoimmune diseases (Pancholi, 2001). Vimentin is a structural protein of the intermediate filament and is highly expressed in meningioma (Hitchcock and Morris, 1987). The tumor suppressor protein ING4 is involved in the p53-dependent pathway and is a known antigen in glioma (Ludwig et al., 2008).

Detection of Meningioma with Multi-Antigen Panels

Besides practical considerations, as the inter-laboratory variability or differences in sample collection, one of the major pitfalls in developing a cost-effective screening test for early detection of cancer is the sensitivity and specificity of the test. The ideal test should detect all cancer patients in the tested population, i.e., producing no false-positives, and at the same time, leaving all individuals without the investigated type of cancer undetected, i.e., producing no false-negatives. This feat is impossible for a single antigen because on the one hand, even the most frequently observed autoantibodies in cancer rarely show a frequency >30–40 %, and on the other hand, the complex nature of the immune systems response against cancer or other diseases or environmental factors. Therefore recent investigations have combined the most promising antigens to multi-antigen panels and evaluated the frequency of autoantibodies in cancer and control groups. With such panels the sensitivity and specificity of the cancer detection has been remarkably increased, e.g., to 88.2 % specificity and 81.6 % sensitivity for prostate cancer using a 22 antigen panel with *Phage Display* (Wang et al., 2005), to 93 % specificity and 90 % sensitivity for breast cancer using a 7 antigen ELISA (Koziol et al., 2003) or to 97 % specificity and 81 % sensitivity in lung cancer using a 10 antigen ELISA (Rom et al., 2010).

The first study investigating multi-antigen panels as diagnostic marker in meningioma was the study of Comtesse and coworkers (Comtesse et al., 2005). They assembled 57 meningioma-associated

antigens and tested 24 meningioma and control sera for reactivity. Beside the determination of the frequency of reactivity for each antigen, statistical methods were tested for their performance to detect meningioma on the basis of their specific antigen pattern. The best results were obtained using a Bayesian approach. Leave-one-out-crossvalidation resulted in a sensitivity of 100 % and a specificity of 82 % for detecting meningioma. This was the first application of multi-antigen panels combined with statistical learning methods for minimal-invasive detection of meningioma.

In a subsequent study using the same set of antigens and an increased number of tested sera, Keller et al. (2006) underlined the feasibility of this antigen panel for meningioma detection. Their minimal invasive multiple marker approach (MIMM) yielded a specificity of 96.2 %, a sensitivity of 84.5 %, and an accuracy of 90.3 % for meningioma detection. When discriminating the three meningioma malignancy grades separately from the healthy controls, the best separation was achieved for WHO grade I meningiomas with specificity, sensitivity and accuracy of 98.6 %, 87.5 % and 95.2 %, respectively. Beside the successful differentiation of meningioma sera from controls, a major result of this study was that not only antigens, that react exclusively with tumour sera, but also antigens that react frequently with control sera might contain valuable information when differentiating tumour and control sera with statistical methods. Using 22 meningioma-associated antigens and an additional 13 glioma-associated antigens, differentiation of glioma sera from meningioma sera was possible with specificity, sensitivity and accuracy of 96.6 %, 80 % and 91.9 %, respectively (Ludwig et al., 2008).

The accuracy of meningioma detection with autoantibodies has been further increased in a study using a approach similar to SEREX, that is based on bacterial expression of antigens on macroarrays (Ludwig et al., 2011). With newly identified antigens, specificity, sensitivity and accuracy of the classification of meningioma versus healthy controls have been increased to 95.62 %, 91.83 % and 93.84 %, respectively. Although these results are promising, autoantibody signatures as biomarkers for meningiomas await further validation in a clinical setting using ELISA format.

References

Anderson KS, LaBaer J (2005) The sentinel within: exploiting the immune system for cancer biomarkers. J Proteome Res 4:1123–1133

Anderson SK, Gallinger S, Roder J, Frey J, Young HA, Ortaldo JR (1993) A cyclophilin-related protein involved in the function of natural killer cells. Proc Natl Acad Sci U S A 90:542–546

Blixt O, Bueti D, Burford B, Allen D, Julien S, Hollingsworth M, Gammerman A, Fentiman I, Taylor-Papadimitriou J, Burchell JM (2011) Autoantibodies to aberrantly glycosylated MUC1 in early stage breast cancer are associated with a better prognosis. Breast Cancer Res 13:R25

Boyle P, Chapman CJ, Holdenrieder S, Murray A, Robertson C, Wood WC, Maddison P, Healey G, Fairley GH, Barnes AC, Robertson JF (2011) Clinical validation of an autoantibody test for lung cancer. Ann Oncol 22:383–389

Chapman C, Murray A, Chakrabarti J, Thorpe A, Woolston C, Sahin U, Barnes A, Robertson J (2007) Autoantibodies in breast cancer: their use as an aid to early diagnosis. Ann Oncol 18:868–873

Chen YT, Scanlan MJ, Sahin U, Türeci O, Gure AO, Tsang S, Williamson B, Stockert E, Pfreundschuh M, Old LJ (1997) A testicular antigen aberrantly expressed in human cancers detected by autologous antibody screening. Proc Natl Acad Sci U S A 94:1914–1918

Comtesse N, Heckel D, Rácz A, Brass N, Glass B, Meese E (1999) Five novel immunogenic antigens in meningioma: cloning, expression analysis, and chromosomal mapping. Clin Cancer Res 5:3560–3568

Comtesse N, Niedermayer I, Glass B, Heckel D, Maldener E, Nastainczyk W, Feiden W, Meese E (2002) MGEA6 is tumor-specific overexpressed and frequently recognized by patient-serum antibodies. Oncogene 21:239–247

Comtesse N, Zippel A, Walle S, Monz D, Backes C, Fischer U, Mayer J, Ludwig N, Hildebrandt A, Keller A, Steudel WI, Lenhof HP, Meese E (2005) Complex humoral immune response against a benign tumor: frequent antibody response against specific antigens as diagnostic targets. Proc Natl Acad Sci U S A 102:9601–9606

DeLeo AB, Jay G, Appella E, Dubois GC, Law LW, Old LJ (1979) Detection of a transformation-related antigen in chemically induced sarcomas and other transformed cells of the mouse. Proc Natl Acad Sci U S A 76:2420–2424

Eichmuller S, Usener D, Dummer R, Stein A, Thiel D, Schadendorf D (2001) Serological detection of

cutaneous T-cell lymphoma-associated antigens. Proc Natl Acad Sci U S A 98:629–634

Heckel D, Brass N, Fischer U, Blin N, Steudel I, Türeci O, Fackler O, Zang KD, Meese E (1997) cDNA cloning and chromosomal mapping of a predicted coiled-coil proline-rich protein immunogenic in meningioma patients. Hum Mol Genet 6:2031–2041

Heckel D, Comtesse N, Brass N, Blin N, Zang KD, Meese E (1998) Novel immunogenic antigen homologous to hyaluronidase in meningioma. Hum Mol Genet 7:1859–1872

Hitchcock E, Morris CS (1987) Immunocytochemistry of intracranial meningiomas. J Neurooncol 5:357–368

Keller A, Ludwig N, Comtesse N, Hildebrandt A, Meese E, Lenhof HP (2006) A minimally invasive multiple marker approach allows highly efficient detection of meningioma tumors. BMC Bioinformatics 7:539

Klade CS, Voss T, Krystek E, Ahorn H, Zatloukal K, Pummer K, Adolf GR (2001) Identification of tumor antigens in renal cell carcinoma by serological proteome analysis. Proteomics 1:890–898

Koziol JA, Zhang JY, Casiano CA, Peng XX, Shi FD, Feng AC, Chan EK, Tan EM (2003) Recursive partitioning as an approach to selection of immune markers for tumor diagnosis. Clin Cancer Res 9:5120–5126

Levy NL, Mahaley MS Jr, Day ED (1972) In vitro demonstration of cell-mediated immunity to human brain tumors. Cancer Res 32:477–482

Ludwig N, Keller A, Comtesse N, Rheinheimer S, Pallasch C, Fischer U, Fassbender K, Steudel WI, Lenhof HP, Meese E (2008) Pattern of serum autoantibodies allows accurate distinction between a tumor and pathologies of the same organ. Clin Cancer Res 15:4767–4774

Ludwig N, Keller A, Heisel S, Leidinger P, Rheinheimer S, Andres C, Stephan B, Steudel WI, Donauer E, Graf N, Burgeth B, Weickert J, Lenhof HP, Meese E (2011) Novel immunogenic antigens increase classification accuracy in meningioma to 93.84 %. Int J Cancer 128:1493–1501

Monz D, Munnia A, Comtesse N, Fischer U, Steudel WI, Feiden W, Glass B, Meese EU (2001) Novel tankyrase-related gene detected with meningioma-specific sera. Clin Cancer Res 7:113–119

Neumann F, Kubuschok B, Ertan K, Schormann C, Stevanovic S, Preuss KD, Schmidt W, Pfreundschuh M (2011) A peptide epitope derived from the cancer testis antigen HOM-MEL-40/SSX2 capable of inducing $CD4^+$ and $CD8^+$ T-cell as well as B-cell responses. Cancer Immunol Immunother 60:1333–1346

Oliveira AM, Ross JS, Fletcher JA (2005) Tumor suppressor genes in breast cancer: the gatekeepers and the caretakers. Am J Clin Pathol 124:S16–S28

Pancholi V (2001) Multifunctional alpha-enolase: its role in diseases. Cell Mol Life Sci 58:902–920

Pees HW, Seidel B (1976) Cell-mediated immune response of patients with meningiomas defined in vitro by a [3H] proline microcytotoxicity test. Clin Exp Immunol 24:310–316

Ramachandran N, Hainsworth E, Bhullar B, Eisenstein S, Rosen B, Lau AY, Walter JC, LaBaer J (2004) Self-assembling protein microarrays. Science 305:86–90

Rittig SM, Haentschel M, Weimer KJ, Heine A, Muller MR, Brugger W, Horger MS, Maksimovic O, Stenzl A, Hoerr I, Rammensee HG, Holderried TA, Kanz L, Pascolo S, Brossart P (2011) Intradermal vaccinations with RNA coding for TAA generate CD8+ and CD4+ immune responses and induce clinical benefit in vaccinated patients. Mol Ther 19:990–999

Rodolfo M, Luksch R, Stockert E, Chen YT, Collini P, Ranzani T, Lombardo C, Dalerba P, Rivoltini L, Arienti F, Fossati-Bellani F, Old LJ, Parmiani G, Castelli C (2003) Antigen-specific immunity in neuroblastoma patients: antibody and T-cell recognition of NY-ESO-1 tumor antigen. Cancer Res 63:6948–6955

Rom WN, Goldberg JD, Addrizzo-Harris D, Watson HN, Khilkin M, Greenberg AK, Naidich DP, Crawford B, Eylers E, Liu D, Tan EM (2010) Identification of an autoantibody panel to separate lung cancer from smokers and nonsmokers. BMC Cancer 10:234

Sahin U, Türeci O, Schmitt H, Cochlovius B, Johannes T, Schmits R, Stenner F, Luo G, Schobert I, Pfreundschuh M (1995) Human neoplasms elicit multiple specific immune responses in the autologous host. Proc Natl Acad Sci U S A 92:11810–11813

Schubert U, Antón LC, Gibbs J, Norbury CC, Yewdell JW, Bennink JR (2000) Rapid degradation of a large fraction of newly synthesized proteins by proteasomes. Nature 404:770–774

Sioud M, Hansen MH (2001) Profiling the immune response in patients with breast cancer by phage-displayed cDNA libraries. Eur J Immunol 31:716–725

Soussi T (2000) p53 Antibodies in the sera of patients with various types of cancer: a review. Cancer Res 60:1777–1788

Trivers GE, De Benedetti VM, Cawley HL, Caron G, Harrington AM, Bennett WP, Jett JR, Colby TV, Tazelaar H, Pairolero P, Miller RD, Harris CC (1996) Anti-p53 antibodies in sera from patients with chronic obstructive pulmonary disease can predate a diagnosis of cancer. Clin Cancer Res 2:1767–1775

Ulanet DB, Torbenson M, Dang CV, Casciola-Rosen L, Rosen A (2003) Unique conformation of cancer autoantigen B23 in hepatoma: a mechanism for specificity in the autoimmune response. Proc Natl Acad Sci U S A 100:12361–12366

von Mensdorff-Pouilly S, Petrakou E, Kenemans P, van Uffelen K, Verstraeten AA, Snijdewint FG, van Kamp GJ, Schol DJ, Reis CA, Price MR, Livingston PO, Hilgers J (2000) Reactivity of natural and induced human antibodies to MUC1 mucin with MUC1 peptides and n-acetylgalactosamine (GalNAc) peptides. Int J Cancer 86:702–712

Wang X, Yu J, Sreekumar A, Varambally S, Shen R, Giacherio D, Mehra R, Montie JE, Pienta KJ, Sanda MG, Kantoff PW, Rubin MA, Wei JT, Ghosh D, Chinnaiyan AM (2005) Autoantibody signatures in prostate cancer. N Engl J Med 353:1224–1235

Treatment of Benign Meningiomas Using Radiosurgery

25

Antonio Santacroce, Marcel A. Kamp, Ioannis Simiantonakis, Hans Jakob Steiger, Wilfried Budach, and Jean Regis

Contents

Abstract

Benign meningiomas represent the second most common primary tumor of the central nervous system in particular of the brain. Nowadays gross total resection including dural base and underlying affected bone is still the usual treatment when achievable. Radiosurgery is a highly conformal technique using steep dose gradients and frame based or frameless patient immobilization. It has been used, in adjuvant setting, as an alternative to microsurgery for those tumours, close to critical neurovascular structure, not amenable to radical resection. Over last 20 years a growing body of literature showed the role of radiosurgery also for small tumours defined by imaging studies as meningiomas where microsurgery or stereotactic biopsy are contraindicated.

This chapter describes the main aspects of radiosurgery with respect to physics, techniques and radiobiological formalisms. The clinical efficacy of radiosurgery for benign intracranial meningiomas in particular, is

A. Santacroce (✉)
Departments of Neurosurgery and Radiation Oncology, Heinrich Heine University Düsseldorf, Moorenstrasse 5, 40225 Düsseldorf, Germany
e-mail: antoniosantacroce@msn.com

M.A. Kamp • H.J. Steiger
Department of Neurosurgery, Heinrich Heine University, Moorenstrasse 5, 40225 Düsseldorf, Germany

I. Simiantonakis • W. Budach
Department of Radiation Oncology, Heinrich Heine University, Moorenstrasse 5, 40225 Düsseldorf, Germany

J. Regis
Department of Stereotactic and Functional Neurosurgery CHU Timone, Public Assistance of the Hospitals of Marseilles, Aix Marseille University, Timone University Hospital, 264 Rue St. Pierre, Marseille 13385, Cedex 05, France

M.A. Hayat (ed.), *Tumors of the Central Nervous System, Volume 11*,
DOI 10.1007/978-94-007-7037-9_25,

presented reviewing the major clinical reports of the literature. Radiosurgery provides when properly indicated, safe and effective management of these common tumours. Radiosurgery is a safe and effective method for treating benign meningiomas even in the long term. According to our data radiosurgery should be considered not to adjuvant after microsurgical resection but, depending from the operator's experience, tumor location, target volume and patients' conditions also as a definitive treatment.

Introduction

Meningiomas account for approximately 13–26 % of primary intracranial and intraspinal neoplasms originating from the meningeal coverings of the brain and the spinal cord. Meningiomas show predominance in women, with a female to male ratio of approximately 2:1 for intracranial, and 10:1 for spinal (Marosi et al., 2008). The morphological features suggest that meningiomas are derived from arachnoidal (meningothelial) cells. The majority of meningiomas corresponds to grade I of WHO classification of CNS tumors and thus are benign, slowly growing tumors (Louis et al., 2007). Within the WHO Grade I group there are several subtypes, including meningothelial, fibrous (fibroblastic), transitional (mixed), psammomatous and angiomatous meningiomas. Grossly the majority of meningiomas are well demarcated solitary masses with a broad based dural attachment and smooth or bosselated surfaces. Meningiomas represent still nowadays a very intriguing oncological entity and a challenge in the field of brain tumours either for their diagnosis as well as for the therapeutics strategies that have to be considered for the optimal management and said this, to treat in the better way possible our patients.

The modern management of meningiomas and most particular benign meningiomas has become a strong matter of debate among physicians. To the present day radical surgical resection including dural base and underlying bone remains the treatment of choice, when achievable. The statement "when achievable" should not be underestimated. According to the standards of modern neurosurgery WHO Grade 1 meningioma, as benign tumour, is amenable to surgical "cure". Nobody nowadays criticise the argument that if a tumour is completely resectable, microsurgery should be the preferred way of treatment. On the other hand if we take in to consideration the often cited Donald Simpson's paper (Simpson, 1957) reporting the recurrence rate of benign meningiomas according to the degree of microsurgical removal, most of the deep located intracranial meningiomas, benign in particular, are not amenable to a Simpson Gr. 0 resection due to a simple and rather intuitive anatomic reason: a removal of dural tail with 2 cm margins of dura mater, even for the most experienced operator, is not possible without exposing the patient to an unacceptable risk of perioperative morbidity/mortality. If we assume for those tumours a lower degree of resection a recurrence rate of 9–40 % is reasonably predictable. In the pioneering era of neurosurgery many advances have been done with respect to better operative techniques, introduction of intraoperative microscope, intraoperative monitoring and neuronavigation systems. According to the pioneering work of Al Mefty (Al-Mefty and Al Mefty, 2011) some predictive factors are to be considered in pursuing safe an total removal of benign meningiomas, which may be divided in pure surgical – bony invasion, Simpson grade of resection, skull base approach selected to reach optimal tumour exposure and pure oncological – histology, pathological anatomy, arachnoidal dissection and cytogenetic features.

Parallel to the development of microsurgery, radiation techniques of the central nervous system have seen, over the twentieth century a tremendous evolution. This was achieved thanks to the simultaneous development of radiation oncology concepts and the raising era of stereotactic/functional neurosurgery. Lars Leksell was surely the first person representing the convergence of these two disciplines. Applying under the use of stereotactic frame based coordinates a single high dose of photon radiation to a small volume was defined in early 1960s the term of stereotactic single session highly conformal radiotherapy also called "Radiosurgery". The development of this technique gives to physicians another way to pursue a safe management of

meningiomas. Its role became very soon well established for vestibular schwannomas but is nowadays matter of debate between physicians, from one side microsurgeons claiming that complete surgical removal is ought to be the first main goal to reach, despite the risks, and claiming the "danger" that radiosurgery may have in the medium to long term. On the other side its role is also discussed by many radiation oncologists preferring dose fractionation supported by radiobiologic concepts defining the brain as "late responding tissue" to radiation exposure and thus, with a prolonged dose fractionation protected by arising of late side effects. The first aim of this chapter is to give clear definitions of radiosurgery the main aspects of radiosurgery with respect to physics, techniques and radiobiological formalisms together with a brief introduction of oncological background of benign meningiomas. The second aim is to state the efficacy of radiosurgery for benign meningioma with respect to imaging tumour control and clinical outcome reviewing the results of the major clinical reports of this technique. The third aim is to define clinical indications and contraindications to perform radiosurgery for benign meningiomas as primary/ adjuvant treatment.

Radiosurgery for the Central Nervous System

The use of "stereotactic coordinates" in medical routine (from the Greek "stereo" (solid) and "taxis" (order)), implies the support of three-dimensional mapping techniques to perform a medical procedure. Strictly speaking it might be applied to diagnostic radiology, radiation therapy and surgery in particular of the central nervous system. Stereotactic radiation is a highly precise technique to deliver conformal radiation to a small target volume, either neoplastic or non-neoplastic sparing surrounding tissue by radiation exposure. This radiation if applied as high single dose-fraction, in most of cases photons, is defined radiosurgery, also named by many authors as stereotactic radiosurgery. If this radiation dose is delivered using more than one dose-fraction, always with support of stereotactic coordinates, is defined stereotactic fractionated radiotherapy. Radiosurgery is the precise destruction of a chosen target containing healthy and/or pathological cells, without significant concomitant or late radiation damage to adjacent tissues (Kondziolka et al., 2007). Historically developed by Lars Leksell, whose initial concept was for the management of functional neurologic disorders, the number of clinical indications has increased greatly. The current radiosurgery concept is that damage to tissue within the target volume (either normal or lesional) is the desired effect. After introduction of the Cobalt based System Gamma Knife, radiosurgery has today a well-established role for the treatment of small volume brain lesions like AVM's schwannomas in particular vestibular schwannomas, and an emerging importance for small remnants recurrent WHO Gr. I meningiomas, imaging diagnosed meningiomas and in more recent times also in the field of functional disorders such as trigeminal neuralgia, pharmacological resistant epilepsies etc.

Radiobiology of Radiosurgery for the Central Nervous System

Before the birth of radiosurgery in early 1960s and its introduction clinical therapeutic protocols in late 1980s dose application in radiation therapy for brain lesions (malignant lesions) consisted in the administration of cumulative dose into a variable number of fractions, usually not more than 2 Gy for standard fractionation more than 2 Gy for hypo-fractionation either in curative or in palliative setting. The rational of avoiding administration of a high single dose is the radiation exposure of the central nervous system and the risk of radiation injuries which might imply. In radiation therapy the relationship between time of radiation, dose and number of fractions to influence biological effect to a given tissue is based on four basic principles of radiobiology defined as the "4R's" of ionizing radiation (Purdy, 2008):

1. Repair capacity of cells after sub-lethal damage radiation induced.
2. Repopulation of surviving tumour stem cells during fractionated radiotherapy.
3. Redistribution of cells between the cell cycle which after radiation injury in equally

distributed radiation sensitive and resistant subpopulations.

4. Re-oxygenation of hypoxic tumour cells after repeated radiation exposure. The radio-sensitivity of cells is inversely proportional to the hypoxic cell rate. The application of a dose fraction produces death of oxygenated tumor cells followed by oxygenation of hypoxic cells now more sensitive to the following dose fraction.

These radiobiological principles are based on "in vitro" experiments applying a dose of ionizing radiation, usually photons, to cell in vitro cultivated, for example fibroblasts. The results of these experimental models together with clinical experience with three-dimensional conformal radiotherapy brought the physicians to conclude that dose fractionation lessens the risk of injury of normal tissues and thus the rate of side effects (Hall and Brenner, 1992). The biological response of a given tissue to radiation and dose fractionation has been theorized with many models. The linear quadratic (LQ) Equation Formula is so far the most used: briefly it defines the biological response of tissue in terms of surviving cell fraction (SF) to a given dose (D) according to a linear dose coefficient α for low doses and α coefficient for the square of the dose β for high dose fraction within a dose range from 1 till 8 Gy: biological effect is proportional to $\alpha D + \beta D^2$. The extrapolated cellular survival curve related to the dose applied allows us to define a linear component of cell killing α and a quadratic component of cell killing β. The ratio of these two variables defines α/β ratio of a tissue and express the point where the linear component α and the exponential (curvier) component of the survival curve β are equal or, in other words, it express the dose at which the two components of cell killing are equal. The linear-quadratic formula is presently the standard way to mathematically represent the effect of radiotherapy to account for the effects of different fractionation schemes (Kondziolka et al., 2007). The clinical consequence of such a model is that normal tissues can be classified in early (high α/β ratio) and late responding tissue (low α/β ratio); the central nervous system is a common example of late responding tissue. The late toxicity of a radiation treatment can be well described with the linear quadratic model applying dose fraction from 1 till 8 Gy given intervals between dose application longer than 6 h. On the other hand for acute toxicity in early responding tissues this model can be applied only for the same total treatment time.

This apparently simple model has limitations if applied to radiosurgery. First some tumours show a considerable variation of α/β ratios despite their malignancy. Second, linear quadratic model cannot be applied with a dose of 8 Gy or more. Third the validity of the linear quadratic model has not been sufficiently investigated for very small target volumes (major diameter < 2cm) so far. This implies that increasing the fractionation for slow growing tumors or non-neoplastic lesion may not bring a biological better response of the tumor if compared to a single dose if we accept a low α/β ratio for benign or slow growing tumours according to the most recent clinical data. Furthermore highly conformal radiosurgery spares dose exposure to surrounding tissue therefore the compromise of dose fractionation to balance between imaging tumour control and normal surrounding tissue reaction might not be a consideration, depending on dose delivered, target volume and eloquence of surrounding structures. To conclude many efforts to extrapolate a survival curve applying high doses to a benign lesions (<10 Gy) giving improbable values for which the risk of missing estimates of α/β ratios is too high, thus confirming the usefulness of such a model in radiosurgery (Flickinger and Niranjan, 2008). A number of experimental models have studied the effects of radiosurgery (Kondziolka et al., 2007). The magnitude of radiosurgical effects remain poorly understood, especially when described in terms of conventional radiation therapy doses. If we consider the application of radiosurgery for benign intracranial lesions like meningiomas, it has been observed that the radiobiological effect on meningiomas and other benign neoplasms is a combination of both cytotoxic and delayed vascular effects as reported by Kondziolka et al. (2007). After both vestibular schwannoma and meningioma radiosurgery they observed a doubling of the

number of apoptotic cells after radiosurgery when compared to controls, within the first 48 h after irradiation. Conversely the vascular effects seem to have a secondary role: available information from AVM radiosurgery or meningioma radiosurgery has shown that normal vessels rarely decrease in size or occlude after radiosurgery and therefore they conclude that the abnormal vessels of neoplasms or vascular malformations have a relative sensitivity to radiosurgery in comparison to normal surrounding vessels since no occurrence of perforator occlusion leading to an infarct has been identified. On the other hand it must also be said that chance to produce a damage of normal capillary vessels is directly proportional to the dose increasing.

The application of radiosurgery to the central nervous system with respect to target and surrounding tissue was classified in four groups, assuming the central nervous system as late responding tissue, (Larson et al., 1992):

1. Late responding target embedded within late responding tissue: AVM.
2. Late responding target surrounded by late responding tissue: meningioma/schwannoma).
3. Early responding target embedded within late responding tissue: low gr. Glioma.
4. Early responding target surrounded by late responding tissue: Glioblastomas/metastases.

According to this oversimplified classification the indication to radiosurgery for benign WHO Gr.1 meningioma appears relatively simple to give. Nevertheless some variables must be considered: the different anatomic parts of central nervous system have not the same uniform tolerance to radiation: 2nd cranial nerve optic chiasm and brainstem represent a dose limiting factor. The target volume plays a role to give a proper indication to radiosurgery. Finally the use of a highly conformal radiation dose is applicable with different techniques whose differences must be considered before applying radiosurgery. To conclude a recent report from the group of Pittsburgh gave clear indications about to radiobiological formalisms of radiosurgery drawing outcomes from radiobiological analysis of clinical data from radiosurgery (Niranjan and Flickinger, 2008): (1) The linear-quadratic equation cannot reliably represent equivalent radiation effects when extrapolating from conventional fractionation (1.5–4 Gy per fraction) to high-dose (12–25 Gy) single fractions for radiosurgery; (2) Mathematical models of radiation injury probability need to take into account that the target/tumor tissue's radiation response may affect the reaction of the surrounding normal tissue; (3) The predominant radiation response of a radiosurgical target is mediated through the target or tumor vasculature.

Physical Considerations

Radiosurgery is based on the use of ionizing radiation delivered to a small target volume. Some definitions must be given: **Radiation:** Event described as energy sent out either as wave (photons) or as particle (protons Heavier ions or electrons) in a given time and space. Radiation may interact with matter delivering its energy thus producing a change in the matter itself. According to this definition radiation is divided then in ionizing and not ionizing or exciting. Ionizing radiation is produced by artificial or natural radioactive nuclides, either particles or high energy electromagnetic waves with enough energy to produce an atomic ionization. The interaction produces changes either in the given matter or the given radiation too. Furthermore the ionization of a given atom can be direct (protons heavier ions or electrons) or indirect (photons). Not ionizing radiation (also called exciting radiation) is produced by electromagnetic waves whose energy is too low to ionize a given atom (for example UV radiation). This second group, due to the poor biological effect produced, has no relevance for clinical radiotherapy and thus radiosurgery.

Radioactivity: Strictly speaking the radioactivity of an element is defined as the capacity or property of an instable atomic nucleus of a given element to send out radiation getting to a stable state. This emission might be α, β or γ rays. Each of them has specific decay modes, different capacity of interaction with matter with respect to energy, depth of shielding and biological efficacy.

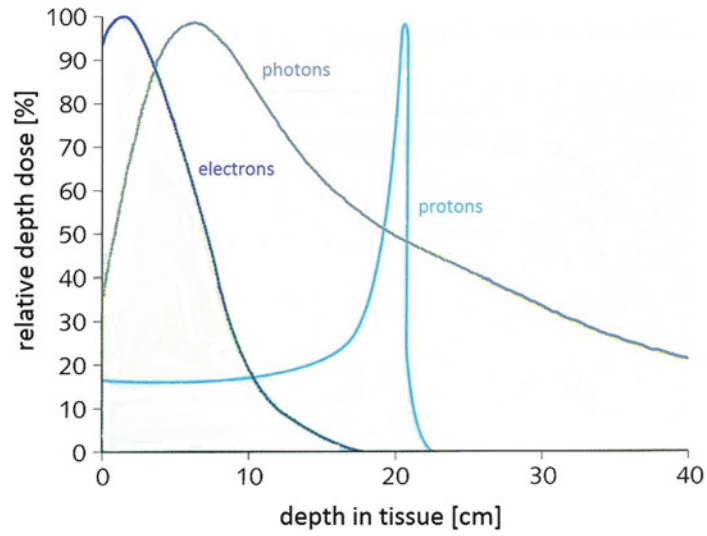

Fig. 25.1 Depth dose distribution of photons compared to electrons and protons

Decay modes: α rays (i.e. double charged helium nuclei): densely ionizing radiation they are not applied in clinical radiotherapy due to their short shield distance and high biological effect which makes it dangerous for human body. β rays: either positive and negative decay. They are weak ionizing rays. ^{60}Co is the most used in particular in radiosurgery, its decay mode is shown in Fig. 25.2. γ rays: electromagnetic radiation photons or neutrons. No mass any charge. They produce indirect and weak ionization. **Atomic particles:** subatomic bodies with given mass, radium and sometimes charge. Protons, neutrons, heavier ions (carbon ions) and electrons are typical examples. **Photons:** electromagnetic bundles-packets of energy without mass and any charge with given wave frequency ν and length λ emitted either as X rays or as γ rays.

The administration of energy dose is applied considering following variables: **Isocentre:** point in space through which the central beam of radiation passes ideally at center of the target; **Isodose line:** curve within a planar point connecting the same dose; **Dose distribution:** distribution of the energy dose in a given space delineated in Isodose curves (%). **Depth dose distribution:** dose distribution along the central radiation beam. **Dose in line profile:** dose distribution along a straight line. **Dose cross line profile:** dose distribution along a straight line perpendicular to central beam. **Dose cross line distribution:** dose distribution in the plan perpendicular to central beam. Transverse and longitudinal dose measurements are taken by a radiation detector in order to characterise the radiation beams from medical linear accelerators. Typically a ionisation chamber and water phantom are used to create these radiation dose profiles. Water is used due to its tissue equivalence. Transverse dose measurements are performed in the x (crossplane) or y (inplane) directions perpendicular to the radiation beam, and at a given depth (z) in the phantom. These are known dose profiles. Dose measurements taken along the z direction create radiation dose distribution known as a depth-dose curve.

In modern radiation therapy clinical relevance is given only to ionizing radiation to deliver energy to a target volume in the human body. This radiation is applied with several techniques (see following paragraph) by using photons with an energy spectrum between 1.2 and 25 MV and particles like protons and heavier ions like carbon ions. A comparison of the depth dose distribution between photons electrons and protons is shown in Fig. 25.1. For radiosurgery in particular a single high dose of energy sent out by ionizing radiation is applied in most cases with photons either produced by a linear accelerator (linac) through emission of x rays emitted with Bremsstrahlung, using a photon energy applied

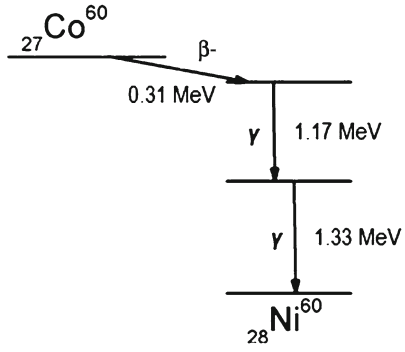

Fig. 25.2 Cascade decay of ^{60}Cobalt applied for the Gamma Knife radiosurgery system: β- decay ray changing in active ^{60}Ni. Afterwards the active Nickel gets stabilized to ^{60}Nickel through emission of two photons γ ray emitting with an average energy of 1.25 MV

of 6 MeV or obtained by the decay of the radioactive isotope of cobalt ^{60}Co whose decay mode provides two γ emitting photons with an average energy of 1.25 MV (Fig. 25.2). A particle based radiation therapy with protons or carbon ions is provided in a few facilities worldwide and plays no role in radiosurgery rather in fractionated intensity modulated radiation therapy (IMRT) and therefore not described in this chapter.

Radiosurgical Techniques and Devices

Radiosurgery was originally envisioned to treat intracranial lesions like AVM's and afterwards benign tumours like vestibular schwannomas or meningiomas. Over the last three decades a growing body of clinical reports, most of them retrospective, showed that in particular for the central-nervous system when a small volume sized lesion must be targeted highly conformal single session radiation delivered with support of stereotactic coordinates is to recommend. In more recent years radiosurgery has been indicated also for extracranial lesions. Together with dose planning volume targeting is an essential issue of radiosurgery for meningiomas thus implying the use of adequate imaging diagnostic tool. MRI imaging offers superior target definition due to better enhancement of the target, less bone artefacts and, by using CISS sequences, better depicting of cranial nerves (Spiegelmann et al., 2010). On the other hand CT scan offers better appreciation of surrounding bone spaces and tissue photon attenuation (Elia et al., 2007). Although some authors recommend fusion of MRI and CT imaging just for small meningiomas using CT based plans for larger meningiomas, we recommend the use of both imaging diagnostic technique to perform radiosurgery for all meningioma cases regardless the volume. A variety of devices are now available for commercial use to perform radiosurgery Radiosurgery for benign meningiomas is nowadays provided using two basic techniques of convergent beam technology: (1) Stereotactic ^{60}Co based system "Gamma Knife"; (2) Linear accelerator also called linac, and modified linac based systems.

Gamma Knife

The "Gamma Knife" uses 201 multiple fixed converging ^{60}Co sources constantly releasing two photons with an average energy of 1.25 MeV for each spontaneous decay aimed to a centre point (Elia et al., 2007). It is based on three structural concepts: A spherical source bounding, collimation helmets and couch with electronic control. The sources are arranged on the surface of a hemispherical shaped shell each aimed at a single isocenter 40 cm from each source called Unit Centre Point. The UCP isocenter is targeted by using a stereotactic coordinate frame (Purdy, 2008). The beams produced by these sources are then secondary collimated with conic collimation helmets of variable diameters (4, 8, 14 and 18 mm). It is possible to close each single of these beams by plugging the conic collimator allowing the individual beam patterns. The constant decay of the cobalt sources implies a daily dose rate which at installation is set by 3–4 Gy/min with a half-life of approximately 5.3 years and thus with a replacement necessary every 7–8 years. ^{60}Co isotopes have a relatively low energy (1.25 MeV). Most plans have an isodose normalisation line of 50 % due to the source size and the steepest dose falloff in cross line dose profile of ^{60}Co. The total time to irradiate a single isocenter is of

a few minutes thus making multiple isocenter plans practical. Since early 1980s many Gamma Knife models have been developed. From the prototype the model U to the model B providing arrangement of the sources on annular section of a hemisphere. Later model C and 4C were introduced with robotic positioning of treatment coordinates and with the last Model PERFEXION the collimation helmets were internally mounted and with different diameters (4, 8, 16 mm). Furthermore a major aperture allows also treatment of the cervical spine (Flickinger and Niranjan, 2008). To conclude cobalt based Gamma Knife has in comparison to linear accelerators several advantages: Constant beam/source pattern, predictable decay by well-known half-life, no daily output fluctuations. On the other hand some disadvantages have to be mentioned: the sources need a reloading after complete decay, the application of normalisation isodose line of usually 50 % required due to its dose cross line profile of ^{60}Co isotope produces a dose inhomogeneity between periphery and central point of the target volume, but not influencing the sharp falloff necessary to guarantee the conformality required for the dose distribution.

Linear Accelerators

A linear accelerator (also called linac) is the most widely and common machine used to conventional radiotherapy. The physical principle at the basis of linac radiation is the *Bremsstrahlung*: ionizing radiation of a given volume produced by the collision of accelerated electrons as microwaves properly amplified with a metal target which, when in photon mode, emits X-rays that are properly collimated to irradiate the target. Linear accelerator based radiosurgery was developed by adapting linacs used for conventional radiotherapy incorporating stereotactic guiding devices to guarantee better conformity and dose falloff. Multiple non coplanar arcs converge to a single isocenter where a spherical dose is created. Arcs are produced by rotation of the gantry and couch angle with a so called “step and shoot” technique. Furthermore modern linac devices provide a single dynamic arc and it is produced by simultaneous rotation of gantry and couch with a “rapid arc” technique. Many linac radiosurgery units use circular collimators reducing beam divergence protecting thereby normal tissue and therefore critical neuro vascular structures adjacent to many skull base meningiomas. To reach better conformality, given a spherical shape of a single isocenter plan, multiple isocenter plans, like with Gamma Knife, are technically possible to reach better conformality but more dose inhomogeneity. On the other hand the use of multiple isocenters in linac radiosurgery increases the total treatment time and is nowadays obsolete. The latest linac radiosurgery devices are equipped with tertiary multileaf collimators, and more recent times, integrated internal multileaf collimator systems to compensate the long treatment time necessary for multiple isocenters plans achieving highly conformal and homogeneous dose distributions obtained by the application of an isodose normalisation line of 80 % delivering radiation to a single isocentre.

As reported by Spiegelmann et al. (2010) the introduction of micro-multilieaf collimators has deeply transformed the practice of linac radiosurgery. Through the use of single isocentre planning and radiation delivery there is a more homogeneous radiation distribution across the target, basically not achievable with multiple isocentres planning. Nevertheless this dosimetric difference, according to clinical data, seems to be not clinically relevant given that inhomogeneity dose distribution within the target does not interfere with the main goal of the treatment which is to control/eliminate the tumour (Spiegelmann et al., 2010). Conversely to Gamma Knife which is a strictly frame based system, the latest linac radiosurgery devices are frameless systems, with the option to switch to a framed based target definition when a very steepest dose falloff is required (anterior optic pathways or brainstem). Currently many devices are used to perform linac based radiosurgery: X Knife (Radion Inc. Burlington MA U.S.A) Novalis (Brainlab Heimstetten Germany) etc. Separate description is deserved to The Cyber Knife (Accuray Inc. Sunnyvale CA U.S.A) due its peculiar structural features (see following paragraph).

Cyber Knife

The Cyber Knife (Accuray Inc. Sunnyvale CA U.S.A) combines the technology of a miniaturized linac on a robotic arm with a system for target tracking and beam realignment. It emits 6 MV photons with circular collimator. Contrary to the latest linac devices Cyber Knife has no multileaf collimators. Multiple fixed beams and isocenters are used. Stereotactic coordinates are defined without frame. Target position is verified during radiation by using to X-rays diagnostic cameras and an optical tracking system constantly proving the patients/target's position. This system is provided also by other linac radiosurgery systems. This feature should not be confused with an image guided radiotherapy technique (IGRT), which provides the combination of a three dimensional imaging with conformal treatment delivery. This is accomplished by the addition of CT imaging capability to a linac unit with stereotactic equipment (see next paragraph). Major advantage of the Cyber Knife is the freedom of movement in the space of the robotic arm to deliver radiation compared to classical linac whose movement is limited by the gantry arc/couch fixed position in the space.

Disadvantage is the technology of the miniaturized linac which makes the total treatment time relatively long and the application of a mask to for treatment time might be uncomfortable for the patient.

Tomotherapy and Image Guided Radiotherapy

Tomotherapy is basically a linear accelerator with a diagnostic CT machine design, not delivering kV X-rays for diagnostic aims rather megavoltage ionizing radiation. Unlike to conventional linacs it has several advantages: no external moving gantry for beam positioning, but inside the housing CT unit, rapidly moving the beam and the patient to irradiate the target from different selected positions. New developed models host also diagnostic X-ray CT to perform also real time target imaging and so equipped performing an IGRT. Tomotherapy can be used for stereotactic fractionated irradiations as well as for IMRT with beam modulation mode. The application of radiation is limited only to coplanar techniques thus making Tomotherapy not ideal to perform radiosurgery. Basically the application of radiation can be performed with multiple convergent cobalt sources, fixed photon arcs, multiple coplanar or non-coplanar photon arcs or angles and, as described previously, with support of a robotic arm.

Charged Particle Therapy – Protons and Carbon Ions Radiotherapy

The introduction of particles like protons and heavier ions (i.e. carbon) for radiation therapy of meningiomas is relatively recent as reported by Flickinger and Niranjan (2008). If compared to photons and electrons either protons or carbon ions have high linear energy transfer (LET) but same relative biological effectiveness (RBE). The greatest advantages of particle radiation units are: (1) beam stops at a depth related to the beam energy; (2) sharp beam edge, in particular for carbon ions; (3) lower integral dose delivery by lack of an exit dose. Particles traverse relatively straight paths through matter slowing down continuously by interaction of atomic electron and nuclei. The energy produced by subatomic particles has the unique property of being delivered nearly completely at the last 2 mm after path length. The depth dose distribution of protons has an extremely sharp falloff and the peak ionization power defines the so called "Bragg peak". The machine employed to deliver this ionizing radiation is a circular accelerator known as "cyclotron": simply speaking working on the same principle of linacs a high energy particle produced by an ion gun is accelerated through a circular trajectory obtained with two bi-polar magnetic fields, known as "Dees" of cyclotron and a deflector. This structure reduces the length of the accelerator bringing the particles to speed close to the speed of light (300.000 km/s) delivering ionizing radiation to the target. The application of particle therapy is performed just in some centres worldwide due to the high costs of equipment and maintenance. This makes particle therapy not yet ideal to perform radiosurgery.

Dose Tolerance for Organ at Risks After Radiosurgery

The application of a high single dose to a target volume implies a cautious evaluation of the radio sensitivity of the organ tissues adjacent to the target. The delivery of a high dose in single session might increase the risk of radio necrosis and the risk of polineuropathy. Variables to consider are the dose delivered and its distribution (isodose line), the volume of the tissue irradiated, the sensitivity of the tissue affected and history of any prior irradiation. Concerning benign meningiomas the most common acute reactions are symptomatic oedema and radio-necrosis (Kollova et al., 2007; Kondziolka et al., 2008; Santacroce et al., 2012). The clinical manifestation may vary greatly according to the volume and the meningioma location (Santacroce et al., 2012). As reported by Flickinger and Niranjan (2008), a prior history of fractionated radiation therapy to the same region of interest appears to have limited effects on the risk of developing post radiosurgery parenchymal edema with exception to the optic nerve. The tolerance of cranial nerves is a crucial point in radiosurgery of benign meningiomas most particularly of the skull base. According to clinical experience with radiosurgery and conventional fractionated radiotherapy sensory nerves appears to most sensitive, followed by somatic sensory nerves and motor nerves (Flickinger and Niranjan, 2008). The anterior optic pathways are the most dose sensitive structures, thus implying that the dose applied the second cranial nerve (optic nerve) should be always a consideration. Many contributions report a dose maximum tolerance of the optic nerve after radiosurgery to be at 8 Gy. Nevertheless more recent studies (Stafford et al., 2003) report and a maximal dose tolerance to be at 10 Gy may be related to better imaging technique available. The correlation of data with dose fractionation to conclude brought physicians to assume an α/β ratio for the optic nerve of c.a. 1 as reference value to calculate dose equivalent between fractionation and radiosurgery dose protocols.

Radiosurgery for Bening Meningiomas

Intracranial Meningiomas

During the last two decades many clinical studies reported about the efficacy of radiosurgery for the management of benign intracranial meningiomas. Complete resection, including dural base and underlying affected bone, is nowadays still the usual treatment for benign intracranial meningiomas when achievable. In other cases, radiosurgery is frequently considered. Although a role for radiosurgery has been well established over the past decade, the optimal management of these relatively common tumours remains unclear despite a large number of reports (Kondziolka et al., 2008). We present the results of the recent report of the European gamma knife society about the clinical experience of radiosurgery for benign intracranial meningiomas drawing conclusions from a cohort of over 4,500 tumours (Santacroce et al., 2012). The primary end point is to evaluate the effect of radiosurgery as assessed by imaging to confirm control of tumor progression and to assess the influence of several variables on outcome. The secondary end point is to confirm treatment safety by establishing clinical neurological stability and complication rates after radiosurgery.

A cohort of 4,565 patients harbouring exactly 5,300 meningiomas was reviewed. All tumours included were either histologically confirmed as World Health Organization (WHO) grade I or were diagnosed presumptively on the basis of imaging. Of 4,565 patients treated, 528 (11.5 %) were lost to follow-up. Detailed results for 4,585 tumors (86.5 %) were collected in the main database. Imaging follow-up ranged from 24 to 233 months, with a total of 817 tumours whose imaging follow-up was less than 24 months being excluded. From this cohort, we obtained follow-up for >5, 7.5, and 10 years in 1,334, 577, and 388 tumours, respectively. Median imaging follow-up was 63 months

(mean, 70.9 months). According to our data, of 3,768 tumours with at least 24 months of follow-up, a total of 2,107 have digitally stored images. We found that 2,187 meningiomas (58 %) had regressed (reduced in size) and 1,300 tumours (34.5 %) had remained unchanged, giving a tumour control rate of 92.5 %. Tumour progression occurred in 281 lesions (7.5 %) at a median of 48.7 months (mean, 56 months). Forty-one patients harbouring 43 tumours underwent further treatment. Conventional radiotherapy or repeat radiosurgery was performed in 13 of these patients, and 27 of them underwent surgery. One patient who underwent repeated radiosurgery (RS) eventually required surgery after further tumour enlargement. The remaining 197 tumours had not required further treatment by the time of last follow-up. The Kaplan-Meier estimations of progression-free survival (PFS) at 5, 7.5, and 10 years showed control rates of 95.2 %, 91.3 %, and 88.5 %, respectively. For those tumours initially treated with microsurgery PFS rates of 92.7 %, 86.4 %, and 83.2 % vs. 96.8 %, 95.1 %, and 92.7 %, respectively, for tumours without histological confirmation ($P < .001$) were observed. Imaging tumour control was better in female gender than in male patients – PFS rate 96.3 %, 93.2 %, 91.6 % vs. 90.3 %, 83.5 %, 78.1 %, respectively ($P < .001$). Better imaging tumour control was seen for patients suffering from single meningioma- PFS rates 95.4 %, 92.7 %, 89.9 %, respectively as opposed to multiple meningiomas 95.4 %, 92.7 %, 89.9 % ($P < .001$). Tumour control was poorer for those meningiomas demonstrating increasing tumour volume ($P = .01$), and skull base tumours were better controlled than convexity lesions – PFS rates 95.9 %, 92.4 %, 90.1 % vs. 91.6 %, 85.9 %, 81.6 %, respectively ($P < .001$). A statistical difference in tumour control between centres is also observed ($P < .001$).

Descriptive clinical follow-up was obtainable for 3,854 patients (84.4 %) and ranged from 6 to 233 months. Clinical improvement was reported in 2,065 patients (53.5 %) at a median follow-up of 61 months (mean, 61.8 months), and complete resolution of symptoms was reported in 865 cases (22.2 %). Complications were observed after radiosurgery in 497 patients (12.9 %). Morbidity rates were 6.3 % (temporary) and 6.6 % (permanent). We assessed mild or intermittent neurological morbidity at 4.7 %, persisting continuous neurological morbidity but not affecting performance in daily life at 6.8 %, and severe disabling neurological morbidity affecting performance in daily life morbidity at 1.3 %. Permanent continuous morbidity was 3.6 % and permanent disabling morbidity was 1.2 %. Morbidity for skull base meningiomas (356 of 2,101 cases) was 16.9 %, including 36 cases (1.7 %) in which disabling morbidity was permanent. Morbidity for convexity/parasagittal locations was seen in 124 of 832 cases (14.9 %), permanent and disabling in 10 cases (1.2 %). In particular, symptomatic edema occurred in 39 cases (4.7 %). Morbidity for cavernous sinus, sellar, and middle cranial fossa locations was seen in 148 of 1,380 cases (10.7 %). Among these complications, 62 were in patients who had harboured tumours that had enlarged, 40 of them previously confirmed (after surgery) as WHO grade I. Four patients who developed a complication eventually died: 3 died of edema/swelling after volume staged radiosurgery for large parasagittal meningiomas and 1 died of hydrocephalus/radionecrosis after radiosurgery for a posterior cranial fossa meningioma. Six patients who developed complications at a mean of 14.5 months after radiosurgery eventually died of unknown causes at a mean of 54 months, although only 2 had previously developed permanent complications. The remaining 6 died of unrelated causes. Five patients underwent surgery despite good tumour control: 2 for chronic subdural hematoma at another location, 2 for cystic degeneration close to the volume irradiated, and 1 for severe facial pain associated with a petroclival meningioma that persisted after radiosurgery. No radiation-induced tumours were seen, but of 8 patients reoperated on for post- radiosurgery tumour enlargement, 6 demonstrated atypical histology (WHO grade II) and 2 were frankly malignant (WHO grade III), all having been reported at previous surgery as having WHO grade I lesions.

Spinal Meningiomas

Radiosurgery is a well-established treatment option for intracranial benign meningiomas. On the other hand its role for spinal meningiomas is not yet clear. Spinal meningiomas are common intradural tumours that cause neurological dysfunction through slow growth and spinal cord compression. They represent 12 % of all meningiomas. The occur predominantly in the thoracic spinal canal followed by the cervical and rarely in the lumbar spine. Most of them are WHO Gr. 1. Microsurgery provides nowadays in most cases definitive treatment. The major concerns with respect to complete surgical resection is to achieve a full resection minimizing the risk of cerebro spinal fluid leak, perioperative morbidity. Spinal cord tolerance to radiosurgery is not well known yet due to the paucity of indications. As reported by Gerszten et al. (2004) in a series of 17 benign tumours treated with Cyber Knife Radiosurgery applying a mean dose of 14 Gy with to an 80 % isodose line no radiation induced toxicity or morbidity at a median Follow up of 18 months was experienced. A more recent series from the group of Pittsburgh (Gerszten et al., 2012) reported outcomes of spine 40 benign lesions treated with spinal radiosurgery. Lesion location included 13 cervical, 9 thoracic, 11 lumbar, and 7 sacral tumors. Thirty-four cases (85 %) were intradural. The most common tumor histologies were schwannoma (15 cases), neurofibroma (7 cases), and meningioma (8 cases). The mean prescribed dose to the gross tumor volume (GTV) was 14 Gy (range 11–17) delivered in a single fraction in 35 cases. In five cases in which the tumor was found to be intimately associated with the spinal cord with distortion of the spinal cord itself, the prescribed dose to the GTV was 18 to 21 Gy delivered in three fractions. No subacute or long term spinal cord or cauda equina toxicity occurred at median follow up time of 26 months. No evidence of tumor growth was seen on serial imaging in any case.

Despite these encouraging results there is still much disagreement concerning indications and contra-indications for spine radiosurgery, treatment dose and fractionation and tolerance dose of the spinal cord, as reported by the Elekta Spine Radiosurgery Research Consortium (Guckenberger et al., 2011). To conclude bigger cohorts with longer follow up are definitely desirable to better appreciate the indications and the possible complications of spinal radiosurgery for benign meningiomas.

Discussion

Imaging Tumour Control

Radiosurgery does not achieve tumour removal, the claimed outcome of a radical microsurgical resection, but it can frequently achieve simple control of tumour volume. The main goal of radiosurgery is to control tumours not amenable to complete resection such as those in high-risk locations where postoperative complications might be anticipated or residual or recurrent tumours. Long-term follow-up is essential for the assessment of the efficacy of radiosurgery in this or, for that matter, other situations. According to our results, various factors may influence imaging outcome. We found, contrary to other series (Kollova et al., 2007) that previous surgery is a significant factor with respect to imaging tumour control. A possible reason may be that highly conformal planning is easier for lesions with a morphology that has not been altered by prior surgery, given the postoperative distortions that enhancing scar tissue can introduce. Poorer control in male than female patients has been previously reported (DiBiase et al., 2004). The reason for this is unknown but may relate to hormonal status (Sanson and Cornu, 2000).

In our experience increasing target volume is a factor predicting poorer imaging tumour control as reported also by Kondziolka et al. (2008) and by a Elia et al. (2007) in a recent review of literature. This is also confirmed by more recent clinical reports (Pollock et al., 2012). Further-more patients harboring multiple meningiomas or suffering from frank meningiomatosis or Neurofibromatosis type 2 is also a variable associated with lower tumor control rate (Santacroce et al., 2012; Kondziolka

et al. 2008). To conclude tumor location is a predictive variable influencing imaging tumor control. Our experience (Santacroce et al., 2012) together with other reports (Kondziolka et al., 2008; Pollock et al., 2012; Kollova et al., 2007) confirmed worse imaging outcome for located in parasagittal region, falx, or convexity compared to skull-base tumours. Although the discrepancy due to gender and prior surgery can be explained on the basis of biologically different tumors in men versus women, and an increased likelihood of microscopic disease that was outside the treatment volume in patients with prior surgery, the reason for worse imaging tumor control for tumors located in parasagittal, falx, or convexity reasons remains elusive. According to Kollova et al. (2007) meningiomas in these locations have a pial blood supply, and a larger volume of brain parenchyma is irradiated, compared with the middle and posterior fossae, where a part of margin faces the cistern with cerebrospinal fluid thus increasing the incidence of symptomatic edema and imaging failure. It is possible that different histologic subtypes of benign meningiomas are more radiosensitive than others, but further study is needed to examine this variable as a predictor of radiosurgical success (Pollock et al., 2012). Further point of discussion is the dose necessary to achieve imaging tumor control. According to the latest contributions in literature (Santacroce et al., 2012; Kondziolka et al., 2008) increasing dose delivered to the margin is not an influencing variable with respect to tumor control. On the other hand if it is predictable that a too high e dose delivery to the target might bring to higher complication rate (Pollock et al., 2012; Kollova et al., 2007) a low dose application to the margin, below to 12 Gy at median isodose line of 50 %, is associated to an increased rate of tumor enlargement (Kollova et al., 2007). This issue is supported also by other data (Elia et al., 2007).

Toxicity After Radiosurgery

Radiosurgery is a safe method for managing benign intracranial meningiomas, as indicated by the very low complication rate published so far. (Santacroce et al., 2012; Kondziolka et al., 2008; Condra et al., 1997). In our experience, while not specifically tested which variables may influence the clinical outcome and the toxicity rate, the permanent morbidity rate of 6.6 % confirms the data reported in literature. More recent contributions (Pollock et al., 2012) show a permanent complication rate of 11 % with more than one-half related to cranial nerve dysfunction. A difference between this series and other recent reports is the radiation dose the median tumor margin dose over the entire study period was 16 Gy. This is greater when compared to Prague (median, 12.6 Gy) (Kollova et al., 2007) Pittsburgh (mean, 14 Gy) (Kondziolka et al., 2008) and the European gamma Knife Society experience (median, 14 Gy) (Santacroce et al., 2012). The variety of side effects that may arise after radiosurgery is related to many factors: tumor location, tumor volume and shape, dose delivered, eloquence of the neuro-vascular structures close to the target volume: symptomatic edema and consequent tumor/brain swelling and cranial nerves dysfunctions are the most frequent; rare are episode of vascular occlusion with an incidence of 1–2 % (Elia et al., 2007; Barami et al., 2007). Delayed hydrocephalus is also reported (Bloch et al., 2012).

As recently reported by Pollock et al. (2012) a multivariate analysis showed that patients with tumors of the parasagittal/falx/convexity regions were three times more likely to develop permanent complications compared to patients with tumors involving the skull-base or tentorium, confirming the evidence of other reports (Kollova et al., 2007). Increasing target volume is also a risk factor with respect to complications treatment related. Kollova et al. (2007) noted that the 5-year risk of post-treatment edema exceeded 30 % for patients with benign meningiomas larger than 10 cm^3 compared to 10 % for patients with tumors less than 5 cm^3. In the University of Pittsburgh meningioma series (Kondziolka et al., 2008) neither tumor location nor prescribed dose rather increasing volume was significant factor associated with treatment related complications. The prescription dose is another variable influencing the incidence of complications. The radiosurgery group from Prague (Kollova et al., 2007)

performed a detailed analysis to determine the optimal radiation dose for benign meningioma radiosurgery. They report that patients receiving a tumor margin dose below 12 Gy had a higher chance of tumor progression, patients receiving a tumor margin dose greater than 16 Gy had an increased risk of post treatment edema. They concluded that a tumor margin dose from 12 to 16 Gy represents the therapeutic window for benign meningioma radiosurgery thus reaching the goal of delivering a therapeutic radiation dose without increasing toxicity. Conversely a recent review of the literature by Bloch et al. (2012) analyzing the factors contributing to radiation toxicity found no correlation between treatment dose and toxicity after radiosurgery. Of note a relationship between increasing tumor size and toxicity is reported ($p < 0.05$). According to other reports tumor location is also a risk factor, reporting higher toxicity for large tumours located in the convexity/parasagittal region more frequently developing symptomatic edema after radiosurgery.

Radiosurgery Versus Stereotactic Fractionated Radiotherapy

Fractionated stereotactic radiotherapy, conversely to radiosurgery, combines the step dose gradients of high conformal radiation with the radiobiological effect of dose fractionation. It is not aim of this chapter to analyze the technical and clinical outcomes reported in the literature about this technique. Therefore we refer the reader to the recent review by Elia et al. (2007) where this radiation technique is described in detail. The rationale to dose fractionation is to spare the nervous tissue adjacent to the target from late complications given the low α/β ratio of 2 assumed using the linear quadratic formula for biological and thus described as late responding tissue. Assuming the same α/β ratio value of 2 for benign meningiomas, there is no radiobiological advantage of dose fractionation with respect to imaging tumour control (van der Kogel, 1991). First difference between radiosurgery and fractionated stereotactic radiotherapy is the imaging response rate: radiosurgery imaging shrinkage rate of the target volume is higher compared to fractionated stereotactic radiotherapy. On the contrary there is no difference with respect to clinical response toxicity between fractionated stereotactic radiotherapy and radiosurgery.

Given the higher incidence of toxicity after radiosurgery by increasing tumour volume and tumor location in eloquent areas like anterior visual pathways, brainstem or convexity (Kollova et al., 2007; Pollock et al., 2012) compared to stereotactic fractionated radiotherapy, according to the most recent reviews of literature (Elia et al., 2007; Bloch et al., 2012) indication to fractionated stereotactic radiation over radiosurgery is for large tumor volumes (>3.5 cm) close to critical structures and optic nerve sheath meningiomas with preserved vision (Kondziolka et al., 2008). Furthermore as reported by Pollock et al. (2012) and Kondziolka et al. (2007) lower control rates are noted at lower prescription doses as also reported by Kollova et al. (2007). This may have a radiobiological explanation. Calculating the normalized tissue dose of 12 Gy given in a single-fraction, this equates to approximately 42 Gy of conformal fractionated radiotherapy EBRT, assuming benign meningiomas an α/β ratio of two and a 2-Gy fraction size for fractionated radiotherapy. Currently fractionation dose schemas for patients with WHO Grade I meningiomas are typically from 50 to 55 Gy in fraction sizes of 1.8 to 2.0 Gy (Elia et al., 2007; Pollock et al., 2012) As a result, single-fraction radiation doses below 13–14 Gy may be too low, and might result in a lower rate of long-term tumor control This gives a rationale to stereotactic dose fractionation when therapeutic dose in single session cannot be applied.

Radiosurgery Versus "wait and see" After Microsurgery

It is still not entirely clear which meningiomas should undergo microsurgery and which should receive radiosurgery as the first treatment option. Meningiomas tend to vary greatly in volume, shape, location, and clinical manifestations

(Santacroce et al., 2012; Kondziolka et al., 2008). A number of reports over the years have proposed radiosurgery not only for patients harbouring recurrent or residual tumours after microsurgery but also for patients with newly diagnosed tumours without histological confirmation (Santacroce et al., 2012; DiBiase et al., 2004; Pollock and Stafford, 2005; Kreil et al., 2005; Zachenhofer et al., 2006; Kondziolka et al., 2008). Many surgeons have advocated monitoring by serial imaging after subtotal resection rather than offering adjuvant radiotherapy or radiosurgery. Our results put this "wait and see" policy in a new perspective. Recurrence after subtotal microsurgical resection is not uncommon, and this "wait and see" question should perhaps be reconsidered with respect to why we are waiting. Simpson (1957) described meningioma (WHO grade I) recurrence rates with reference to the degree of resection, reported to be 9 % after complete resection including dural base, 19 % after excision and coagulation of the dural base, 29 % after excision without coagulation of the dural base, and 40 % after subtotal resection.

Condra et al. (1997) confirmed Simpson's results, publishing outcomes in 262 tumours by comparing local tumour control among three treatment subgroups: surgery alone, radiotherapy alone, and surgery combined with fractionated radiotherapy. They reported a 70 % rate of tumour progression for those tumours partially resected without adjuvant radiotherapy. Pollock et al. (2003) compared tumour control rates after surgical resection or RS for patients with small/medium intracranial meningiomas, finding no statistically significant difference in the 3- and 7-year actuarial PFS rate between patients with Simpson grade 1 resections (100 % and 96 %, respectively) and patients who underwent radiosurgery (100 % and 95 %, respectively; P = .94). radiosurgery provided a higher PFS rate than Simpson grade 2 resection (3- and 7-year PFS rate, 91 % and 82 %, respectively; P = .05) and grade 3–4 resections (3- and 7-year PFS rate, 68 % and 34 %, respectively; P < .001). These outcomes have been confirmed in other studies (Sankila et al., 1992).

Kaye recently commented (Kondziolka et al., 2008) that methods of reporting control in radiosurgical series might overestimate success rates because the cohort analysed may also include patients who could otherwise have been followed up for many years with serial imaging before intervention might have been deemed necessary. On the other hand, the purely incidental diagnosis of meningioma is reported to be unusual, suggesting that the majority of these lesions are presenting and being treated, having produced some form of clinical picture that led to their discovery. Vernooij et al. (2007) reporting incidental findings on brain MRI from a review of more than 2,000 scans, found that in only 18 cases (0.9 %) were incidental meningiomas diagnosed. Furthermore, conservative management of intracranial meningiomas has already been analysed in many studies (Yoneoka et al., 2000; Van Havenbergh et al., 2003; Niiro et al., 2000; Nakamura et al., 2003; Herscovici et al., 2004; Nakasu et al., 2005). These studies report imaging tumour growth in 24–76 % of tumours, suggesting that active treatment is usually required. To raise the question is to imply its own answer: The "wait and see" policy with serial MRI should be reserved for asymptomatic elderly patients with calcified convexity meningiomas (Kollova et al., 2007; Niiro et al., 2000; Nakamura et al., 2003; Nakasu et al., 2005; Santacroce et al., 2012).

Radiosurgery Versus Microsurgery

Radical surgical resection is still the treatment of choice for intracranial meningiomas when achievable. However the morbidity associated with the aggressive resection of many meningiomas located along the skull-base or involving the dural sinuses can be significant, and a planned sub-total tumor removal is now often performed to reduce the chance of new postoperative neurologic deficits (Pollock et al. 2012). It is extremely important for clinicians either neurosurgeons or radiation oncologists, to appreciate surgical outcome and quality of life after meningioma microsurgery. A comparison of big radiosurgery series with a microsurgery series in a specific

intracranial location would not be reliable, given the variability in terms of shape volume of meningiomas and critical neurovascular structures adjacent to them: a recent review of the literature about outcomes and quality of life after meningioma microsurgery (Huang et al. 2011) report a detailed surgical outcome according to meningioma location. Morbidity rates ranged from 8 to 10 % for convexity/parasagittal and falcine meningiomas and from 0 to 61.5 % for skull base meningiomas respectively. Mortality rates for convexity/parasagittal and falcine meningiomas was reported to range from 0 to 3 % conversely for skull base tumours from 0 to 8.7 %. Functional improvement was reported at 55 % for patients harbouring a convexity meningioma and ranged from 0 to 100 % for patients operated for skull base meningioma. These outcomes are then compared with stereotactic radiotherapy and radiosurgery series reporting outcomes of imaging tumour control ranging from 90 to 100 % and clinical improvement from 13 to 45 %. These results confirm the largest contributions reported so far (Pollock et al. 2012; Kondziolka et al. 2008; Kollova et al. 2007; Santacroce et al. 2012). The authors conclude that since resection for skull base meningiomas is often limited owing to involvement of critical neurovascular structures radiosurgery is an appealing option and to be considered as treatment option for small to medium sized skull base meningiomas. Sughrue et al. (2010) recently reviewed the tumor recurrence rate of 373 patients with WHO grade I meningiomas having surgery from 1991 to 2008. With a median follow-up of 3.7 years, there was no difference in the 5-year recurrence rates for patients having Simpson grade I–IV resections. They concluded that although the goal of meningioma surgery should still be to remove as much tumor as possible, heroic efforts to remove all affected dura and bone should be discouraged to minimize the risk of postoperative neurologic deficits. These outcomes were recently commented by Sheehan (Santacroce et al. 2012) suggesting that the benefits of Simpson grade I vs. grade II resections may be negligible, coupled with the validated efficacy of radiosurgery for meningiomas, is resulting in a paradigm shift in neurosurgery. An approach where in one performs cytoreductive surgery leaving behind small portions of tumor adjacent to critical neurovascular structures, bone, or dura, followed by radiosurgery to treat the residual meningioma, is providing patients with very acceptable, if not superior, results. Furthermore patients undergoing primary radiosurgery have not been exposed to the risks of an open surgical procedure brain exposure brain retraction anaesthesia, intensive care stay. How much is that of value? (Kondziolka et al. 2008).

We do not advocate radiosurgery as being definitive or absolute; the end point for any treatment must be long-term efficacy and safety in the management of benign meningiomas. Each case should be carefully evaluated with respect to risk, outcome, and morbidity/mortality, regardless of the mode of management used. Treatment policy should be determined after both options are considered. As microsurgical procedures and imaging techniques have improved decade by decade, radiosurgery has also improved, not only because of this improved imaging but also by virtue of better appreciation of indications and improved planning software. As for microsurgery, radiosurgery is to a considerable extent operator dependent, and the individual radiosurgeon's experience may have the same importance than the microsurgeon's. According to our centre stratified analysis (Santacroce et al. 2012) tumour control rates is demonstrated in the pioneering era and in less experienced groups in more recent times.

Conclusions – Clinical Indications to Radiosurgery

The delivery of a high dose of ionizing radiation can be performed with different techniques based on photon emission. In order to spare the cerebral tissue from radiation exposure small target volume, a sharply defined target, accurate dose delivery avoiding under dosing and high conformality are key points for optimal treatment. Patient harbouring a benign meningioma have many powerful options to reach a cure defined as tumour remission and imaging/clinical control.

Benign spinal meningiomas are not ideal candidate to undergo primary/adjuvant radiosurgery given the high standards of microsurgical procedures, imaging techniques and feasibility of a full surgical resection with acceptable morbidity rate. Despite the paucity of data available about target volume definition, spinal cord tolerance to single session radiation and dose planning, the first short term clinical results are encouraging.

On the other hand a benign intracranial meningioma can undergo surgical resection or radiosurgery with a same chance of reaching an imaging/clinical tumour control, given the compromise that should be considered between the risks of open surgical resection and the simple tumour control without reaching a remission of the meningioma irradiated. Gross total resection is the preferred treatment of bening meningiomas, in particular for tumours needing decompression of neuro-vascular structures. Radiosurgery is a safe and effective method of managing benign intracranial meningiomas either recurring after resection or incompletely resected. The data show further emerging and clearer role of radiosurgery also as primary treatment for those tumours not achievable to resection due to unacceptable risk of perioperative morbidity. Analysis of the imaging tumour control data shows better outcomes for skull base location, female gender, sporadic and imaging-defined (not previously operated) tumours. The low neurological morbidity rate indicates patient safety. Clinical improvement is reported in 50 % of patients treated and complete resolution of symptoms in 20 % of patients treated (Santacroce et al. 2012).

According to the most recent literature indication for radiosurgical treatment should be given for: tumour remnant or recurrence after surgical resection, with maximum major tumour diameter, 3 cm and with acceptable dose delivery to adjacent eloquent structures; symptomatic primary tumours in locations associated with higher risk for resection with maximum major tumour diameter, 3 cm and with acceptable dose delivery to adjacent eloquent structures; concomitant medical illnesses or advanced age, in younger patients who chose radiosurgery over other available options; patients with minimal symptoms or asymptomatic who chose against observation Contraindications or exclusion criteria include large tumor volume (mean diameter >3.5 – 4 cm), tumors with symptomatic optic nerve or chiasmal compression, optic nerve sheath tumors with preserved vision, elderly patients with asymptomatic tumors, or tumors with atypical imaging features and no prior histological diagnosis (Kondziolka et al. 2008). Clinical observation with serial imaging should be reserved for asymptomatic elderly patients with calcified convexity/parasagittal meningiomas (Santacroce et al. 2012; Kollova et al. 2007). Fractionated stereotacic radiotherapy is recommended over radiosurgery for larger tumours or close to critical structures (less than 2–4 mm) (Elia et al. 2007) and all cases of optic nerve sheath meningiomas with preserved vision (Kondziolka et al. 2008).

References

Al-Mefty O, Al Mefty RO (2011) Meningiomas: a personal perspective. In: Al-Mefty's O, DeMonte F, McDermott MW (eds) Al-Mefty's meningiomas, vol 1. Thieme press, New York/Stuttgart, pp 3–12

Barami K, Grow A, Brem S, Dagnew E, Sloan AE (2007) Vascular complications after radiosurgery for meningiomas. Neurosurg Focus 22:E9

Bloch O, Kaur G, Jian BJ, Parsa AT, Barani IJ (2012) Stereotactic radiosurgery for benign meningiomas. J Neurooncol 107:13–20

Condra KS, Buatti JM, Mendenhall WM, Friedman WA, Marcus RB Jr, Rhoton AL (1997) Benign meningiomas: primary treatment selection affects survival. Int J Radiat Oncol Biol Phys 39:427–436

DiBiase SJ, Kwok Y, Yovino S, Arena C, Naqvi S, Temple R, Regine WF, Amin P, Guo C, Chin L (2004) Factors predicting local tumor control after gamma knife stereotactic radiosurgery for benign intracranial meningiomas. Int J Radiat Oncol Biol Phys 60:1515–1519

Elia AE, Shih HA, Loeffler JS (2007) Stereotactic radiation treatment for benign meningiomas. Neurosurg Focus 23:1–9

Flickinger JC, Niranjan A (2008) Stereotactic radiosurgery and radiotherapy. In: Halperin EC, Perez CA, Brady LW (eds) Perez and Brady's principles and practice of radiation oncology, vol 15. Lippincott Williams & Wilkins Ed, Philadelphia, pp 387–388

Gerszten PC, Ozhasoglu C, Burton SA, Vogel WJ, Atkins BA, Kalnicki S, Welch WC (2004) Cyberknife frameless stereotactic radiosurgery for spinal lesions: clinical experience in 125 cases. Neurosurgery 55:89–98

Gerszten PC, Quader M, Novotny J, Flickinger JC (2012) Radiosurgery for benign tumors of the spine: clinical experience and current trends. Technol Cancer Res Treat 11:133–139

Guckenberger M, Sweeney RA, Flickinger JC, Gerszten PC, Kersh R, Sheehan J, Sahgal A (2011) Clinical practice of image-guided spine radiosurgery–results from an international research consortium. Radiat Oncol 15:172–183

Hall JE, Brenner DJ (1992) The radiobiology of radiosurgery: rationale for different treatment regimens for AVMs and malignancies. Int J Radiat Oncol Biol Phys 25:381–385

Herscovici Z, Rappaport Z, Sulkes J, Danaila L, Rubin G (2004) Natural history of conservatively treated meningiomas. Neurology 63:1133–1134

Huang AP-H, Medani K, Black PM (2011) Chapter 44: Outcomes and quality of life after surgery of meningiomas. In: Al-Mefty's O, DeMonte F, McDermott MW (eds) Al-Mefty's meningiomas, 2nd edn. Thieme press, New York/Stuttgart, pp 413–426

Kollova A, Liscak R, Novotny J Jr, Vladyka V, Simonova G, Janouskova L (2007) Gamma knife surgery for benign meningioma. J Neurosurg 107:325–336

Kondziolka D, Niranjan A, Lunsford LD, Flickinger JC (2007) Radiobiology of radiosurgery. Prog Neurol Surg 20:16–27

Kondziolka D, Mathieu D, Lunsford LD, Martin JJ, Madhok R, Niranjan A, Flickinger JC (2008) Radiosurgery as definitive management of intracranial meningiomas. Neurosurgery 62:53–58

Kreil W, Luggin J, Fuchs I, Weigl V, Eustacchio S, Papaefthymiou G (2005) Long term experience of gamma knife radiosurgery for benign skull base meningiomas. J Neurol Neurosurg Psychiatry 76:1425–1430

Larson DA, Flickinger JC, Loeffler JS (1992) The radiobiology of radiosurgery. Int J Radiat Oncol Biol Phys 25:557–561

Louis DN, Ohgaki H, Wiestler OD, Cavenee WK, Burger PC, Jouvet A, Scheithauer BW, Kleihues P (2007) The 2007 WHO classification of tumours of the central nervous system. Acta Neuropathol 114:97–109

Marosi C, Hassler M, Roessler K, Reni M, Sant M, Mazza E, Vecht C (2008) Meningioma. Crit Rev Oncol Hematol 67:153–171

Nakamura M, Roser F, Michel J, Jacobs C, Samii M (2003) The natural history of incidental meningiomas. Neurosurgery 53:62–70

Nakasu S, Fukami T, Nakajima M, Watanabe K, Ichikawa M, Matsuda M (2005) Growth pattern changes of meningiomas: long-term analysis. Neurosurgery 56:946–955

Niiro M, Yatsushiro K, Nakamura K, Kawahara Y, Kuratsu J (2000) Natural history of elderly patients with asymptomatic meningiomas. J Neurol Neurosurg Psychiatry 68:25–28

Niranjan A, Flickinger JC (2008) Radiobiology, principle and technique of radiosurgery. Prog Neurol Surg 21:32–42

Pollock BE, Stafford SL (2005) Results of stereotactic radiosurgery for patients with imaging defined cavernous sinus meningiomas. Int J Radiat Oncol Biol Phys 62:1427–1431

Pollock BE, Stafford SL, Utter A, Giannini C, Schreiner SA (2003) Stereotactic radiosurgery provides equivalent tumor control to Simpson Grade 1 resection for patients with small- to medium-size meningiomas. Int J Radiat Oncol Biol Phys 55:1000–1005

Pollock BE, Stafford SL, Link MJ, Brown PD, Garces YI, Foote RL (2012) Single-fraction radiosurgery of benign intracranial meningiomas. Neurosurgery 71:604–613

Purdy JA (2008) Principles of radiologic physics, dosimetry and treatment planning. In: Halperin EC, Perez CA, Brady LW (eds) Perez and Brady's principles and practice of radiation oncology, vol 5. Lippincott Williams & Wilkins Ed, Philadelphia, pp 142–165

Sankila R, Kallio M, Jaaskelainen J, Hakulinen T (1992) Long-term survival of 1986 patients with intracranial meningioma diagnosed from 1953 to 1984 in Finland. Comparison of the observed and expected survival rates in a population-based series. Cancer 70:1568–1576

Sanson M, Cornu P (2000) Biology of meningiomas. Acta Neurochir (Wien) 142:493–505

Santacroce A, Walier M, Régis J, Liščák R, Motti E, Lindquist C, Kitz K, Lippitz B, Martínez Álvarez R, Pedersen PH, Yomo S, Lupidi F, Dominikus K, Blackburn P, Mindermann T, Bundschuh O, van Eck AT, Fimmers R, Horstmann GA (2012) Long-term tumor control of benign intracranial meningiomas after radiosurgery in a series of 4565 patients. Neurosurgery 70:32–39

Simpson D (1957) The recurrence of intracranial meningiomas after surgical treatment. J Neurol Neurosurg Psychiatry 20:22–39

Spiegelmann R, Cohen ZR, Nissim O, Alezra D, Pfeffer R (2010) Cavernous sinus meningiomas: a large LINAC radiosurgery series. J Neurooncol 98:195–202

Stafford SL, Pollock BE, Leavitt JA, Foote RL, Brown PD, Link MJ, Gorman DA, Schomberg PJ (2003) A study on the radiation tolerance of the optic nerves and chiasm after stereotactic radiosurgery. Int J Radiat Oncol Biol Phys 55:1177–1181

Sughrue ME, Kane AJ, Shangari G, Rutkowski MJ, McDermott MW, Berger MS, Parsa AT (2010) The relevance of Simpson Grade I and II resection in modern neurosurgical treatment of World Health Organization Grade I meningiomas. J Neurosurg 113:1029–1035

van der Kogel A (1991) Central nervous system radiation injury in animal models. In: Gutin P, Leibel S, Sheline G (eds) Radiation injury to the nervous system. Raven, New York, pp 91–111

Van Havenbergh T, Carvalho G, Tatagiba M, Plets C, Samii M (2003) Natural history of petroclival meningiomas. Neurosurgery 52:55–62

Vernooij MW, Ikram MA, Tanghe HL, Vinvent AJPE, Hofman A, Kerstin GP, Niessen WJ, Breteler MMB,

van de Lugt A (2007) Incidental findings on brain MRI in the general population. N Engl J Med 357:1821–1828

Yoneoka Y, Fujii Y, Tanaka R (2000) Growth of incidental meningiomas. Acta Neurochir (Wien) 142:507–511

Zachenhofer I, Wolfsberger S, Aichholzer M, Bertalanffy A, Roessler K, Kitz K, Knosp E (2006) Gamma-knife radiosurgery for cranial base meningiomas: experience of tumor control, clinical course, and morbidity in a follow-up of more than 8 years. Neurosurgery 58:28–36

Rhabdoid Meningiomas: Histopathological Diagnosis

26

Ewa Matyja and Wiesława Grajkowska

Contents

Abstract

Rhabdoid meningioma (RM) is an uncommon, aggressive variant of meningioma, designated as WHO grade III malignancy. It is characterized by a high risk to local recurrences, neoplastic dissemination and remote metastases. So far, the majority of reported cases of RMs have been found as secondary rhabdoid lesions in tumour recurrences.

The histological pattern of RM is characterized by the presence of neoplastic cells of distinctive rhabdoid morphology associated with polyphenotypic immunohistochemical profile. Rhabdoid cells usually stain diffusely for vimentin and S-100 protein and show focal expression of epithelial membrane antigen and cytokeratins. The tumour exhibits brisk mitotic activity and high MIB-1 labelling index.

The accurate histopathological diagnosis of rhabdoid subtype of meningioma is often difficult because of its similarity to other primary or secondary brain tumours that exhibit rhabdoid morphology. Particularly, the distinction from atypical teratoid/rhabdoid tumours (AT/RTs) and metastatic carcinomas is challenging and requires a wide spectrum of immunohistochemical and electron microscopic studies. The diagnosis of rhabdoid meningioma might be supported by evidence of SNF5 (INI1) protein expression, that allows to exclude AT/RT. Ultrastructural features characteristic for meningothelial cell phenotype i.e. interdigitating cell processes, numerous

E. Matyja (✉) • W. Grajkowska
Department of Experimental and Clinical Neuropathology, Mossakowski Medical Research Centre, Polish Academy of Sciences, ul Pawinskiego 5, 02-106 Warsaw, Poland
e-mail: matyja@cmdik.pan.pl

M.A. Hayat (ed.), *Tumors of the Central Nervous System, Volume 11*,
DOI 10.1007/978-94-007-7037-9_26,

desmosomes and paranuclear whorls of intermediate filaments might be helpful in confirming the diagnosis.

Introduction

Meningiomas are common primary intracranial tumours derived from meningothelial cells. They demonstrate considerable histological diversity and variation in tumour biology (Louis et al., 2000; Perry, 2006). The current 2007 World Health Organization (WHO) Classification of tumours of the central nervous system distinguishes 15 histopathological variants of meningiomas that correspond to WHO grade I, II and III (Perry et al., 2007). The vast majority of meningiomas are benign, WHO grade I lesions.

Rhabdoid meningioma (RM) is a rare, highly malignant histological subtype of meningiomas, characterized by rhabdoid cytology and polyphenotypic immunohistochemical profile. Rhabdoid transformation in meningothelial tumours was firstly described by Kepes et al. (1998). The term "rhabdoid meningioma" was originally introduced by Perry et al. (1998) and included to the 2000 WHO classification of tumours of the nervous system as a subtype with increased risk of recurrences (Louis et al. 2000). The rhabdoid meningioma tends to occur in middle-aged and elderly individuals (Horn et al., 1992; Arrazola et al., 2000; Pimentel et al., 2003; Kim et al., 2007). Only rarely does the tumour is diagnosed in children (Hojo and Abe, 2001; Rittierodt et al., 2001; Martinez-Lage et al., 2006). Most commonly the RMs are associated with rhabdoid transformation of meningothelial cells and are most often seen in recurrent specimens (Kepes et al., 1998; Perry et al., 1998; Rittierodt et al., 2001; Jansen et al., 2003; Pimentel et al., 2003; Endo et al., 2004; McMaster et al., 2007).

Rhabdoid variant of meningioma is assigned to WHO grade III tumour with considerable aggressive biology (Perry et al., 1998; Arrazola et al., 2000; Kevasan, 2000; Hojo and Abe, 2001). The clinical course of RM is determined by local recurrences, invasion of adjacent brain and/or dura, widespread leptomeningeal dissemination, remote metastases and fatal clinical outcome (Jansen et al., 2003; Endo et al., 2004; Al-Habib et al., 2005; Koenig et al., 2005; Wakabayashi et al., 2005; Santhosh et al., 2008). The histological malignancy is illustrated by high mitotic activity, infiltrative growth with brain tissue invasion and focal tumour necrosis. Occasionally, rhabdoid meningiomas might appear as extensively necrotic tumours associated with death within a few months of initial diagnosis (Matyja et al., 2010). The cases of "rhabdoid meningiomas" without evident cytologic features of malignancy have been also reported, but their prognostic significance remains unclear and the diagnosis of atypical meningiomas WHO grade II in such examples seems to be most appropriate (Cooper et al., 2004). The diagnosis of RM is of high prognostic importance and differential diagnosis ought to consider its histological similarities with certain brain tumour, particularly the atypical teratoid/rhabdoid tumours (AT/RT) and metastatic carcinomas.

Histopathology

The principal histological features of RM are sheets of neoplastic cells with distinctive rhabdoid morphology. The cells of classic rhabdoid phenotype are large, round or ovoid with abundant, eosinophilic cytoplasm and prominent, vesicular, often eccentrically located nuclei with conspicuous nucleoli (Fig. 26.1a, b). The paranuclear eosinophilic hyaline masses resembling cytoplasmic inclusions are frequently encountered. The rhabdoid foci often reveal an abundance of reticulin fibres. Only occasionally RM appears as a tumour of completely rhabdoid morphology without typical meningothelial areas. Most commonly, the tumour exhibits a histological evidence of meningothelial differentiation and contains areas with conventional meningiomatous pattern. However, according to 2007 WHO classification, the diagnosis of RM may be established when meningothelial tumour displays predominant rhabdoid morphology. Occasionally, the cells

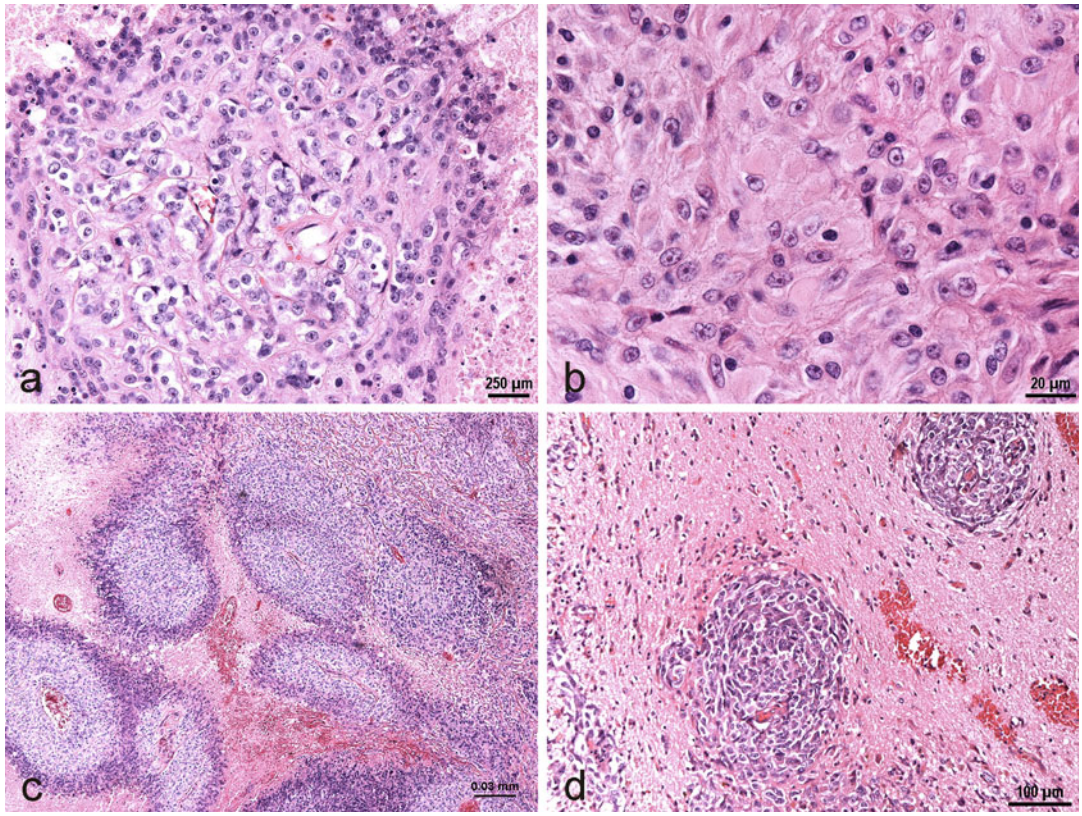

Fig. 26.1 Histopathology of rhabdoid meningioma: (**a**) sheet with rhabdoid cells with abundant eosinophilic cytoplasm and prominent, eccentrically located nuclei (H&E), (**b**) typical rhabdoid cells with abundant eosinophilic cytoplasm and prominent, eccentrically located nuclei (H&E), (**c**) neoplastic foci within necrotic tissue (H&E), (**d**) tumour invasion into the adjacent brain tissue (H&E). Bars; (**a**) – 250 µm; (**b**) – 20 µm; (**c**) – 0.03 mm; (**d**) – 100 µm

with rhabdoid morphology might be combined with distinct papillary architecture. Foci of necrosis are usually present and occasionally the tumour appears as a highly necrotic lesion (Fig. 26.1c). Other histopathological features of malignancy, including invasion of the adjacent brain (Fig. 26.1d), abundant mitotic figures and high proliferative index are commonly encountered.

Immunohistochemistry

The immunohistochemical profile of rhabdoid tumours demonstrates the polyphenotypic nature of neoplastic cells, suggesting their divergent differentiation. The rhabdoid cells are strongly positive for vimentin (Fig. 26.2a) and show diffuse S-100 protein immunostaining (Fig. 26.2b). The expression of epithelial membrane antigen (EMA) (Fig. 26.2c) and cytokeratins (CKs) is demonstrated, but most often focally. The meningothelial parts of tumour usually show diffuse EMA reactivity. Both, vimentin and cytokeratins typically display a strong paranuclear reaction in rhabdoid cells, corresponding with cytoplasmic hyaline inclusions, seen in H&E staining. The co-expression of different antigens might be also observed. Immunoreactivity for neuronal makers is less common but expression of synaptophysin is usually present in individual rhabdoid tumour cells (Fig. 26.2d). Staining for GFAP might be encountered but usually is patchy and weak. Desmin immunoreactivity is detected only

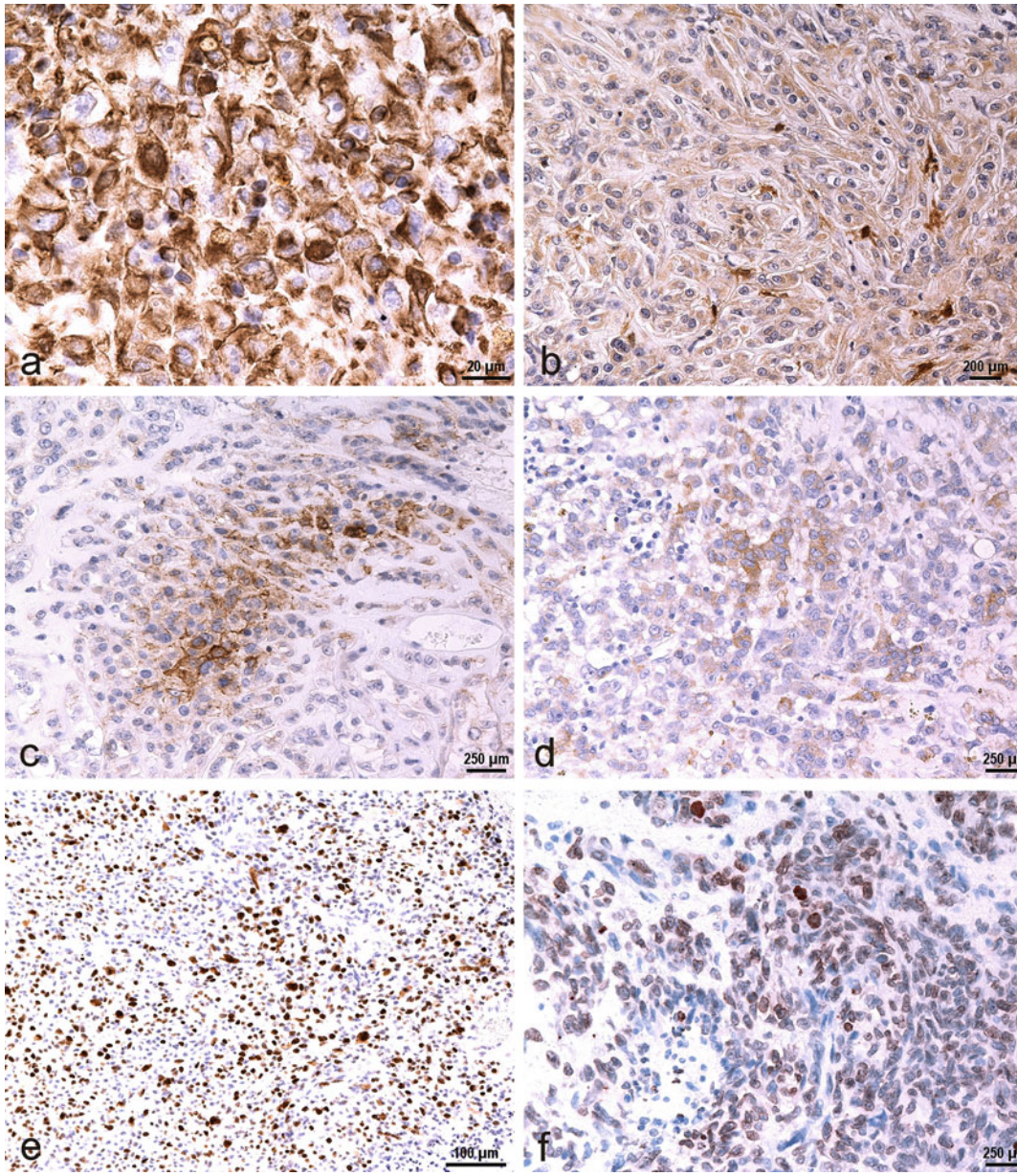

Fig. 26.2 Immunohistochemistry of rhabdoid meningioma: (**a**) rhabdoid cells with strong immunoreactivity for vimentin, (**b**) diffuse immunopositivity for S-100 protein, (**c**) focal expression of EMA, (**d**) slight synaptophysin immunoreactivity in individual rhabdoid cells, (**e**) high MIB-1 labelling index, (**f**) INI1 nuclear immunoreactivity in rhabdoid cells. Bars: (**a**) – 20 µm; (**b**) – 200 µm; (**c**, **d**, **f**) – 250 µm; (**e**) – 100 µm

sporadically. The rhabdoid cells display increased mitotic activity with high MIB-1 labelling index (Fig. 26.2e). Most rhabdoid meningiomas exhibit nuclear expression of SNF5 (INI1) protein (Fig. 26.2f).

Ultrastructure

Ultrastructurally, the rhabdoid cells contain paranuclear accumulation of tightly whorled bundles of filaments that often occupy the majority of the

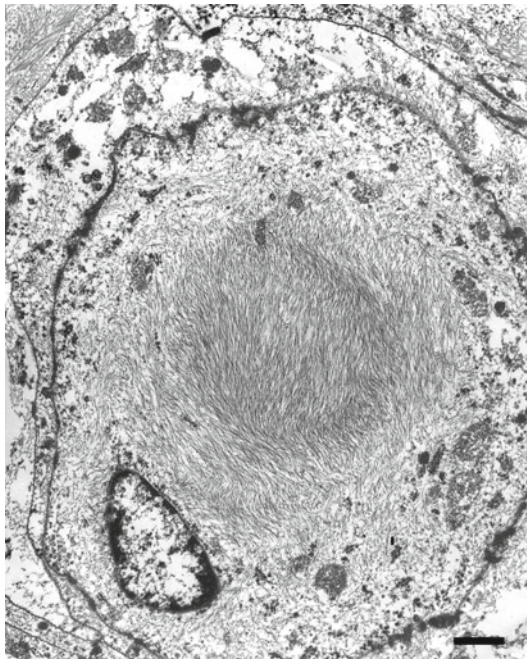

Fig. 26.3 Ultrastructure of rhabdoid meningioma. Typical rhabdoid cell with paranuclear aggregation of intermediate filaments. Bar: 1 μm

cytoplasm (Fig. 26.3); these filaments are known to be aggregates of intermediate filaments corresponding to vimentin immunopositive cytoplasmic inclusions. The entrapped lysosomes or other cytoplasmic organelles are commonly seen within these whorls of filaments. The classic ultrastructural features of meningiomas including numerous interdigitating cell processes and intercellular junctions such as well-formed desmosomes, hemidesmosomes and gap junction are usually seen. The groups of neoplastic cells might be surrounded by basal lamina.

Differential Diagnosis

Rhabdoid meningioma often occurs difficult to recognize as a tumour of meningothelial origin because of its predominant rhabdoid features. The cells of rhabdoid morphology typically exhibit abundant, plump, eosinophilic cytoplasm with eccentric nuclei, prominent nucleoli, and hyaline inclusions adjacent to the nuclei. Fortunately, in most cases of RMs, the areas including conventional meningioma can be noted at least focally. The entirely rhabdoid tumour lacking classical meningothelial features is uncommon and requires distinction from other rhabdoid tumours. In such cases the polyphenotypic immunohistochemical profile and/or ultrastructural evidence of meningothelial differentiation might be decisive. Most rhabdoid cells are diffusely immunopositive for vimentin and S-100 protein and show focal EMA and CKs expression. Immunoreactivity for neuronal markers including synaptophysin and neurofilament and expression of glial fibrillary acidic protein might be demonstrated in individual tumour cells. The final diagnosis of meningothelial origin of neoplastic cells can be established ultrastructurally by demonstration of interdigitating cell processes joined by numerous desmosomes. It has been also documented that cells of rhabdoid morphology contain typically paranuclear whorls of intermediate filaments (Ota et al., 1993; Inenaga et al., 2003).

In the cases where rhabdoid features create the predominant histopathologic pattern, distinction from primary malignant rhabdoid tumour of the central nervous system, known as atypical teratoid/rhabdoid tumour (AT/RT), is a particular diagnostic challenge. AT/RT is commonly reported in infants and young children less than 2 years of age, although it may rarely occur in adults (Rorke et al., 1996; Lutterbach et al., 2001; Kawaguchi et al., 2004; Rezanko et al., 2006; Makuria et al., 2008). The adult cases of AT/RT require special attention and should be confirmed by molecular analysis. AT/RT displays mutation or loss of the *INI1/hSNF5* (HIV-integrase interactor 1/human homolog of *Saccharomyces cerevisiae* sucrose-nonfermenting 5) tumour suppressor gene on chromosome 22q11.2 (Biegel et al., 2002; Judkins et al., 2004; Raisanen et al., 2005). These genetic abnormalities are evidenced in approximately 70 % of AT/RT tumours, whereas reduced gene expression at the RNA or protein level could be observed in 20–25 % of tumours. AT/RT usually demonstrates lack of nuclear INI1 protein expression and immunohistochemistry for INI1 protein might be helpful in the differential diagnosis

(Perry et al., 2005). Moreover, molecular studies with fluorescence in situ hybridization (FISH) might support the abnormalities of *INI1* gene. The evidence of INI1 protein nuclear positivity by the tumour cells often becomes decisive in distinction between AT/RT and rhabdoid meningioma.

In the differential diagnosis, other tumours with "rhabdoid" features, including choroid plexus carcinoma, glioblastoma with rhabdoid transformation and metastatic carcinoma or malignant melanoma ought to be also considered. Immunohistochemical markers of epithelial differentiation and some specific markers for choroid plexus cells such as transthyretin should distinguish choroid plexus carcinoma from RM. Glioblastoma with epithelial or rhabdoid differentiation usually present focally strong GFAP immunoreactivity, whereas cytokeratin immunopositivity is sometimes misleading. Diagnosis of malignant melanoma has to be confirmed by immunoreactivity of melanocytic markers such as MelanA or HMB45.

Occasionally, rhabdoid morphology in meningiomas might be combined with other cytoarchitectural patterns, including papillary and epithelioid structures (Saito et al., 2001). The unique case of mixed rhabdoid and papillary meningioma located entirely within the brain parenchyma and accompanied by a fulminant clinical course has been reported (Al-Habib et al., 2005). The proper diagnosis of such cases requires special attention.

References

Al-Habib A, Lach B, Al-Khani A (2005) Intracerebral rhabdoid and papillary meningioma with leptomeningeal spread and rapid clinical progression. Clin Neuropathol 24:1–7

Arrazola J, Pedrosa I, Mendez R, Saldana C, Scheithauer BW, Martinez A (2000) Primary malignant rhabdoid tumour of the brain in an adult. Neuroradiology 42:363–367

Biegel JA, Kalpana G, Knudsen ES, Packer RJ, Roberts CW, Thiele CJ, Weissman B, Smith M (2002) The role of INI1 and the SWI/SNF complex in the development of rhabdoid tumors: meeting summary from the workshop on childhood atypical teratoid/rhabdoid tumors. Cancer Res 62:323–328

Cooper WA, Shingde M, Lee VK, Allan RS, Wills EJ, Harper C (2004) "Rhabdoid meningioma" lacking malignant features. Report of two cases. Clin Neuropathol 23:16–20

Endo K, Tanaka S, Komagata M, Ikegami H, Kosaka T, Imakiire A, Serizawa H (2004) Rhabdoid transformation of recurrent meningioma in the cervical cord: a case report. J Orthop Sci 9:323–326

Hojo H, Abe M (2001) Rhabdoid papillary meningioma. Am J Surg Pathol 25:964–969

Horn M, Schlote W, Lerch KD, Steudel WI, Harms D, Thomas E (1992) Malignant rhabdoid tumor: primary intracranial manifestation in an adult. Acta Neuropathol 83:445–448

Inenaga C, Toyoshima Y, Mori H, Nishiyama K, Tanaka R, Takahashi H (2003) A fourth ventricle atypical teratoid/rhabdoid tumor in an infant. Brain Tumor Pathol 20:47–52

Jansen JC, Turner J, Sheehy J, Fagan PA (2003) Recurrent rhabdoid meningioma: case report. Skull Base 13:51–54

Judkins AR, Mauger J, Ht A, Rorke LB, Biegel JA (2004) Immunohistochemical analysis of hSNF5/INI1 in pediatric CNS neoplasms. Am J Surg Pathol 28: 644–650

Kawaguchi T, Kumabe T, Watanabe M, Tominaga T (2004) Atypical teratoid/rhabdoid tumour with leptomeningeal dissemination in an adult. Acta Neurochir 146:1033–1038

Kepes JJ, Moral LA, Wilkinson SB, Abdullah A, Llena JF (1998) Rhabdoid transformation of tumor cells in meningiomas: a histologic indication of increased proliferative activity. Am J Surg Pathol 22:231–238

Kevasan S (2000) Meningioma with rhabdoid transformation. Singapore Med J 41:464–467

Kim EY, Weon YC, Kim ST, Kim HJ, Byun HS, Lee JI, Kim JH (2007) Rhabdoid meningioma: clinical features and MR imaging findings in 15 patients. AJNR Am J Neuroradiol 28:1462–1465

Koenig MA, Geocadin RG, Kulesza P, Olivi A, Brem H (2005) Rhabdoid meningioma occurring in an unrelated resection cavity with leptomeningeal carcinomatosis. Case report. J Neurosurg 102:371–375

Louis DN, Scheithauer BW, Budka H, von Deimling A, Kepes JJ (2000) Meningiomas. In: Kleihues P, Cavenee WK (eds) WHO classification of tumours: pathology and genetics of tumours of the nervous system. IARC, Lyon, pp 176–184

Lutterbach J, Liegibel J, Koch D, Madlinger A, Frommhold H, Pagenstecher A (2001) Atypical teratoid/rhabdoid tumors in adult patients: case report and review of the literature. J Neurooncol 52:49–56

Makuria AT, Rushing EJ, McGrail KM, Hartmann D-P, Azumi N, Ozdemirli M (2008) Atypical teratoid rhabdoid tumor (AT/RT) in adults: review of four cases. J Neurooncol 88:321–330

Martinez-Lage JF, Ferri Niguez B, Sola J, Perez-Espejo MA, Ros de San Pedro J, Fernandez-Cornejo V (2006) Rhabdoid meningioma: a new subtype of malignant meningioma also apt to occur in children. Childs Nerv Syst 22:325–329

Matyja E, Grajkowska W, Nauman P, Bonicki W, Bojarski P, Marchel A (2010) Necrotic rhabdoid meningiomas with aggressive clinical behavior. Clin Neuropathol 29:307–316

McMaster J, Ng T, Dexter M (2007) Intraventricular rhabdoid meningioma. J Clin Neurosci 14:672–675

Ota S, David CG, Crabbe DCG, Tran TN, Triche TI, Shimada H (1993) Malignant rhabdoid tumor. A study with two established cell lines. Cancer 71:2862–2872

Perry A (2006) Meningiomas. In: McLendon RE, Rosenblum NK, Bigner DD (eds) Russell and Rubinstein's pathology of tumours of the nervous system, 7th edn. Hodder Arnold, London, pp 427–474

Perry A, Scheithauer BW, Stafford SL, Abell-Aleff PC, Meyer FB (1998) "Rhabdoid" meningioma: an aggressive variant. Am J Surg Pathol 22:1482–1490

Perry A, Fuller CE, Judkins AR, Dehner LP, Biegel JA (2005) INI1 expression is retained in composite rhabdoid tumors, including rhabdoid meningiomas. Mod Pathol 18:951–958

Perry A, Louis DN, Scheithauer BW, Budka H, von Deimling A (2007) Meningiomas. In: Louis DN, Ohgaki H, Weistler OD, Cavenee WK (eds) WHO classification of tumours of the central nervous system. IARC, Lyon, pp 163–172

Pimentel J, Silva R, Pimentel T (2003) Primary malignant rhabdoid tumors of the central nervous system: considerations about two cases of adulthood presentation. J Neurooncol 61:121–126

Raisanen J, Biegel JA, Hatanpaa KJ, Judkins A, White CL, Perry A (2005) Chromosome 22q deletions in atypical teratoid/rhabdoid tumors in adults. Brain Pathol 15:23–28

Rezanko T, Tunakan M, Kahraman A, Sucu HK, Gelal F, Akkol I (2006) Primary rhabdoid tumor of the brain in an adult. Neuropathology 26:57–61

Rittierodt M, Tschernig T, Samii M, Walter GF, Stan AC (2001) Evidence of recurrent atypical meningioma with rhabdoid transformation and expression of pyrogenic cytokines in a child presenting with a marked acute-phase response: case report and review of the literature. J Neuroimmunol 120:129–137

Rorke LB, Packer RJ, Biegel JA (1996) Central nervous system atypical teratoid/rhabdoid tumors of infancy and childhood: definition of an entity. J Neurosurg 85:56–65

Saito A, Nakazato Y, Yoshii Y, Hyodo A, Harakuni T, Toita T, Ogawa K, Horikawa K, Terada Y, Kinjo S, Minei S (2001) Anaplastic meningioma with papillary, rhabdoid, and epithelial features: a case report. Brain Tumor Pathol 18:155–159

Santhosh K, Kesavadas C, Radhakrishnan VV, Thomas B, Kapilamoorthy TR, Gupta AK (2008) Rhabdoid and papillary meningioma with leptomeningeal dissemination. J Neuroradiol 35:286–291

Wakabayashi K, Suzuki N, Mori F, Kamada M, Hatanaka M (2005) Rhabdoid cystic papillary meningioma with diffuse subarachnoid dissemination. Acta Neuropathol 110:196–198

Part VI

Schwannomas

Multiple Schwannomas: Diagnosis and Treatment

27

Takashi Eguchi, Keiichiro Takasuna, Atsushi Sato, Yusaku Shimizu, Yohei Hidai, Makoto Matsubara, Atsunori Shinoda, Masayuki Fujiwara, Kazuo Yoshida, and Jun Amano

Contents

T. Eguchi (✉) • K. Yoshida
Department of Thoracic Surgery, Shinshu University School of Medicine, Matsumoto, Japan
e-mail: tks1976@shinshu-u.ac.jp

K. Takasuna
Department of Thoracic Surgery, Ina Central Hospital, Ina, Japan

A. Sato
Department of Neurosurgery, Ina Central Hospital, Ina, Japan

Y. Shimizu
Department of Neurology, Ina Central Hospital, Ina, Japan

Y. Hidai
Department of Orthopedics, Ina Central Hospital, Ina, Japan

M. Matsubara • A. Shinoda
Department of Radiology, Ina Central Hospital, Ina, Japan

M. Fujiwara
Department of Pathology, Ina Central Hospital, Ina, Japan

J. Amano
Department of Surgery, Shinshu University School of Medicine, Matsumoto, Japan

Abstract

Multiple schwannomas occur in association with neurofibromatosis type 2 (NF2) and schwannomatosis. NF2 is a dominantly inherited tumor prediction syndrome which is characterized by bilateral vestibular schwannomas. Schwannomatosis is the third major form of neurofibromatosis and involves the development of multiple schwannomas in the absence of vestibular schwannomas. In general, schwannomas associated with NF2 or schwannomatosis grow slowly and do not become malignant, whereas neurofibromas with NF1 have a propensity for malignant transformation. Usually, these tumors can be detected by magnetic resonance imaging and a diagnosis is made using each criterion. The mainstay of the current treatment for multiple schwannomas is the surgical removal of symptomatic tumors. Considering the natural course of schwannomas and the risk of surgery, the mere presence of a tumor is not an indication for its surgical removal. Radiation therapy is a management option in some patients.

Introduction

Most schwannomas are single sporadic tumors. Multiple schwannomas are encountered occasionally in approximately 3–4 % of patients with

M.A. Hayat (ed.), *Tumors of the Central Nervous System, Volume 11*,
DOI 10.1007/978-94-007-7037-9_27,

spinal or peripheral schwannomas (Kehoe et al., 1995; Seppala et al., 1995), and have been thought to occur in association with neurofibromatosis (NF) (Evans et al., 2005; MacCollin et al., 2005). NF consists of a group of genetic disorders featuring the development of tumors of the nervous system, particularly of the nerve sheath, and three major forms of NF are recognized as distinct entities: neurofibromatosis type 1 (NF1), neurofibromatosis type 2 (NF2), and schwannomatosis (McClatchey, 2007).

NF1 is one of the most common known genetic disorders (incidence of 1/3,500) and has some distinguishing features including abnormal skin pigmentation (café-au-lait spots), learning disabilities, and the development of neurofibromas in the peripheral nerves. Neurofibromas are composed of all cell types found in the peripheral nerves, including Schwann cells. Transformation to a malignant peripheral nerve sheath tumor can occur from a plexiform neurofibroma, which is one of the morphological variants of neurofibroma (Bhattacharyya et al., 2004; McClatchey, 2007).

In contrast to NF1, the signature tumors of NF2 and schwannomatoses are schwannomas, which unlike neurofibromas are composed only of Schwann cells (McClatchey, 2007). NF2, which arises much less frequently than NF1 (with an incidence of 1/25,000), is characterized by the development of bilateral vestibular schwannomas. In NF2 patients, additional schwannomas may also occur on other cranial, spinal, and peripheral nerves. Other manifestations of NF2 are intracranial, spinal and optic nerve sheath meningiomas, and low grade ependymomas and gliomas of the central nervous system (Evans et al., 2005; McClatchey, 2007).

Schwannomatosis, of which the incidence is similar to that of NF2 (1/30,000), was recently recognized as the third major form of NF. The characteristics of schwannomatoses include the development of multiple non-vestibular schwannomas without other features of NF2 (MacCollin et al., 2005; McClatchey, 2007). In contrast to NF1 and NF2, both of which are inherited dominantly, most schwannomatosis cases are sporadic although some instances of dominant transmission have been reported (MacCollin et al., 2003, 2005).

In general, schwannomas with NF2 or schwannomatoses grow slowly and do not become malignant, whereas neurofibromas with NF1 have a propensity for malignant transformation (Bhattacharyya et al., 2004). However, because of their multifocality, care in selecting the appropriate therapy, including the timing of this treatment and regard to the risk of treatment-related complications, should be taken in the management of multiple schwannomas. In this chapter, we discuss the current practices in the diagnosis and treatment of multiple schwannomas with NF2 or schwannomatosis.

Diagnosis

NF2 and Schwannomatosis

Some researchers have previously considered schwannomatoses to be an attenuated form of NF2 (Evans et al., 1997). More recently however, schwannomatosis has been regarded as a third major form of NF and to have fundamental clinical and genetic differences from NF2 (Jacoby et al., 1997; Evans et al., 2005; MacCollin et al., 2005; McClatchey, 2007). The clinical diagnostic criteria used for NF2 and schwannomatosis are described in the Tables 27.1 and 27.2 and their use is highly specific. However, the differential diagnosis of NF2 from schwannomatosis is occasionally difficult, particularly in younger patients, because the appearance of a peripheral schwannoma may precede that of a vestibular schwannoma in some cases (Mautner et al., 1993). Although non-vestibular intracranial schwannomas can arise in schwannomatosis by definition, schwannomatosis

Table 27.1 Diagnostic criteria for NF2 (Evans et al. 2005)

Bilateral vestibular schwannoma
First-degree family relative with NF2 plus unilateral vestibular schwannoma or any two of meningioma, schwannoma, glioma, neurofibroma, cataract
Unilateral vestibular schwannoma and any two of meningioma, schwannoma, glioma, neurofibroma, cataract
Multiple meningiomas (two or more) and unilateral vestibular schwannoma or any two of schwannoma, glioma, neurofibroma, cataract

Table 27.2 Diagnostic criteria for schwannomatosis (MacCollin et al. 2005)

Definite schwannomatosis
Age >30 years and two or more non-intradermal schwannomas, at least one with histologic confirmation. No evidence of vestibular tumor of high-quality MRI scan and no known constitutional NF2 mutation
One pathologically confirmed non-vestibular schwannoma plus a first-degree relative who also meets the above criteria
Possible schwannomatosis
Age <30 years and two or more non-intradermal schwannomas, at least one with a histologic confirmation. No evidence of a vestibular tumor on a high-quality MRI scan and no known constitutional NF2 mutation
Age >45 years and two or more non-intradermal schwannomas, at least one with histologic confirmation. No symptoms of 8th nerve dysfunction and no known constitutional NF2 mutation
Radiographic evidence of a non-vestibular schwannoma and a first degree relative also meeting the criteria for definite schwannomatosis

patients do not tend to develop intracranial tumors, and the appearance of meningiomas should be considered as part of the clinical picture in NF2 patients (Jacoby et al., 1997; Evans et al., 2005). Pre-senile ocular cataracts are also a characteristic symptom in NF2 patients (Asthagiri et al., 2009).

The NF2 gene on chromosome 22q behaves as a tumor-suppressor gene in which mutations have been detected not only in schwannomas of NF2 patients but also in schwannomatosis and sporadic schwannoma cases (MacCollin et al., 2005). However, in contrast to NF2, no germ line NF2 mutations have been found in schwannomatosis patients (Jacoby et al., 1997). Recently, the SMARCB1 germ line mutations in schwannomatosis patients have been reported (Rousseau et al., 2011).

In terms of prognosis, NF2 is associated with high levels of morbidity (Evans, 2009). Although the range of disease progression is highly variable, most NF2 patients are rendered deaf and many will eventually need wheelchair assistance (Asthagiri et al., 2009). In addition, more than 40 % of these patients are expected to die by the age of 50 (Evans et al., 1992). In contrast to NF2 patients, there is no evidence that patients with schwannomatosis have a decreased life span (MacCollin et al., 2005).

Radiological Findings

Magnetic resonance imaging (MRI) is thought to be the most reliable modality for the precise radiological diagnosis of cranial, spinal and peripheral schwannomas (Bhattacharyya et al., 2004; Evans et al., 2005; MacCollin et al., 2005). However, CT scans are occasionally helpful in these cases, particularly in demonstrating the remodeling of adjacent bony structures such as the neural foramina or spinal canal (Bhattacharyya et al., 2004).

The MRI appearance of schwannoma is characterized by a well-circumscribed elliptical or spherical tumor, with low to intermediate signal intensity on T1-weighted images and a non-homogeneous high signal intensity on T2-weighted images (Sakai et al., 1992; Beaman et al., 2004; Bhattacharyya et al., 2004) (Fig. 27.1). Although the MRI signal characteristics of multiple schwannomas resemble those of an isolated schwannoma, it remains unclear whether there are radiographic differences between sporadic schwannomas, NF2-associated schwannomas, and schwannomatosis-associated schwannomas outside of their multiplicity and the appearance of vestibular tumors (MacCollin et al., 2005).

Pathological Findings

Schwannomas are encapsulated tumors composed of Schwann cells only (McClatchey, 2007). Microscopically, a typical schwannoma consists of alternating areas of densely cellular (Antoni A) and loosely arranged (Antoni B) regions, with a palisading nuclear organization (Verocay bodies). These tumors stain positively for S-100 protein by immunohistochemistry (Bhattacharyya et al., 2004).

As is the case in radiological findings, there is no single, constant identifiable feature that distinguishes schwannomas that arise sporadically, in patients with NF2 or in schwannomatosis cases. However, some reports have described pathological differences between these lesions. Sobel (1993) have reported that vestibular schwannomas in NF2 can be multifocal and have a more

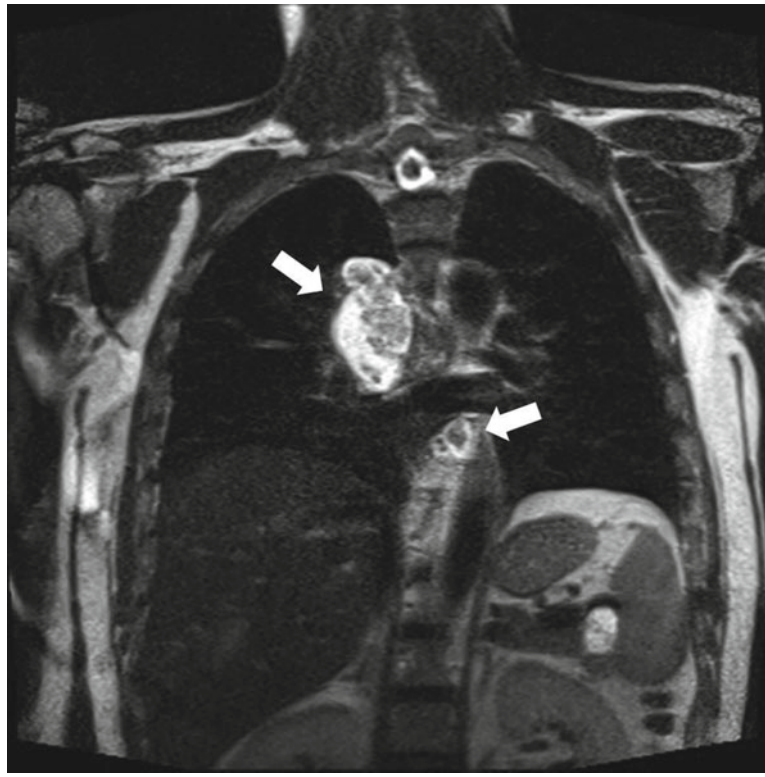

Fig. 27.1 T2-weighted MRI scan of the chest of a schwannomatosis patient revealing bilateral mediastinum nodules (*arrows*) with a non-homogeneous high signal intensity

lobular architecture than sporadic schwannomas. MacCollin et al. (2005) have reported that some features, including a peri-tumoral edema in the adjacent nerve, prominent intra-tumoral myxoid changes, and an intraneural growth pattern, appear to be more common in schwannomatosis.

Plexiform schwannoma, a rare morphological variant, can occur in patients with NF2 or schwannomatosis (Fig. 27.2). In contrast to plexiform neurofibroma in NF1 patients, which can become a malignant peripheral nerve sheath tumor, plexiform schwannomas do not have a propensity for malignant transformation (Bhattacharyya et al., 2004).

Treatment

Surgical removal has been the mainstay of treatment for schwannomas. Recently, however, with a greater understanding of the natural course of these tumors and improvements in surgical and radiological techniques, there are a variety of other treatment options for affected patients. These include conservative clinical and radiologic observations, surgery, radiosurgery, and combined modalities (Hajioff et al., 2008; Martin et al., 2008; Mejico, 2010).

Surgery

Because schwannomas are generally benign and slow growing tumors, surgery should only be indicated following adequate attention to both the benefits of such an intervention and the risks of postoperative complications. The mere presence of a tumor is not an indication for its surgical removal, and this treatment should be reserved for symptomatic tumors (Evans et al., 2005; MacCollin et al., 2005). In addition, to avoid iatrogenic neural damage, intraoperative

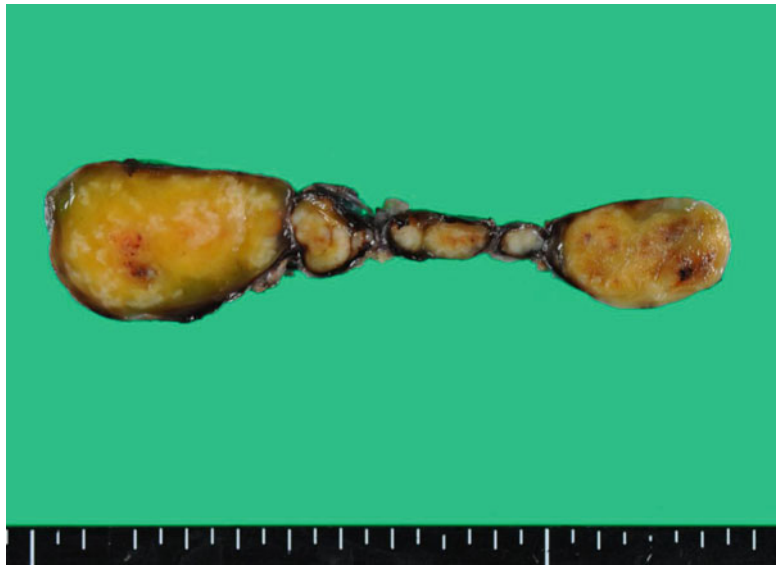

Fig. 27.2 Section of plexiform schwannomas arising in the mediastinal vagus nerve showing a multinodular formation of tumor-like beads

electrophysiological evaluations should be performed (Bhattacharyya et al., 2004; MacCollin et al., 2005).

The surgical removal of vestibular schwannomas in NF2 patients has many difficult management problems, most notably loss of hearing, and serious thought must therefore be given to the benefits and the risks of surgery in these cases (Evans et al., 2005). This is not discussed any further in this chapter. It is uncommon for non-vestibular intracranial schwannomas to require removal because these lesions appear to have a much slower growth pattern than vestibular schwannomas in NF2 patients (Evans, 2009). Surgery should be considered for larger tumors, more rapidly growing tumors, instances involving a greater degree or rate of cranial nerve dysfunction, and lesions that compromise the surrounding structures. However, persistent worsening of cranial nerve function in the post-operative period does occur in one half to two thirds of these patients (Mejico, 2010).

Spinal schwannomas are mostly considered for excision if they are producing clear symptoms or physical signs. Although it is a rare occurrence, elective decompression of the spine to avoid the risk of future injury should be considered in asymptomatic patients if a tumor impinging on the spinal cord is growing radiologically (MacCollin et al., 2005). The optimum time for surgery in each individual case may be determined by repeat MRI examinations (Seppala et al., 1995).

Mediastinal schwannomas frequently arise from a spinal nerve root but may involve any thoracic nerve (Strollo et al., 1997). Recently, thoracoscopic procedures have been added to standard method for the treatment of the mediastinal schwannomas (Canvasser and Naunheim, 1996; Zierold and Halow, 2000). In case of dumbbell tumors in the mediastinum, which have both a spinal and a thoracic component connected by a narrow foraminal segment, combined neurosurgical and thoracic operation should be required (Grillo et al., 1983; Canvasser and Naunheim, 1996).

In the treatment of schwannomas arising in the other peripheral nerves, surgical indication also should be determined carefully, and surgery should be performed with expertise in micro-neurosurgical techniques combined with intra-operative electrophysiological evaluation (Bhattacharyya et al., 2004).

Radiation Therapy

In the treatment of vestibular schwannomas in NF2 patients, the potential effectiveness of stereotactic radiosurgery (SRS) has been examined as a way of avoiding the risks of surgery without delaying a therapeutic intervention. Though the effectiveness of SRS in these cases is lower than in sporadic vestibular schwannoma patients, this approach should still be considered as a management option in selected patients (Rowe et al., 2003; Evans et al., 2005; Mathieu et al., 2007). However, the risk of radiation-induced malignant changes need also to be considered if SRS is proposed (Baser et al., 2000). There have been some reports of the effectiveness of SRS for the treatment of intracranial nonvestibular schwannoma (Showalter et al., 2008; Mejico, 2010) but it remains unclear whether this treatment is effective against these tumors in NF2 or schwannomatosis patients. There remains a paucity of literature on the use of radiation to treat non-intracranial schwannomas.

Conclusions

Multiple schwannomas occur in NF2 patients and in schwannomatosis patients. Although the mainstay of the current treatment approach to cases of multiple schwannoma is the surgical removal of symptomatic tumors, the indication for such an intervention should be determined with careful consideration of the underlying disease, the natural course of the tumors, and the risk of the surgery itself.

References

Asthagiri AR, Parry DM, Butman JA, Kim HJ, Tsilou ET, Zhuang Z, Lonser RR (2009) Neurofibromatosis type 2. Lancet 373:1974–1986

Baser ME, Evans DG, Jackler RK, Sujansky E, Rubenstein A (2000) Neurofibromatosis 2, radiosurgery and malignant nervous system tumours. Br J Cancer 82:998

Beaman FD, Kransdorf MJ, Menke DM (2004) Schwannoma: radiologic-pathologic correlation. Radiographics 24:1477–1481

Bhattacharyya AK, Perrin R, Guha A (2004) Peripheral nerve tumors: management strategies and molecular insights. J Neurooncol 69:335–349

Canvasser DA, Naunheim KS (1996) Thoracoscopic management of posterior mediastinal tumors. Chest Surg Clin N Am 6:53–67

Evans DG (2009) Neurofibromatosis type 2 (NF2): a clinical and molecular review. Orphanet J Rare Dis 4:16

Evans DG, Huson SM, Donnai D, Neary W, Blair V, Newton V, Harris R (1992) A clinical study of type 2 neurofibromatosis. Q J Med 84:603–618

Evans DG, Mason S, Huson SM, Ponder M, Harding AE, Strachan T (1997) Spinal and cutaneous schwannomatosis is a variant form of type 2 neurofibromatosis: a clinical and molecular study. J Neurol Neurosurg Psychiatry 62:361–366

Evans DG, Baser ME, O'Reilly B, Rowe J, Gleeson M, Saeed S, King A, Huson SM, Kerr R, Thomas N, Irving R, MacFarlane R, Ferner R, McLeod R, Moffat D, Ramsden R (2005) Management of the patient and family with neurofibromatosis 2: a consensus conference statement. Br J Neurosurg 19:5–12

Grillo HC, Ojemann RG, Scannell JG, Zervas NT (1983) Combined approach to "dumbbell" intrathoracic and intraspinal neurogenic tumors. Ann Thorac Surg 36:402–407

Hajioff D, Raut VV, Walsh RM, Bath AP, Bance ML, Guha A, Tator CH, Rutka JA (2008) Conservative management of vestibular schwannomas: third review of a 10-year prospective study. Clin Otolaryngol 33:255–259

Jacoby LB, Jones D, Davis K, Kronn D, Short MP, Gusella J, MacCollin M (1997) Molecular analysis of the NF2 tumor-suppressor gene in schwannomatosis. Am J Hum Genet 61:1293–1302

Kehoe NJ, Reid RP, Semple JC (1995) Solitary benign peripheral-nerve tumours. Review of 32 years' experience. J Bone Joint Surg Br 77:497–500

MacCollin M, Willett C, Heinrich B, Jacoby LB, Acierno JS Jr, Perry A, Louis DN (2003) Familial schwannomatosis: exclusion of the NF2 locus as the germline event. Neurology 60:1968–1974

MacCollin M, Chiocca EA, Evans DG, Friedman JM, Horvitz R, Jaramillo D, Lev M, Mautner VF, Niimura M, Plotkin SR, Sang CN, Stemmer-Rachamimov A, Roach ES (2005) Diagnostic criteria for schwannomatosis. Neurology 64:1838–1845

Martin TP, Tzifa K, Kowalski C, Holder RL, Walsh R, Irving RM (2008) Conservative versus primary surgical treatment of acoustic neuromas: a comparison of rates of facial nerve and hearing preservation. Clin Otolaryngol 33:228–235

Mathieu D, Kondziolka D, Flickinger JC, Niranjan A, Williamson R, Martin JJ, Lunsford LD (2007) Stereotactic radiosurgery for vestibular schwannomas in patients with neurofibromatosis type 2: an analysis of tumor control, complications, and hearing preservation rates. Neurosurgery 60:460–470

Mautner VF, Tatagiba M, Guthoff R, Samii M, Pulst SM (1993) Neurofibromatosis 2 in the pediatric age group. Neurosurgery 33:92–96

McClatchey AI (2007) Neurofibromatosis. Annu Rev Pathol 2:191–216

Mejico LJ (2010) Nonvestibulocochlear cranial nerve schwannomas. Curr Treat Options Neurol 12:37–42

Rousseau G, Noguchi T, Bourdon V, Sobol H, Olschwang S (2011) SMARCB1/INI1 germline mutations contribute to 10 % of sporadic schwannomatosis. BMC Neurol 11:9

Rowe JG, Radatz MW, Walton L, Soanes T, Rodgers J, Kemeny AA (2003) Clinical experience with gamma knife stereotactic radiosurgery in the management of vestibular schwannomas secondary to type 2 neurofibromatosis. J Neurol Neurosurg Psychiatry 74:1288–1293

Sakai F, Sone S, Kiyono K, Maruyama A, Ueda H, Aoki J, Kawai T, Ishii K, Morimoto M, Haniuda M et al (1992) Intrathoracic neurogenic tumors: MR-pathologic correlation. AJR Am J Roentgenol 159:279–283

Seppala MT, Haltia MJ, Sankila RJ, Jaaskelainen JE, Heiskanen O (1995) Long-term outcome after removal of spinal schwannoma: a clinicopathological study of 187 cases. J Neurosurg 83:621–626

Showalter TN, Werner-Wasik M, Curran WJ Jr, Friedman DP, Xu X, Andrews DW (2008) Stereotactic radiosurgery and fractionated stereotactic radiotherapy for the treatment of nonacoustic cranial nerve schwannomas. Neurosurgery 63:734–740

Sobel RA (1993) Vestibular (acoustic) schwannomas: histologic features in neurofibromatosis 2 and in unilateral cases. J Neuropathol Exp Neurol 52: 106–113

Strollo DC, Rosado-de-Christenson ML, Jett JR (1997) Primary mediastinal tumors: part II. Tumors of the middle and posterior mediastinum. Chest 112: 1344–1357

Zierold D, Halow KD (2000) Thoracoscopic resection as the preferred approach to posterior mediastinal neurogenic tumors. Surg Laparosc Endosc Percutan Tech 10:222–225

Treatment of Patients with Vestibular Schwanommas Using Gamma Knife Radiosurgery

28

Toshinori Hasegawa

Contents

Abstract

Gamma Knife radiosurgery (GKRS) has proved to be a safe and effective approach for small- to medium-sized vestibular schwannomas (VSs). Since VSs are histologically benign tumors, it is essential to elucidate long-term results, particularly when applied to young patients with a long life expectancy. In our analysis of 440 patients harboring VSs with a median tumor volume of 2.8 cm^3 and treated at a median marginal dose of 12.8 Gy, the actuarial 5- and 10-year or longer progression-free survival was 93 and 92 %, respectively, with a median follow-up period of 12.5 years. With respect to functional outcomes, facial palsy as an adverse radiation effect seldom develops after GKRS using current radiosurgical techniques with a marginal dose of 13 Gy or less. Even if facial palsy develops, it is commonly transient. Hearing preservation after GKRS depends on hearing function at the time of treatment, treatment dose or follow-up period after treatment. In limited patients who retain Gardner-Robertson Class I hearing, a hearing preservation rate seems to be nearly 70 % at present. Special attention should be paid for delayed adverse radiation effects including malignant change and cyst formation, although such complications appear to be extremely rare.

In conclusions, GKRS is currently a reasonable alternative to microsurgical resection for small- to medium-sized VSs. From our experience for more than 20 years, GKRS

T. Hasegawa (✉)
Department of Neurosurgery, Gamma Knife Center, Komaki City Hospital, 1-20 Jobushi, Komaki, Aichi Prefecture 485-8520, Japan
e-mail: h-toshi@komakihp.gr.jp

M.A. Hayat (ed.), *Tumors of the Central Nervous System, Volume 11*,
DOI 10.1007/978-94-007-7037-9_28,

is safe and effective in the long term. Management strategies including 'wait-and-see' approach, microsurgery and stereotactic radiosurgery should be decided for each patient, considering various factors such as age, comorbidities, tumor size, preserved hearing level or patients' preference.

Introduction

Since Gamma Knife radiosurgery (GKRS) for vestibular schwannomas (VSs) was first documented by Hirsch et al. (1979), numerous investigators have reported the safety and effectiveness of stereotactic radiosurgery for patients harboring VSs (Chopra et al., 2007; Hasegawa et al., 2005; Yamakami et al., 2003). Before the advent of stereotactic radiosurgery, surgical resection had been the mainstay of treatment for benign intracranial tumors such as VSs. Although complete resection is definitely the ideal treatment for VSs, it is not easy to achieve it without any complications, even for experienced neurosurgeons, despite recent refined microsurgical techniques. The more completely VSs are tried to remove, the higher risk of complications cannot be avoided, because this tumor usually strongly attaches to cochlear and facial nerves, stretches them and sometimes compresses the brainstem. Samii and Matthies (1997) reported the results of surgical resection in 1,000 VSs, 979 of which were completely removed and 21 alone were partially removed. However, 11 patients (1.1 %) died postoperatively, and major surgical complications including tetraparesis in one patient, hemiparesis in ten patients, and caudal cranial nerve palsies in 5.5 % of the cases developed. These issues made stereotactic radiosurgery establish as one of the less invasive and safer treatment options for VSs for recent decades. At present, treatment strategies for VSs include 'wait-and-see', microsurgery and streotactic radiosurgery. Decision of treatment strategies should be made for each patient depending on age, comorbidities, tumor size, hearing function and patients' preference.

Gamma Knife Radiosurgery

Patient Selection and Tumor Control

At present, there are many published articles reporting that GKRS is effective for short- to middle-term tumor control. Since VSs are histologically benign, the achievement of long-term tumor control is essential. However, there is little information regarding long-term tumor control beyond 20 years after treatment. Although it seems to keep effective over 20 years from our 20 years' experience of GKRS since 1991, it is extremely important to know which type of tumors can be successfully treated using radiosurgery or should be surgically removed.

In the results of 440 patients treated with GKRS between 1991 and 2000 at our institution (Hasegawa et al., 2013), the actuarial 5- and 10-year or longer progression-free survival was 93 and 92 %, respectively, with a median follow-up period of 12.5 years. Median tumor volume was 2.8 cm^3 and median marginal dose was 12.8 Gy. If limited to tumors less than 10 cm^3, these values increased to 95 and 94 %, respectively. No patient developed treatment failure beyond 10 years after treatment. Significant factors related to worse progression-free survival included brainstem compression with a deviation of the fourth ventricle ($p<0.0001$), marginal dose of 13 Gy or less ($p=0.01$), prior treatment ($p=0.02$) and female gender ($p=0.02$). According to our data, the most important factor causing treatment failure was the existence of brainstem compression with a deviation of the fourth ventricle on magnetic resonance imaging (MRI) before treatment, because slight tumor expansion or peritumoral edema can easily cause gait disturbance, resulting in craniotomy. The actuarial 10-year or longer progression-free survival was 76 % in tumors with a deviation of the fourth ventricle, compared to 95 % in tumors without a deviation of the fourth ventricle. On the other hand, mild brainstem compression without a deviation of the fourth ventricle was not a significant factor for treatment failure. Although less treatment

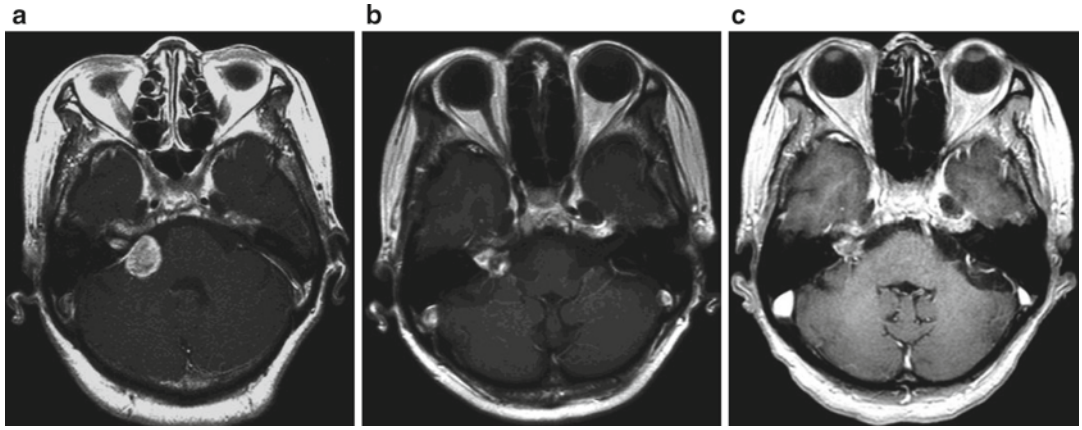

Fig. 28.1 Axial T1-weighted images with Gadolinium-enhancement demonstrating a right vestibular schwannoma at the time of Gamma Knife radiosurgery (**a**), 5 and 10 years after treatment (**b** and **c**). The tumor size remarkably decreased without any complications

dose was significantly associated with treatment failure in our study, this tendency was strongly related to the fact that larger tumors were treated with lower treatment dose to avoid adverse radiation effect such as peritumoral edema or cranial nerve palsy. Actually, when calculated in limited patients with small tumors of less than 10 cm^3 in volume, there was no significant difference for tumor control between marginal dose groups. Chopra et al. (2007) reported the long-term results of GKRS in 216 patients with VSs treated at a recent optimum dose of 12–13 Gy with a median follow-up period of 68 months. Although three patients eventually required tumor resection including a complete tumor resection for solid tumor growth in two and a partial resection for an adjacent enlarged subarachnoid cyst in 1, the actuarial 10-year resection-free tumor control rate was 98.3 %. Arthurs et al. (2011) reviewed contemporary studies on GKRS for VSs. A total of 1,850 patients were analyzed with a mean tumor volume of 2.3 cm^3. Tumor control rates ranged from 85 to 97 % in the treatment of a mean marginal dose of 12.6 Gy.

Tumor Expansion

The typical postradiosurgical course of follow-up MRI scans demonstrates the loss of central enhancement after 3–6 months, which is called 'central necrosis', followed by the re-enhancement of the area after 1 year. Thereafter, the tumor volume gradually decreases over 3 years, and then markedly regresses over 10 years. Some tumors do not shrink, but remains stable over time. However, we often encounter a certain problem, that is, tumor expansion. The incidence of tumor expansion varies from 17 to 77 %, depending on the definition of tumor expansion (Hasegawa et al., 2006; Nagano et al., 2010; Yu et al., 2000). Although this phenomenon causes some confusion regarding whether or not salvage treatment should be performed, the expanding tumors seldom keep growing, but are likely to become smaller than the original tumor size over time.

Illustrative Case

A typical VS case after GKRS is demonstrated in Fig. 28.1. The patient was a 59-year-old female who presented with hearing disturbance, floating sense and right facial numbness. Magnetic resonance imaging scan revealed a right cerebellopontine angle tumor, radiologically diagnosed as a VS. She refused craniotomy and was referred to our hospital for GKRS. The tumor was 3.2 cm^3 in volume and treated at a marginal dose of 12 Gy. After treatment, the tumor volume gradually

decreased with a resolution of her facial numbness. At 10 years after treatment, the tumor remarkably shrank.

Functional Outcomes

In the treatment of VS patients, of the greatest interest is to preserve good neurological function as well as long-term tumor control. In the early era of GKRS, VSs were treated at higher marginal dose than the current optimum dose of 12–13 Gy, resulting in a relatively high rate of transient or persistent facial palsy. Therefore, treatment dose has been gradually reduced. At present, a risk of facial palsy after radiosurgery is extremely low. In our experience, 5 % of patients who were treated at a marginal dose of higher than 13 Gy developed transient or persisitent facial palsy, whereas 1 % of patients who were treated at a marginal dose of 13 Gy or less developed transient facial palsy and no one experienced persistent palsy with recent radiosurgical techniques. According to the analysis of 23 published studies (2,204 patients) of GKRS for VSs (Yang et al., 2009), facial nerve preservation rates were 94.7 and 98.5 % in patients treated at a marginal dose of higher than 13 Gy, and 13 Gy or less, respectively ($p<0.0001$). They also found that tumor volume and patient age were significantly related to facial nerve preservation. Facial preservation rates in patients who had tumors with a volume of smaller than 1.5 cm^3 or whose age was 60 years old or younger was 99.5 % ($p<0.0001$) or 96.8 % ($p<0.0001$), respectively. Nagano et al. (2010) also described in their 87 consecutive unilateral VS patients who were followed for longer than 5 years after GKRS that 14 patients (16 %) experienced some degree of facial palsy caused by transient tumor expansion, all of whom naturally resolved with tumor shrinkage, meaning that transient facial palsy caused not by radiation injury but mild compression from the expanding tumor.

Currently, the most important issue of VS radiosurgery is hearing deterioration after treatment. In general, the majority of patients with VSs present with unilateral hearing disturbance. More recently, however, VS patients who preserve serviceable hearing at the time of diagnosis tend to increase because of the advances of computed tomography and MRI scans. Nevertheless, the results of hearing function after GKRS still remain unsatisfactory. It is essential to establish a radiosurgical technique with which both hearing preservation and long-term tumor control can be achieved. In our study of 117 patients who retained serviceable hearing at the time of GKRS, hearing preservation was evaluated (Hasegawa et al., 2011). Before treatment, 56 patients had Gardner-Robertson (GR) Class I hearing and 61 had Class II hearing. With a median tumor volume of 1.9 cm^3 and a median marginal dose of 12 Gy, actuarial 3-, 5- and 8-year hearing preservation rates were 55, 43 and 34 %, respectively, but long-term hearing results in this study may reflect the results of patients treated with old GKRS techniques. In a limited number of patients who were treated with the recent dose planning techniques and who had GR Class I hearing before treatment, the 3- and 5-year hearing preservation rates increased to 80 and 70 %, respectively. Kano et al. (2009) reported the results of GKRS in 77 patients who retained serviceable hearing of GR Class I or II. At a median follow-up period of 20 months, 71 % of patients retained serviceable hearing. When limited to patients who retained GR Class I hearing at the time of GKRS, a hearing preservation rate increased to 89 %. Tamura et al. (2009) also reported the results of GKRS in 74 patients with GR Class I hearing in whom 3 years or longer follow-up data were available. At the last follow-up period, serviceable hearing was preserved in 78 % of patients. They described a Kaplan-Meier curve for hearing preservation that showed a plateau at more than 70 % at 6–7 years after treatment. Hearing preservation rates depends on patient selection, treatment dose and follow-up period. It is not surprising to contribute to better hearing results in patients who retain normal hearing function before treatment. The use of lower treatment dose also results in better hearing preservation rates. Interestingly, several authors have pointed out that lower cochlear dose significantly led to better hearing results. Although it is

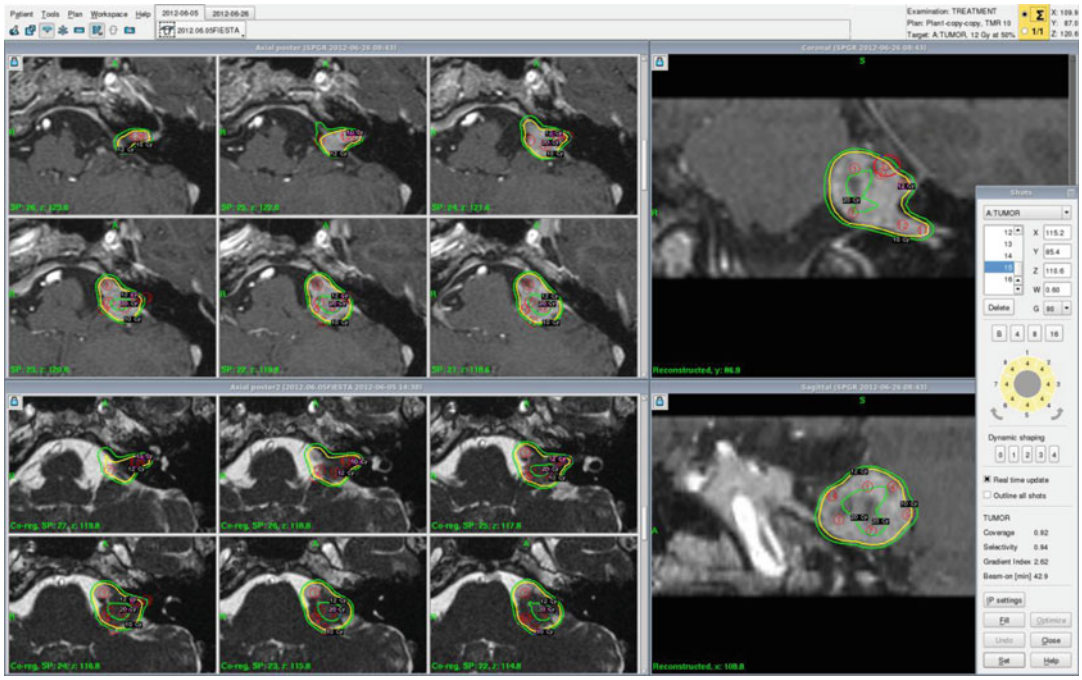

Fig. 28.2 A dose planning for a left vestibular schwannoma treated with the Gamma Knife Perfection. The tumor was treated at a marginal dose of 12 Gy (*yellow line*) with 15 isocenters. *Green isodose lines* shows 20 and 10 Gy. Axial spoiled gradient echo (SPGR) images with gadolinium-enhancement (*upper left*), axial fast imaging employing steadystate acquisition (FIESTA) images (*lower left*), a reconstructed coronal SPGR image (*upper right*) and a reconstructed sagittal SPGR image (*lower right*)

still unknown whether hearing deterioration is directly associated with radiation toxicity to the cochlea, attention should be paid to the cochlea dose when making a dose-planning. From our hearing results, it seems to keep worsening hearing function even beyond the first 3 years after GKRS despite unchanged hearing function on the contralateral side, as hearing function in patients with 'wait-and-see' approach constantly gets worse with time. Hence, it is necessary to evaluate longer-term hearing results to know the true hearing preservation rate after radiosurgery, if possible, with a new Gamma Knife unit of Perfection (Elekta Instruments, AB), the use of which would make long-term hearing outcomes much better. A recent dose planning using multiple isocenters with the Gamma Knife Perfection is depicted in Fig. 28.2. As the other cranial nerve complications, facial spasm and facial numbness are raised. Facial spasm is usually transient. Although trigeminal nerve injury can occur in cases of relatively large tumors, the incidence is less than 5 %.

Late Adverse Radiation Effect

Delayed cyst formation is one of the most common late adverse radiation effects. In our experience of 440 patients treated with GKRS more than 10 years before, 10 patients (2.2 %) developed delayed cyst formation between 30 and 142 months after GKRS (Hasegawa et al., 2013). Of these, three patients alone underwent salvage treatment. The others did not require any additional treatments because the cysts were stable in size without any neurological deficits or naturally collapsed. Nine patients had originally solid tumors and one had a cystic tumor. Regardless of irradiation doses, relatively large solid tumors

were likely to develop delayed cyst formation in our cases. Delayed cyst formation is classified into two progressive patterns of intratumoral and extratumoral cyst formation. Although the mechanism of cyst formation is still unclear, it is postulated that intratumoral cyst formation is caused by radiation-induced repeat microbleeding or increased vascular permeability. On the other hand, extratumoral cyst appears to be cerebrospinal fluid trapped by adhesion of irradiated tumors, and it is postulated that the cyst expands due to an osmotic effect. Murakami et al. (2011) reported that in 5 of 449 VS patients (1.1 %) treated with GKRS, 3 had delayed newly developed cysts and 2 had enlarged preexisting cysts. Of these, 3 patients developed intratumoral cyst and 2 developed extratumoral cyst. Of interest, all the tumors were classified into Koos grade IV and eventually required salvage microsurgery. The authors found that intratumoral cysts contained hemorrhage or necrotic debris, whereas extratumoral cyst was composed of thin and semitransparent membrane with xanthochromic fluid and there were no tumor cells on the cyst wall.

Another important late adverse effect is malignant transformation. So far, malignant transformation of benign VSs after radiosurgery has been believed to be extremely rare. To the best of our knowledge, 15 malignant transformations of VSs following stereotactic radiosurgery have been reported (Hasegawa et al., 2013). Of approximately a thousand VS patients treated at our institution, only one experienced malignant transformation. Currently, the true incidence of radiation-induced malignant transformation or tumorigenesis is still unclear, because the follow-up period after radiosurgery is too short to conclude it. On the basis of data accumulated by Leksell Gamma Knife Society, between 1991 and the end of 2010, an estimated 10,514 VSs were treated with GKRS at 55 units in Japan. To date, there are four previously published VSs with malignant transformation or secondary neoplasms after GKRS in Japan. The case reported by Hanabusa et al. (2001) had malignant transformation only 6 months after GKRS. This case would be possible that the atypical or malignant component existed before GKRS, because the latency interval is too short to develop radiation-induced malignancy. Excluding this case, the estimated incidence of malignant transformation or secondary neoplasms after GKRS performed in Japan is predicted to be 0.03 %. Even if calculated excluding 3,423 recent cases treated between 2007 and 2010 due to insufficient latency interval to develop radiation-induced malignancy, the estimated incidence is only 0.04 %. Although these figures may be underestimated because of lack of publication of a few radiation-induced malignancies, the incidence appeared to be less than 0.1 % at worst. Importantly, this fatal risk appeared to be much lower than the postoperative mortality rate of 0.5 % (22/4,886 patients) in the analysis of VS treated with microsurgery at a total of 374 hospitals in the United States from 1994 to 2003 reported by McClelland et al. (2011), or 0.6 % (25/3,969 patients) in a review of 15 microsurgical studies reported by Yamakami et al. (2003). Considering these surgical results, the estimated risk of malignant transformation after GKRS would be acceptable. Although this fatal risk is extremely low, every patient should be informed of the possibility of such late complication before GKRS. It is mandatory to elucidate the true risk of these late adverse radiation effects, which usually develop over 5 years in the treatment of radiosurgery, to justify GKRS for benign tumors such as VSs, especially in young patients who have long life expectancy.

Discussion

Currently, treatment strategies for VSs include craniotomy, stereotactic radiosurgery and 'wait-and-see' approach with serial radiological images. Surgical resection is undoubtedly the best management for large VSs compressing the brainstem with a deviation of the forth ventricle, because radiosurgery for such a large tumor easily induces peritumoral edema causing gait disturbance. In such cases, it is the most important to avoid severe complications such as cranial nerve, brainstem or vascular injuries. The aim of surgical resection is not to

achieve complete tumor resection, but to safely decompress the brainstem with internal tumor decompression. The residual tumor can be safely controlled by GKRS as an adjuvant treatment. Although complete removal without any complications is an ideal goal for any benign intracranial tumors, it is not so easy for most neurosurgeons in cases of deep-seated tumors or tumors located in the eloquent area. There is no benefit to try complete resection with higher risk of complications, if considering GKRS as an adjuvant treatment, on condition that fetal adverse radiation effects such as malignant transformation remain extremely rare in future as currently demonstrated.

In small- to medium-sized VSs, decision-making strategy is dependent on patients' preference, because the best management is still controversial, especially in younger patients or patients who preserve serviceable hearing. According to several published articles concerning the natural history of VSs (Smouha et al., 2005; Sughrue et al., 2010a; Yoshimoto, 2005), mean growth rates vary from 1 to 3 mm per year, and 30–50 % of patients who selected 'wait-and-see' approach have a growing tumor during follow-up periods over 3 years. From this point of view, either surgical resection or radiosurgery is recommended except for aged patients, because the percentages of patients who require intervention must increase over time. If patients can never receive a risk of hearing deterioration due to intervention, 'wait and see' strategy may be a treatment choice until their serviceable hearing is lost. However, they should know that any intervention after hearing loss never recovers their hearing function. Recently, surgical outcomes for VSs are getting improved with a refinement of microsurgical techniques or the use of various intraoperative cranial nerve monitoring systems. Despite these facts, a complication of facial nerve palsy is still a big issue. Yamakami et al. (2003) reported in a meta-analysis of VSs treated with microsurgery that 10 % of patients harboring small- to medium-sized tumors developed postoperative facial palsy, and the mortality rate was 0.6 %. A recent large surgical series by Bloch et al. (2011) showed that 255 (41 %) of 624 patients had facial palsy of House-Brackmann Grade III or higher at 6 months after microsurgery. These results indicate that it is impossible even for experienced neurosurgeons to preserve facial nerve function as GKRS does. On the other hand, which approach is superior for hearing preservation, microsurgery or GKRS? According to a meta-analysis of hearing preservation after microsurgical resection of VSs in 49 articles involving 998 patients retaining preoperative serviceable hearing reported by Sughrue et al. (2010b), an overall hearing preservation rate was 52 % with a follow-up duration ranging from 6 months to 7 years. They documented that tumor size >1.5 cm and the retrosigmoid approach, compared with the middle fossa approach, were significant for loss of serviceable hearing postoperatively. These results are comparable to hearing results after GKRS. In limited patients who retained GR Class I hearing at the time of GKRS, a hearing preservation rate is nearly 70 % with recent radiosurgical techniques (Hasegawa et al., 2011; Kano et al., 2009; Tamura et al., 2009). In patients with GR Class II, however, a hearing preservation rate decreases to be less than 50 %. In a prospective cohort study of 82 patients who had VSs with a tumor diameter of less than 3 cm, Pollock et al. (2006) compared the results between GKRS and microsurgery. They concluded that GKRS should be considered the best management strategy for the majority of patients unless the long-term follow-up showed frequent tumor progression at the current used radiation doses, because of the superior functional outcomes in terms of normal facial function and preserved serviceable hearing after radiosurgery as well as no difference in tumor control between them.

In conclusions, GKRS is currently a reasonable alternative to microsurgical resection for small- to medium-sized VSs. From our experience for longer than 20 years, GKRS is safe and effective in the long term. Management strategies including 'wait-and-see' approach, microsurgery and stereotactic radiosurgery should be decided for each patient, considering various factors such as age, comorbidities, tumor size, preserved hearing level or patients' preference.

References

Arthurs BJ, Fairbanks RK, Demarkas JJ, Lamoreaux WT, Giddings NA, Mackay AR, Cooke BS, Elaimy AL, Lee CM (2011) A review of treatment modalities for vestibular schwannoma. Neurosurg Rev 34:265–277

Bloch O, Sughrue ME, Kaur R, Kane AJ, Rutkowski MJ, Kaur G, Yang I, Pitts LH, Parsa AT (2011) Factors associated with preservation of facial nerve function after surgical resection of vestibular schwannoma. J Neurooncol 102:281–286

Chopra R, Kondziolka D, Niranjan A, Lunsford LD, Flickinger JC (2007) Long-term follow-up of acoustic schwannoma radiosurgery with marginal tumor doses of 12 to 13 Gy. Int J Radiat Oncol Biol Phys 68:845–851

Hanabusa K, Morikawa A, Murata T, Taki W (2001) Acoustic neuroma with malignant transformation. Case report. J Neurosurg 95:518–521

Hasegawa T, Fujitani S, Katsumata S, Kida Y, Yoshimoto M, Koike J (2005) Stereotactic radiosurgery for vestibular schwannomas: analysis of 317 patients followed more than 5 years. Neurosurgery 57:257–264

Hasegawa T, Kida Y, Yoshimoto M, Koike J, Goto K (2006) Evaluation of tumor expansion after stereotactic radiosurgery in patients harboring vestibular schwannomas. Neurosurgery 58:1119–1128

Hasegawa T, Kida Y, Kato T, Iizuka H, Yamamoto T (2011) Factors associated with hearing preservation after Gamma Knife surgery for vestibular schwannomas in patients who retain serviceable hearing. J Neurosurg 115:1078–1086

Hasegawa T, Kida Y, Kato T, Iizuka H, Kuramitsu S, Yamamoto T (2013) Long-term safety and efficacy of stereotactic radiosurgery for vestibular schwannomas: evaluation of 440 patients more than 10 years after treatment with Gamma Knife surgery. J Neurosurg 118(3):557–565

Hirsch A, Noren G, Anderson H (1979) Audiologic findings after stereotactic radiosurgery in nine cases of acoustic neurinomas. Acta Otolaryngol 88:155–160

Kano H, Kondziolka D, Khan A, Flickinger JC, Lunsford LD (2009) Predictors of hearing preservation after stereotactic radiosurgery for acoustic neuroma. J Neurosurg 111:863–873

McClelland S 3rd, Guo H, Okuyemi KS (2011) Morbidity and mortality following acoustic neuroma excision in the United States: analysis of racial disparities during a decade in the radiosurgical era. Neuro Oncol 13: 1252–1259

Murakami K, Jokura H, Kawaguchi J, Watanabe M, Tominaga T (2011) Development of intratumoral cyst or extratumoral arachnoid cyst in intracranial schwannomas following gamma knife radiosurgery. Acta Neurochir (Wien) 153:1201–1209

Nagano O, Serizawa T, Higuchi Y, Matsuda S, Sato M, Yamakami I, Okiyama K, Ono J, Saeki N (2010) Tumor shrinkage of vestibular schwannomas after Gamma Knife surgery: results after more than 5 years of follow-up. J Neurosurg 113(Suppl):122–127

Pollock BE, Driscoll CLW, Foote RL, Link MJ, Gorman DA, Bauch CD, Mandrekar JN, Krecke KN, Johnson CH (2006) Patient outcomes after vestibular schwannoma management: a prospective comparison of microsurgical resection and stereotactic radiosurgery. Neurosurgery 58:77–85

Samii M, Matthies C (1997) Management of 1000 vestibular schwannomas (acoustic neuromas): surgical management and results with an emphasis on complications and how to avoid them. Neurosurgery 40:11–21

Smouha EE, Yoo M, Mohr K, Davis RP (2005) Conservative management of acoustic neuroma: a meta-analysis and proposed treatment algorithm. Laryngoscope 112:450–454

Sughrue ME, Yang I, Aranda D, Lobo K, Pitts LH, Cheung SW, Parsa AT (2010a) The natural history of untreated sporadic vestibular schwannomas: a comprehensive review of hearing outcomes. J Neurosurg 112:163–167

Sughrue ME, Yang I, Aranda D, Kane AJ, Parsa AT (2010b) Hearing preservation rates after microsurgical resection of vestibular schwannoma. J Clin Neurosci 17:1126–1129

Tamura M, Carron R, Yomo S, Arkha Y, Muraciolle X, Percheron D, Thomassin JM, Roche PH, Régis J (2009) Hearing preservation after gamma knife radiosurgery for vestibular schwannomas presenting with high-level hearing. Neurosurgery 64:289–296

Yamakami I, Uchino Y, Kobayashi E, Yamaura A (2003) Conservative management, gamma-knife radiosurgery, and microsurgery for acoustic neurinomas: a systematic review of outcome and risk of three therapeutic options. Neurol Res 25:682–690

Yang I, Sughrue ME, Han SJ, Fang S, Aranda D, Cheung SW, Pitts LH, Parsa AT (2009) Facial nerve preservation after vestibular schwannoma Gamma Knife radiosurgery. J Neurooncol 93:41–48

Yoshimoto Y (2005) Systematic review of the natural history of vestibular schwannoma. J Neurosurg 103:59–63

Yu CP, Cheung JY, Leung S, Ho R (2000) Sequential volume mapping for confirmation of negative growth in vestibular schwannomas treated by gamma knife radiosurgery. J Neurosurg 93(Suppl 3):82–89

Schwannomas in the Craniocervical Region: Complete Surgical Removal

29

Zaman Mirzadeh and Robert F. Spetzler

Contents

Abstract

Schwannomas of the craniocervical region are rare and formidable surgical lesions. Most patients become symptomatic with vague symptoms of headache or neck pain although some show evidence of lower cranial nerve dysfunction, including dysphagia or hoarseness. In addition to complete resection, the primary surgical goals in the modern era include preservation and restoration of function of the lower cranial nerves and of hearing and facial nerve function. Achieving these goals requires a nuanced understanding of several skull base approaches and their combinations, including the far-lateral approach and its extensions. With improvements in preoperative planning, advanced imaging, surgical techniques, and postoperative care, modern surgical series have demonstrated improved postoperative morbidity profiles, with special attention to postoperative swallowing function, and successful clinical outcomes in this patient population.

Introduction

The craniocervical region encompasses (1) the bony craniovertebral junction, which comprises the occipital bone and includes the clivus, which surrounds the foramen magnum, and the atlas and axis vertebrae; and (2) the neurovascular structures surrounded by these bony elements, including the

Z. Mirzadeh • R.F. Spetzler (✉)
Division of Neurological Surgery,
Barrow Neurological Institute, St. Joseph's Hospital and Medical Center, 350 W. Thomas Rd., Phoenix, AZ 85013, USA
e-mail: neuropub@dignityhealth.org

M.A. Hayat (ed.), *Tumors of the Central Nervous System, Volume 11*,
DOI 10.1007/978-94-007-7037-9_29,

medulla oblongata, the cervicomedullary junction, the upper cervical spinal cord, cranial nerves (CNs) VII–XII, cervical nerves 1 and 2, the vertebral and basilar arteries, and the vertebrobasilar junction (Rhoton and de Oliveira, 1998; Menezes, 2005). Several neoplastic diseases can occur in this region, most commonly meningiomas and neurofibromas, with other possible diagnoses including schwannomas, chordomas, chondrosarcomas, chondromas, metastases, and more rarely dermoid tumors, teratomas, lipomas, arachnoid cysts, and paragangliomas. Intramedullary tumors of this region include astrocytomas, ependymomas, hemangioblastomas, medulloblastomas, and choroid plexus papillomas.

Schwannomas represent 5–10 % of all intracranial tumors (Zulch, 1965; Russell and Rubinstein, 1989), and 25 % of all schwannomas are found in the head and neck region (Katz et al., 1971). Intracranial schwannomas can arise from any cranial nerve (CN), but they typically arise from the vestibular portion of CN VIII, with an annual incidence of 1 in 100,000 (Rosenberg, 2000). Of nonvestibular schwannomas, trigeminal nerve (CN V) schwannomas are the most common (Sarma et al., 2002). Schwannomas of the craniocervical region are more rare skull base neoplasms arising from CNs IX, X, XI, and XII and cervical nerves 1 and 2. Schwannomas arising from CN IX-XII without associated neurofibromatosis are relatively uncommon—only 2.9 % of all intracranial schwannomas (Tan et al., 1990). In a recent large case series, jugular foramen (CN IX–XI) schwannomas accounted for 1 % of 2,200 intracranial tumors and for 4 % of 570 intracranial schwannomas, with a ratio of 1 jugular foramen schwannoma to 24 vestibular schwannomas (Samii et al., 1995). Despite the rarity of schwannomas of the lower cranial nerves compared to the more common vestibular lesions, they all share the same symptoms, surgical approaches, and complications.

This chapter first briefly reviews the histopathology of schwannomas in general and the clinical presentation of craniocervical schwannomas in particular. It then focuses on surgical approaches to these formidable lesions and their clinical outcomes.

Histopathology

Conventional schwannomas are benign nerve sheath tumors (World Health Organization (WHO) grade 1) composed entirely of well-differentiated neoplastic Schwann cells. They are typically encapsulated. Microscopically, these tumors have two basic growth patterns, termed Antoni A and Antoni B, which are present in different proportions in any given lesion. The Antoni A pattern consists of areas of compact, elongated cells with occasional nuclear palisading. The palisades are formed by closely apposed tumor cells with alternating, parallel rows of tumor cell nuclei and their densely packed, aligned cell processes. Antoni B tissue consists of fewer cellular areas, with loosely arranged cells with indistinct processes and variable lipidization. The vasculature in schwannomas is typically thick-walled and hyalinized; a common finding is dilated blood vessels surrounded by hemorrhage (Louis et al., 2007).

Clinical Presentation

Patients harboring craniocervical junction schwannomas most often become symptomatic in the fifth decade with their symptoms corresponding to the origin and extension of the tumor. Jugular foramen schwannomas (CN IX–XI) usually manifest with headaches (53–66 % patients depending on the series), with other common symptoms including hearing loss (35–50 %), dysphagia (35–38 %), and hoarseness (29–38 %) (Samii et al., 1995; Cavalcanti et al., 2011) related to compression of cranial nerves IX and X as they pass through the jugular foramen.

One study of jugular foramen schwannomas suggested that the timing and symptoms of presentation correlated with the precise location of the tumor with respect to the jugular foramen (Kaye et al., 1984). This study categorized these lesions as follows: type A, primarily intracranial with only a small extension into the bone; type B, primarily within the bone with or without intracranial extension; type C, primarily extracranial

with only a minor extension into bone; and type D, saddlebag-shaped tumors with both significant intra- and extracranial components (classifications further discussed below) (Kaye et al., 1984; Pellet et al., 1988). The authors found that deafness, vertigo, and ataxia were all present to some degree at presentation in patients with type A tumors without significant deficits of the lower CNs, while patients with types B and C tumors had earlier involvement of the CNs of the jugular foramen and often presented with elements of the jugular foramen syndromes (e.g., Vernet's syndrome).

Patients with CN XII schwannomas may present with motor deficits related to anterolateral brainstem compression or with hoarseness or tongue atrophy, sometimes associated with CN XI impairment. Patients with cervical nerve 1 or 2 schwannomas usually become symptomatic with paresthesias, neck pain, or motor impairment related to spinal cord compression, and in a few cases, with urinary incontinence (Cavalcanti et al., 2011).

Operative Techniques

Schwannomas involving the craniocervical region pose a significant surgical challenge because these lesions can extend along the posterior fossa cisterns and within the internal auditory canal, jugular foramen, hypoglossal canal, foramen magnum, and spinal canal. As a result, several CNs and the vertebral and cerebellar arteries can be placed at risk. Undue traction exerted on this area, on the lower CNs, or on the brainstem or cervical spinal cord itself can be devastating for the patient. The goals of surgery are not only complete resection but also preservation and restoration of function of the lower cranial nerves and of hearing and facial nerve function.

Various surgical approaches, from almost all angles, have been used to address these tumors and to reduce postoperative morbidity. Anterior approaches provide a direct corridor to these tumors, which are usually located anterolaterally on a lower cranial nerve along the cervicomedullary junction. However, transoral access is required and is hampered by the narrow operative field, the difficulty of dural repair, and the high risks of cerebrospinal fluid (CSF) leakage and infection. Posterior approaches are limited by the need for visualizing the ventral cervicomedullary junction, which would require excessive retraction. Lateral approaches, which offer adequate visualization of the anterolateral cervicomedullary junction and circumvent the limitations of anterior approaches, have therefore been used most often to access tumors of this region.

Lateral approaches have undergone tremendous evolution. They were first described when Kuttner (1917) reported a technique for exposing the transverse processes of the superior cervical vertebrae. Years later, Henry (1966) described how to expose the vertebral artery, and all modern techniques are based on his technique. Henry's approach was modified and expanded by Elkin and Harris (1946), who applied it to the treatment of arteriovenous malformations of the vertebral artery. In 1968, Verbiest reviewed the evolution of these techniques and modified them to increase exposure—by sectioning the attachments of the longus colli and longus capitis muscles, while alternately retracting the sternocleidomastoid muscle anteriorly and posteriorly (Verbiest, 1968).

Beginning in the 1980s, several new modifications to the aforementioned techniques were introduced and are still in use today, largely unchanged. Lateral approaches can be divided into the anterolateral or extreme lateral approaches and the posterolateral or far-lateral approaches. Table 29.1 summarizes the variations of lateral approaches to the craniocervical junction. The anterolateral approaches emphasized the importance of detaching the sternocleidomastoid muscle to improve cervical exposure. George et al. (1988) reported the surgical removal of 14 benign tumors involving the anterior rim of the foramen magnum via a lateral extension of the standard posterior transcervical exposure. They described transposing the vertebral artery medially and sectioning the sigmoid sinus after amputating the mastoid tip to gain an almost frontal plane to the tumor. Sen and Sekhar (1990) reported six cases of benign intradural tumors resected through an extreme lateral approach, with

Table 29.1 Literature review of variations in lateral approaches to the craniocervical junction

Reference	Nomenclature	Patient position	Skin incision	Muscle dissection	Extent of condylar resection	Mobilize VA	Mastoidectomy
Spetzler and Grahm (1990)	Far lateral	Modified park bench	Inverted hockey stick	Medial to lateral	Posteromedial third	Yes	No
Hakuba (1990)	Unilateral suboccipital transcondylar	Sitting	Paramedian	Division of muscles	Medial third	No	No
Sen and Sekhar (1990, 1991)	Extreme lateral transcondylar	Lateral decubitus	Paramedian hooked	Lateral to medial	Posterior half to two-thirds	Yes	Yes
Bertalanffy and Seeger (1991)	Dorsolateral suboccipital transcondylar	Sitting	Vertical paramedian	Division parallel to muscle fibers	Posteromedial 6–8 mm	Yes	No
Canalis et al. (1993)	Lateral approach	Supine head rotated	Postauricular to midline hyoid bone	Division of muscles including SCM	Variable	Yes	Yes
Lang et al. (1993)	Suboccipital transcondylar	Modified park bench	Inverted hockey stick or paramedian	Medial to lateral or division of muscles	Posteromedial third	Yes	No
Ammirati et al. (1993)	Presigmoid transversarium transcondylar	Upright	Curvilinear from above auricle to SCM	Superior to inferior with division of muscles	Medial third	Yes	Yes
Baldwin et al. (1994)	Far lateral	Modified park bench	Inverted hockey stick	Medial to lateral	Posteromedial third to two-thirds	Yes	Option
Babu et al. (1994)	Extreme lateral transcondylar	Modified Sugita lateral	Inverted horseshoe or C shape	Lateral to medial	One third to one half if intradural; all if extradural	Yes	Yes
Rohde et al. (1994)	Extreme lateral transcondylar	Sitting	Paramedian curvilinear	Division of muscles	Posteromedial third	No	No
Tew and van Loveren (1994)	Lower lateral suboccipital	Lateral oblique	Inverted hockey stick	Medial to lateral	Medial third	Yes	No

George and Lot (1995)	Posterolateral	Mostly sitting	Inverted hockey stick	Medial to lateral	Medial third	Yes	Yes
	Posteromedial	Supine with head rotated	Anterior upper SCM to mastoid	Division of muscles	Medial third	Yes	Yes
Day and Giannotta (1995)	Extreme lateral inferior transcondylar	Lateral	Lazy "S"	Division of muscles	Posterior third to two-thirds	Option	Option
Al-Mefty et al. (1996)	Transcondylar	Half-lateral decubitus	C shape	Superolateral to inferomedial	All if needed	Yes	Yes

Adapted with permission from Alleyne and Spetzler (1999)
VA vertebral artery, *SCM* sternocleidomastoid muscle

only limited dissection of the neurovascular neck structures and temporal bone. Finally in 1990, Spetzler and Grahm described the far-lateral or posterolateral approach to treat numerous vascular and neoplastic lesions of the lower clivus and cervicomedullary junction. This technique, further described below, was a modification of existing posterior approaches and involved no dissection of anterior neck structures or temporal bone.

The Far-Lateral Approach and Its Variations

The far-lateral approach evolved from the lateral suboccipital approach, which had been used extensively to treat lesions of the lower clivus (Heros, 1986). The new modified approach incorporated removal of the inferior rim of the foramen magnum, part of the occipital condyle, and the posterolateral arch of atlas to the sulcus arteriosus. The result was significantly improved exposure of the vertebral artery, inferior clivus, upper cervical canal, and neural elements of the craniocervical junction. Several variations of the basic far-lateral approach, referred to here as the transcondylar, paracondylar, and supracondylar extensions, provide versatility for addressing lesions around the atlanto-occipital joint. A detailed description of these approaches is beyond the scope of this chapter and can be found elsewhere (Spetzler and Grahm, 1990; Alleyne and Spetzler, 1999; Rhoton, 2000), but a brief overview of the key steps in the procedures follows.

The basic far-lateral exposure includes (1) dissection of the muscles in the posterolateral aspect of the craniocervical junction to expose the C1 transverse process and suboccipital triangle, (2) early identification of the vertebral artery above the posterior arch of atlas or in its course between the transverse foramina of atlas and axis, and (3) a suboccipital craniectomy with removal of at least half of the posterior arch of atlas (Rhoton, 2000). The optimal position for patients is the modified park-bench position, which differs from the routine park-bench position in two ways. First, rather than placing the dependent arm under the patient with an axillary roll, the arm is allowed to drop off the end of the table and is cradled in the head holder beneath the edge of the table. This modification improves venous return, decreases the risk of brachial plexus compression, and increases the amount of cranial rotation and flexion. Second, the head is *not* placed in the straight lateral position. Rather, it is (1) flexed until the chin is one-finger's breath from the sternum, (2) rotated downward away from the lesion, and (3) tilted away from the ipsilateral shoulder. The goals of these maneuvers are to place the inferior clivus perpendicular to the floor, to open the posterior cervical-to-suboccipital angle maximally, and to increase the ability to move the microscope in the operative field. The main advantage of this position is the range of cranial motion it allows. Others advocate using the sitting position, but the position as described here avoids the risk of air embolism.

After the skin incision is made, the suboccipital muscles are dissected from the skull and the laminae of C1 and C2. Rhoton (2000) emphasizes that contrary to standard posterior and posterolateral approaches, where an understanding of the individual suboccipital muscles is not essential, these muscles provide important landmarks for the far-lateral approach. His description contains instructive photographs of the anatomical relationships. After the lateral mass of C1 and the vertebral artery from C1 to its dural entry are exposed, a C1 laminotomy is performed with a B1 bit and foot plate. The contralateral lamina is cut across the midline, and the ipsilateral lamina is cut at the sulcus for the vertebral artery. If the vertebral artery needs to be mobilized, the posterior root of the transverse foramen also may be removed. The suboccipital craniotomy should extend contralaterally across the midline and ipsilaterally as far laterally as possible. At the level of the foramen magnum, the craniotomy should exit medial to the entry of the vertebral artery on the contralateral side. Ipsilaterally, the rim of the foramen magnum is removed with a bone rongeur to the lateral mass of C1 and the occipital condyle. This radical removal of the lateral foramen magnum to the occipital condyle was the most important aspect of the lateral suboccipital approach of Heros

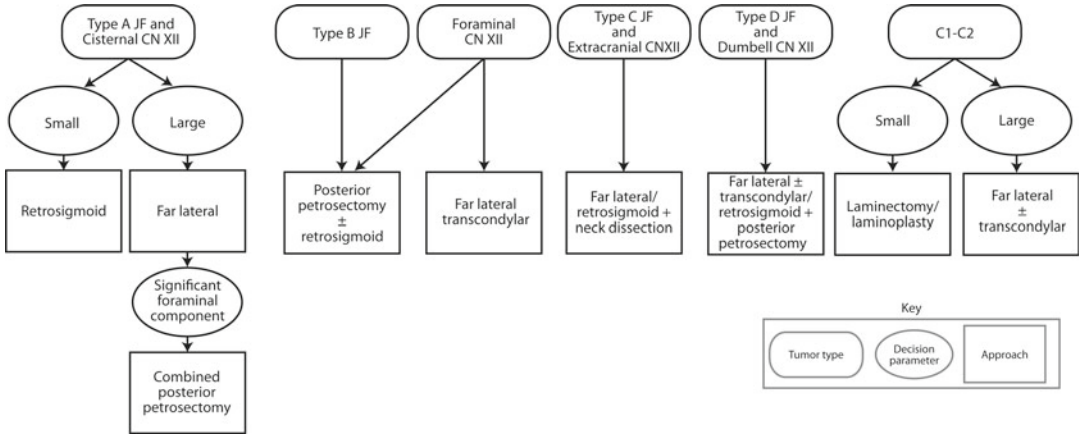

Fig. 29.1 Decision tree for surgical management of schwannomas in the craniocervical junction. *JF* jugular foramen (Used with permission from Journal of Neurosurgery)

(1986). The important aspect of this modified approach is the removal of the C1 lamina with the option of drilling the posterior occipital condyle and C1 lateral mass.

Importantly, the basic far-lateral approach extends to but does not include removal of the posterior part of the occipital condyle. Drilling the posterior condyle is the key component of the transcondylar extension, which is now a routine adjunct to the far-lateral approach. Doing so allows a more anterior trajectory that minimizes the need for neural retraction. An anatomic study showed that condylectomy provides a shorter distance to the anterior foramen magnum via corridors superior and inferior to the hypoglossal nerve as well as a wider angle of exposure (Acikbas et al., 1997). The condylectomy is performed by drilling away the posteromedial third of the occipital condyle while protecting the extracranial vertebral artery with an instrument. The bone is removed to create a 1-cm gap between the dural entry of the vertebral artery and the resected occipital condyle (Spetzler and Grahm, 1990). Alternatively, entry into the condylar canal, marked by brisk bleeding from the posterior condylar emissary vein, signifies adequate lateral exposure (Alleyne and Spetzler, 1999). Limiting drilling to the posteromedial third of the condyle reduces the risk of injury to the hypoglossal canal, which is located in the anteromedial third of the condyle (Wen et al., 1997). Importantly, after the hypoglossal canal is exposed above the condyle, the jugular tubercle, a rounded prominence at the junction of the basilar and condylar portions of the occipital bone, is also drilled to gain additional exposure. Extensive removal of the condyle and lateral mass of C1 eliminates the last bony shelf obstructing direct vision to the clivus and anterior brain stem and allows lateral movement of the extradural vertebral artery when the dura is incised and tented (Spetzler and Grahm, 1990).

In addition to the transcondylar extension, there are two extensions of the far-lateral approach: the supracondylar and paracondylar. The supracondylar approach provides access to the region medial to the hypoglossal canal and jugular tubercle. The paracondylar approach, which includes drilling of the jugular process of the occipital bone in the area lateral to the occipital condyle, accesses the posterior portion of the jugular foramen and the posterior aspect of the facial nerve and mastoid on the lateral side of the jugular foramen. The indications and techniques for these approaches have been reviewed previously (Wen et al., 1997; Rhoton, 2000).

Ultimately, the ideal approach to craniocervical schwannomas depends on the extension of the tumor and its relationship to the dura and neurovascular structures (Fig. 29.1). To this end, the far-lateral approach can also be combined with other approaches to address lesions that extend

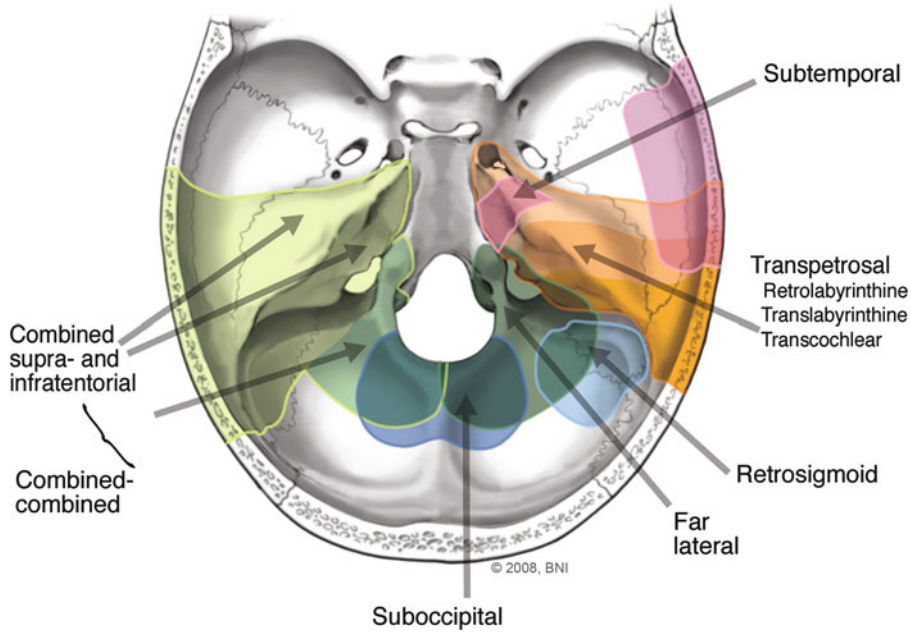

Fig. 29.2 Illustration of skull base approaches to the brainstem and anterolateral foramen magnum region. The far-lateral approach can be used in combination with one of these approaches for lesions that extend beyond its routine scope (Used with permission from Barrow Neurological Institute)

beyond its routine scope (Fig. 29.2). For example, for lesions that extend rostrally, the far-lateral can be combined with the supra- and infratentorial approach (Baldwin et al., 1994). This configuration combines the far-lateral transcondylar approach with a petrosectomy and subtemporal craniotomy to provide access to the anterior and lateral brain stem and craniovertebral junction. A posterior petrosectomy (including infralabyrinthine, retrolabyrinthine, or transcochlear) can be combined with a far-lateral exposure to allow mobilization of the sigmoid sinus for removal of a tumoral extension around the jugular bulb. A retrosigmoid far-lateral combined approach widens the surgical exposure from the cerebellar tentorial surface to beyond the cervicomedullary junction to improve the view of the upper brainstem and upper clivus (Fig. 29.3a–c). An anatomi-cal study recently demonstrated the versatility of this combined approach (Safavi-Abbasi et al., 2010). This combination is ideally suited for the removal of tumors with a large intracranial component and minimal foraminal or extracranial components.

The disadvantages of the far-lateral approach, including the potential to injure the vertebral artery cranial nerves, should also be noted. Extensive condylar drilling can cause postoperative atlanto-occipital instability. A biomechanical study of the stability of the craniovertebral junction after unilateral condylar resection revealed that resection of 50 % or more of the occipital condyle produced statistically significant hypermobility of the atlanto-occipital motion segment (Vishteh et al., 1999). If more than 50 % of the condyle is resected, an occipitocervical fusion may be necessary. Such extensive condylar drilling is almost never required unless the tumor itself has already destroyed the bone. In a series of 125 cases of craniocervical junction pathology (114 tumors and 11 non-tumoral processes) treated via a transcondylar approach, Lot and George (1999) had only 26 cases that required more than a third of the condyle to be removed, 14 of which required more than one half removed. In all 26 cases, the bony structures were already invaded or involved. There were 10 primary bone tumors, 14 chordomas, 1 case of rheumatoid

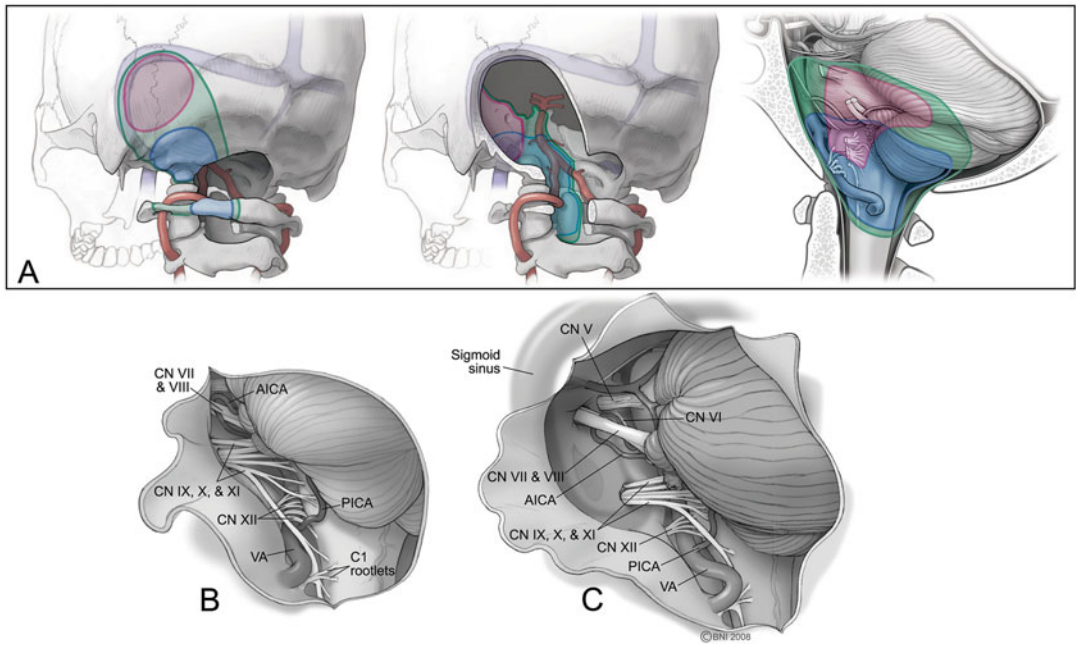

Fig. 29.3 Illustrations demonstrating the far-lateral and retrosigmoid approaches and their combination, which widens the surgical exposure from the cerebellar tentorial surface to beyond the cervicomedullary junction. This exposure provides an improved view of the upper brainstem and upper clivus. (**a**) Sequential images showing the craniotomy and access via the retrosigmoid (*red*), far-lateral (*blue*), and combined (*green*) approaches. View of exposure through the far-lateral (**b**) and combined far-lateral retrosigmoid (**c**) approaches (Used with permission from Barrow Neurological Institute)

arthritis, and 1 case of degenerative spondylosis. More recently Margalit et al. (2005) reported 42 patients with tumors involving the anterior foramen magnum. They only encountered occipitocervical instability requiring fusion in patients with bone-involving tumors. In summary, with appropriate preoperative planning and an understanding of the access provided by these various approaches, the vast majority of craniocervical schwannomas can be safely resected.

Case Example

A 17-year-old boy sought treatment after experiencing 1 month of headaches and neck pain. His neurological examination was normal. Diagnostic imaging revealed an enhancing, partially cystic mass approaching the left jugular foramen, with some displacement of the brain stem to the right (Fig. 29.4a). He underwent a far-lateral transcondylar approach, with partial drilling of the condyle to the level of the condylar vein, for microsurgical gross total resection of a CN IX schwannoma (Fig. 29.4b).

Comparison of Approaches: Focus on Jugular Foramen Schwannomas

As mentioned, several other approaches are commonly used to access schwannomas in the craniocervical junction, in particular to address jugular foramen schwannomas. Previous authors have postulated that the position of these schwannomas with respect to the jugular foramen depends on their point of origin from the nerves as they pass through the pars nervosa. Accordingly, jugular foramen schwannomas have been classified into four types based on their growth pattern: types A, B, and C originally described by Kaye et al. (1984) and type D later added by Pellet et al. (1988). The more proximal lesions enlarge into the posterior fossa and are primarily intracranial

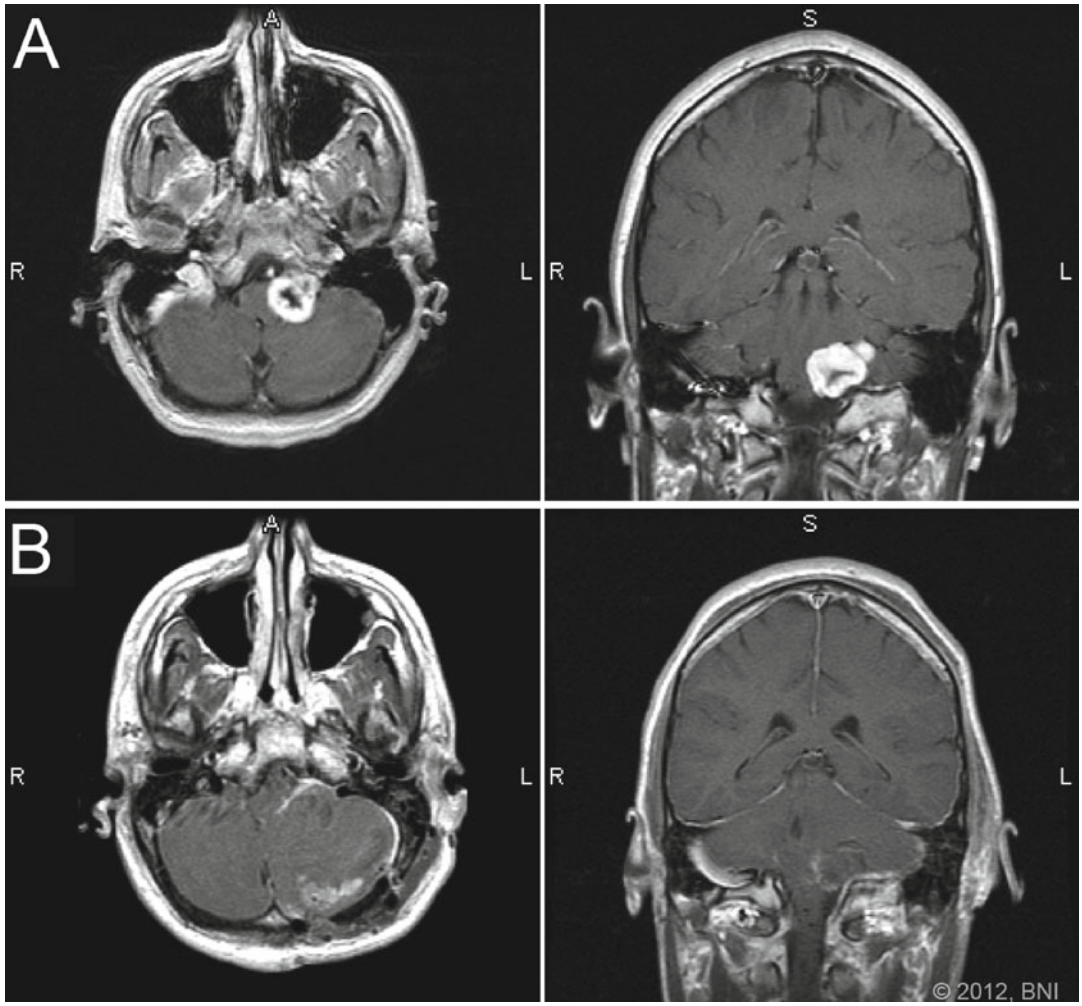

Fig. 29.4 Pre- (**a**) and postoperative (**b**) axial and coronal images of a left-sided glossopharyngeal nerve schwannoma that was resected through a far-lateral transcondylar approach (Used with permission from Barrow Neurological Institute)

with only a small extension into the bone (type A). The more distal lesions expand inferiorly out of the skull base and are primarily extracranial with a minor extension into the bone (type C). Lesions arising in the midregion expand primarily into the bone and may have only minor intra- or extracranial components (type B). Tumors with both significant intra- and extracranial components, linked via the jugular foramen, acquire a saddlebag shape (type D). When treating a jugular foramen schwannoma, the approach chosen usually depends on this classification of the tumor.

In their original description of the tumor types, Kaye et al. (1984) presented their series of 13 patients with jugular foramen schwannomas. All patients were treated by a joint neurosurgical-otological approach, usually a posterior fossa exploration combined with a translabyrinthine transcochlear or infralabyrinthine procedure. During preoperative planning, the most important aspects of determining the approach were the extent of intracranial involvement and the superior limit of the lesion. Specifically, if the patient's internal auditory canal was intact or if the patient's hearing was normal with no

evidence of sensorineural hearing loss or vestibular dysfunction, an infralabyrinthine approach to the skull base was used. Conversely, if high-resolution computed tomography (CT) showed that the tumor involved the internal auditory canal, or if the tumor extended superior to the internal auditory canal to the middle fossa tegmen, the superior limit of the tumor could not be reached by an infralabyrinthine approach. Consequently, a transcochlear translabyrinthine procedure was chosen.

These otological approaches to the skull base and extracranial tumor extension have been described in detail (Fisch and Pillsbury, 1979). In their series, all six patients with type A tumors had a suboccipital craniotomy (four in sitting position, two in park-bench). Only one required a translabyrinthine transcochlear excision of a small bone extension (Kaye et al., 1984). Of the five patients with type B tumors, four had a suboccipital craniotomy and an otological procedure. One type B tumor with minimal intracranial involvement required only a translabyrinthine transcochlear approach for complete excision. Of the two type C tumors, one was removed using solely an infralabyrinthine procedure; the other, with tumor extension into the posterior fossa, also required a suboccipital craniotomy. Type D tumors, as described by Pellet et al. (1988), are particularly challenging because they have significant involvement in the posterior fossa and in the infratemporal region. Pellet et al. (1988) described a widened transcochlear approach, which involved a petrosectomy to link the posterior fossa to the superior carotid-nasopharyngeal region. Using this approach they addressed these saddlebag-shaped tumors, which occupy both spaces, in a single operation.

In their series of 16 patients with jugular foramen schwannomas, Samii et al. (1995) similarly based their operative approach on the tumor's origin and extension as classified into types A–D. Type A tumors were approached via a lateral suboccipital route with patients in a semi-sitting (lounging) position. Types B, C, and D were approached via a cervical-transmastoid route with the patient supine and the head turned. For type A tumors with an extension into the jugular foramen, the dorsal portion of the jugular foramen was opened extradurally and the dural incision was extended to the foramen to facilitate intraluminal tumor removal. Briefly, the cervical-transmastoid approach for types B–D tumors involved (1) mobilizing the sternocleidomastoid muscle and the posterior belly of the digastric muscle to expose the mastoid, (2) performing a lateral suboccipital craniectomy to expose the transverse and sigmoid sinuses, (3) mobilizing the sigmoid sinus from its groove caudally down to the jugular foramen, and (4) removing the mastoid tip and the posterior occipital condyle to open the jugular foramen dorsolaterally (in comparison to the paracondylar extension of the far-lateral approach, which opens the foramen dorsomedially) (Samii et al., 1995).

In Sekhar's series of nonvestibular intracranial schwannomas, nine cases of jugular foramen tumors were addressed by a variety of approaches based on the tumor's extension (Sarma et al., 2002). For two patients in whom the tumors were entirely cisternal (type A), a retrosigmoid approach was used. Two other patients with tumor extension into the jugular foramen required a retrosigmoid and transjugular combined approach. Two patients had tumors that were predominantly extradural, and they were addressed via an extreme lateral approach combined with a transmastoid approach. Finally, one patient with tumor extending into the extradural petroclival and cavernous sinus region required a subtemporal/infratemporal approach.

Finally, the far-lateral approach and its extensions are also well suited to address a variety of jugular foramen schwannomas. In the series by Cavalcanti et al. the far-lateral approach was used to resect six type A, one type C, and three type D jugular foramen schwannomas. A posterior petrosectomy (two infralabyrinthine, one retrolabyrinthine, and one transcochlear) was combined with a far-lateral approach in four cases, and a retrosigmoid combined approach was used in one case (Cavalcanti et al., 2011). Jugular foramen schwannomas represent a heterogeneous group of lesions, depending on the tumor's origin and extension. Adequate preoperative planning and an understanding of the tumor's extension into various

surgical spaces are required to choose the optimal approach for safe tumor removal.

Clinical Outcomes

Over the past 25 years, the goals of surgery for craniocervical junction schwannomas have been refined. Complete excision was once paramount, as stated by Kaye et al. (1984) in their series of patients treated between 1974 and 1983. In more recent series (Samii et al., 1995; Sarma et al., 2002; Cavalcanti et al., 2011) a major goal continues to be gross total resection, but this goal is balanced by other primary goals, including the preservation and restoration of function of the lower cranial nerves, and of hearing and facial nerve function. This change in perspective, which has been supported by the advent of radiosurgical adjuvant therapies, has significantly reduced postoperative morbidity.

In their series of jugular foramen schwannomas, Kaye et al. (1984) achieved a complete resection in all 13 cases. Postoperatively, however, all of their patients had some degree of difficulty with swallowing and sputum retention. Postoperatively, all but one of their patients experienced CN IX, X, and XI dysfunction, and the remaining patient had CN IX and X palsy only. They also reported that all patients had some degree of postoperative hoarseness, which was severe enough in five patients to warrant injection of Teflon into the vocal cord. Three of their patients developed transient facial nerve weakness. They encountered one CSF leak.

In comparison, in our series of 36 patients with craniocervical schwannomas treated between 1989 and 2009, gross total resection was achieved in just 25 patients (69.4 %) (Cavalcanti et al., 2011). Of the patients with subtotal resection, 8 were treated with adjunctive radiosurgery and the remaining patients were followed with serial magnetic resonance imaging. At a mean follow-up of 24.6 months, all patients had a shrinking or stable tumor. Accordingly, we found a reduction in postoperative morbidity in our series. Swallowing impairment developed or worsened in 9 cases, including 8 of 17 cases of jugular foramen schwannomas and 1 of 6 cases of hypoglossal nerve schwannomas. Six patients required a temporary tracheostomy with enteral feedings. At last follow-up, all patients had recovered the ability to eat. Five patients underwent medialization thyroplasty to improve their hoarseness. There were three CSF leaks.

Other modern series have likewise reported improved postoperative morbidity profiles. In their series of 9 jugular foramen schwannomas, Sarma et al. (2002) reported complete tumor excision in all but one case. Postoperatively, there were two CSF leaks, one case of bacterial meningitis, 2 patients that required thyroplasty, and 1 temporary jejunostomy. In their series of 16 jugular foramen schwannomas, Samii et al. (1995) achieved total tumor removal in all cases. The temporary rate of CN morbidity was 38 % and included three patients with facial palsy, one with abducent palsy, one with swallowing problems, and one with tongue weakness. At follow-up all patients with a new postoperative CN dysfunction showed considerable improvement. Two cases of mastoiditis were treated with antibiotics, and there was one CSF leak. Other series have reported similar outcomes (Wilson et al., 2005).

Finally, because our series included schwannomas of the jugular foramen, hypoglossal foramen, and upper cervical region (C1 and C2), we were also able to analyze our postoperative outcomes based on tumor location within the craniocervical junction. Jugular foramen tumors were associated with the highest morbidity rates and cervical tumors with the lowest. Patients with hypoglossal schwannomas had a significant increase in their Karnofsky Performance Scale (KPS) score, from a mean of 58.3 preoperatively to 75 postoperatively. KPS scores were not significantly different before and after surgery for patients with jugular foramen schwannomas. Although the KPS scores of patients with C1 or C2 schwannomas showed a large average increase (from 70 to 93.1), the difference did not reach statistical significance (Cavalcanti et al., 2011).

The most important aspect of postoperative care in these patients is an early swallow evaluation. The period immediately after extubation is critical. Temporary tracheostomy and enteral feeding are mandatory in patients that do not

recover safe swallowing function. The tracheostomy should be maintained until the patient is able to begin rehabilitation for swallowing. A team of specific professionals is essential for this process. As in the case series reviewed above, adjuvant treatment, including laryngeal framework surgery, should be considered as an option.

In conclusion, surgical treatment of craniocervical schwannomas is formidable. When surgeons receive appropriate training in skull base surgery and attain a nuanced understanding of the possible approaches to this delicate operative region, precise preoperative planning, and clarity regarding the goals of surgery for individual patients, safe resection and successful patient outcomes can be achieved.

References

Acikbas SC, Tuncer R, Demirez I, Rahat O, Kazan S, Sindel M, Saveren M (1997) The effect of condylectomy on extreme lateral transcondylar approach to the anterior foramen magnum. Acta Neurochir (Wien) 139:546–550

al-Mefty O, Borba LA, Aoki N, Angtuaco E, Pait TG (1996) The transcondylar approach to extradural nonneoplastic lesions of the craniovertebral junction. J Neurosurg 84:1–6

Alleyne CH Jr, Spetzler RF (1999) The transcondylar approach. Oper Tech Neurosurg 2:74–86

Ammirati M, Ma J, Canalis R, Martin N, Black K, Cheatham M, Bloch J, Becker D (1993) A combined intradural presigmoid-transtransversarium-transcondylar approach to the whole clivus and anterior craniospinal region: anatomic study. Skull Base Surg 3:193–200

Babu RP, Sekhar LN, Wright DC (1994) Extreme lateral transcondylar approach: technical improvements and lessons learned. J Neurosurg 81:49–59

Baldwin HZ, Miller CG, van Loveren HR, Keller JT, Daspit CP, Spetzler RF (1994) The far lateral/combined supra- and infratentorial approach. A human cadaveric prosection model for routes of access to the petroclival region and ventral brain stem. J Neurosurg 81:60–68

Bertalanffy H, Seeger W (1991) The dorsolateral, suboccipital, transcondylar approach to the lower clivus and anterior portion of the craniocervical junction. Neurosurgery 29:815–821

Canalis RF, Martin N, Black K, Ammirati M, Cheatham M, Bloch J, Becker DP (1993) Lateral approach to tumors of the craniovertebral junction. Laryngoscope 103:343–349

Cavalcanti DD, Martirosyan NL, Verma K, Safavi-Abbasi S, Porter RW, Theodore N, Sonntag VK, Dickman CA, Spetzler RF (2011) Surgical management and outcome of schwannomas in the craniocervical region. J Neurosurg 114:1257–1267

Day JD, Giannotta SL (1995) Surgical management of vertebro-PICA aneurysms. In: Schmidek HH, Sweet WH (eds) Operative neurosurgical techniques. Indications, methods, and results. Saunders, Philadelphia

Elkin DC, Harris MH (1946) Arteriovenous aneurysm of the vertebral vessels. Ann Surg 124:934–951

Fisch U, Pillsbury HC (1979) Infratemporal fossa approach to lesions in the temporal bone and base of the skull. Arch Otolaryngol 105:99–107

George B, Lot G (1995) Anterolateral and posterolateral approaches to the foramen magnum: technical description and experience from 97 cases. Skull Base Surg 5:9–19

George B, Dematons C, Cophignon J (1988) Lateral approach to the anterior portion of the foramen magnum. Application to surgical removal of 14 benign tumors: technical note. Surg Neurol 29:484–490

Hakuba A (1990) Foramen magnum neurinoma. Total removal via unilateral suboccipital transcondylar approach. In: Kikuchi H, Hakuba A (eds) Illustrated techniques in microneurosurgery. Igaku-Shoin Ltd., Tokyo

Henry AK (1966) Extensile exposure. Livingstone Ltd., Edinburg/London

Heros RC (1986) Lateral suboccipital approach for vertebral and vertebrobasilar artery lesions. J Neurosurg 64:559–562

Katz AD, Passy V, Kaplan L (1971) Neurogenous neoplasms of major nerves of face and neck. Arch Surg 103:51–56

Kaye AH, Hahn JF, Kinney SE, Hardy RW Jr, Bay JW (1984) Jugular foramen schwannomas. J Neurosurg 60:1045–1053

Kuttner H (1917) Die Verletzungen und traumatischer aneurysmen der vertebral gefasse an halse und ihre operative Behandlung. Beitr Klin Chir 108:1–60

Lang DA, Neil-Dwyer G, Iannotti F (1993) The suboccipital transcondylar approach to the clivus and craniocervical junction for ventrally placed pathology at and above the foramen magnum. Acta Neurochir (Wien) 125:132–137

Lot G, George B (1999) The extent of drilling in lateral approaches to the cranio-cervical junction area from a series of 125 cases. Acta Neurochir (Wien) 141:111–118

Louis DN, Ohgaki H, Wiestler OD, Cavenee WK (eds) (2007) World Health Organization classification of tumours of the central nervous system. International Agency for Research on Cancer, Lyon

Margalit NS, Lesser JB, Singer M, Sen C (2005) Lateral approach to anterolateral tumors at the foramen magnum: factors determining surgical procedure. Neurosurgery 56(2 Suppl):324–336

Menezes AH (2005) Developmental abnormalities of the craniovertebral junction. In: Winn HR (ed) Youmans neurological surgery. Saunders, Philadelphia, pp 3331–3346

Pellet W, Cannoni M, Pech A (1988) The widened transcochlear approach to jugular foramen tumors. J Neurosurg 69:887–894

Rhoton AL Jr (2000) The far-lateral approach and its transcondylar, supracondylar, and paracondylar extensions. Neurosurgery 47(3 Suppl):S195–S209

Rhoton AL, de Oliveira E (1998) Anatomical basis of surgical approaches to the region of the foramen magnum. In: Dickman CA, Spetzler RF, Sonntag V (eds) Surgery of the craniovertebral junction. Thieme, New York, pp 13–57

Rohde V, Schaller C, Hassler W (1994) The extreme lateral transcondylar approach to aneurysms of the vertebrobasilar junction, the vertebral artery, and the posterior inferior cerebellar artery. Skull Base Surg 4:177–180

Rosenberg SI (2000) Natural history of acoustic neuromas. Laryngoscope 110:497–508

Russell DS, Rubinstein LJ (1989) Pathology of tumours of the nervous system. Williams and Wilkins, Baltimore

Safavi-Abbasi S, de Oliveira JG, Deshmukh P, Reis CV, Brasiliense LB, Crawford NR, Feiz-Erfan I, Spetzler RF, Preul MC (2010) The craniocaudal extension of posterolateral approaches and their combination: a quantitative anatomic and clinical analysis. Neurosurgery 66(3 Suppl Operative):54–64

Samii M, Babu RP, Tatagiba M, Sepehrnia A (1995) Surgical treatment of jugular foramen schwannomas. J Neurosurg 82:924–932

Sarma S, Sekhar LN, Schessel DA (2002) Nonvestibular schwannomas of the brain: a 7-year experience. Neurosurgery 50:437–448

Sen CN, Sekhar LN (1990) An extreme lateral approach to intradural lesions of the cervical spine and foramen magnum. Neurosurgery 27:197–204

Sen CN, Sekhar LN (1991) Surgical management of anteriorly placed lesions at the craniocervical junction–an alternative approach. Acta Neurochir (Wien) 108:70–77

Spetzler RF, Grahm TW (1990) The far-lateral approach to the inferior clivus and the upper cervical region: technical note. BNI Quarterly 6:35–38

Tan LC, Bordi L, Symon L, Cheesman AD (1990) Jugular foramen neuromas: a review of 14 cases. Surg Neurol 34:205–211

Tew JM Jr, van Loveren HR (1994) Lower lateral suboccipital approach. In: Tew JM Jr, van Loveren HR (eds) Atlas of operative microneurosurgery. Saunders, Philadelphia

Verbiest H (1968) A lateral approach to the cervical spine: technique and indications. J Neurosurg 28:191–203

Vishteh AG, Crawford NR, Melton MS, Spetzler RF, Sonntag VK, Dickman CA (1999) Stability of the craniovertebral junction after unilateral occipital condyle resection: a biomechanical study. J Neurosurg 90(1 Suppl):91–98

Wen HT, Rhoton AL Jr, Katsuta T, de OE (1997) Microsurgical anatomy of the transcondylar, supracondylar, and paracondylar extensions of the far-lateral approach. J Neurosurg 87:555–585

Wilson MA, Hillman TA, Wiggins RH, Shelton C (2005) Jugular foramen schwannomas: diagnosis, management, and outcomes. Laryngoscope 115:1486–1492

Zulch KJ (1965) Brain tumors: their biology and pathology. Springer, New York

Cranial Base Surgery of Hypoglossal Schwannomas

30

Yoichi Nonaka and Takanori Fukushima

Contents

Abstract

Lesions of the ventrolateral brainstem, craniovertebral junction, and infrajugular-high cervical area pose significant challenges for surgeons, and the rate of morbidity and mortality from classic neurosurgical approaches has proven to be unacceptably high. The Extreme Lateral Infrajugular Transcondylar-transtubercular Exposure (ELITE) approach, which is an improved skull base version of the extreme lateral suboccipital approach, provides sufficient exposure for these formidable cranial base lesions such as intracranial or dumbbell-shaped hypoglossal schwannomas. Based on our experience and literature analysis, we proposed the following modified grading scale to facilitate surgical planning: Type A, intradural tumors; Type B, dumbbell-shaped tumors; Type C, extracranial skull base tumors; and Type D, peripheral tumors.

Hypoglossal nerve reconstruction using a sural nerve or greater auricular nerve graft can be performed to improve tongue atrophy and movement after tumor resection.

Introduction

Hypoglossal schwannomas are extremely rare cranial base neoplasms arising from the hypoglossal nerve. They may grow anywhere along the course of the hypoglossal nerve and may be entirely intradural or extradural or even sublingual and these sometimes grow fairly rapidly.

Y. Nonaka (✉)
Division of Neurosurgery, Duke University Medical Center, Durham, NC 27710, USA

International Neurosurgery Education and Research Foundation, 4030 Wake Forest Road Suite 115, Raleigh, NC 27609, USA
e-mail: Ynonaka1971@yahoo.co.jp

T. Fukushima
Division of Neurosurgery, Duke University Medical Center, Durham, NC 27710, USA

Carolina Neuroscience Institute, International Neurosurgery Education and Research Foundation, 4030 Wake Forest Road Suite 115, Raleigh, NC 27609, USA

M.A. Hayat (ed.), *Tumors of the Central Nervous System, Volume 11*,
DOI 10.1007/978-94-007-7037-9_30,

Headache with unilateral tongue atrophy and dysphagia were the most frequent initial presenting symptoms. An important factor contributing to the high morbidity and mortality rate associated with these tumors has been the delay in diagnosis because of the rarity of the tumor, its long natural history, and the variety of associated symptoms and signs (Nonaka et al., 2011).

Hypoglossal schwannomas are benign slowly growing tumors; thus complete resection affords the patient a chance for cure. Surgical treatment of these tumors requires detailed knowledge of the anatomy around the craniovertebral junction (CVJ). Traditional surgical approaches have usually not allowed for gross total resection of large or combined intra- and extracranial hypoglossal schwannomas without significant patient morbidity. Traditional lateral suboccipital approach provides access to the cerebellopontine angle (CPA), but exposure of the hypoglossal canal (HC) and infrajugular-high cervical area are extremely limited unless the skin incision, suboccipital muscle dissection, and bone removal are extended inferolaterally. Like other standard skull base approaches, far-lateral transcondylar approach gradually developed and modified by several innovative surgeons over the last three decades to provide access to these inaccessible regions (Seeger, 1978; Hakuba et al., 1979; Heros, 1986; Gilsbach et al., 1987; George et al., 1988; Bertalanffy and Seeger, 1991). Finally, Fukushima developed the combination of a transmastoid-transcondylar drilling and high cervical exposure with a lateral suboccipital approach in 1987.

Recent advances in the understanding of skull base microanatomy and these operative approaches facilitated the development of the Extreme Lateral Infrajugular Transcondylar-transtubercular Exposure (ELITE) technique, which was named by Fukushima in 1987. This skull base approach consists of an extended lateral suboccipital craniectomy with partial removal of the occipital condyle (OC) and jugular tubercle (JT) which provides a wider view of the cerebello-medullary and medullary cisterns without excessive cerebellar retraction. This extended procedure entails a mastoidectomy, skeletonization of the sigmoid sinus (SS) and jugular bulb (JB) with decompression and/or mobilization of the vertebral artery (VA) (Fukushima and Nonaka, 2010).

Hypoglossal Schwannoma

Intracranial schwannomas are benign tumors that constitute less than 10 % of all intracranial tumors. In our schwannoma series, hypoglossal schwannomas constitute about only 1 % of all intracranial schwannomas. Our review of the literature revealed 121 reported articles and 160 cases of hypoglossal schwannomas (Nonaka et al., 2011). Hypoglossal schwannoma was reported for the first time by De Martel et al. in 1933. These tumors are most often seen in middle-aged women and usually arise intradurally and may grow into the HC followed by enlargement or erosion of the HC. Half of the intracranial hypoglossal schwannomas grow through the HC and have a dumbbell-shaped appearance. Ipsilateral hemiatrophy and weakness of the tongue were present at the time of diagnosis in over 90 % of these tumors. Twelfth nerve palsies usually appear as signs rather than symptoms. Unilateral tongue atrophy or paralysis usually does not disturb speech, chewing, or swallowing. Because of these minimal disabilities, many patients do not complain or may not notice of the 12th cranial nerve (CN) deficits. Most of patients harboring a hypoglossal schwannoma present quite late, by which time they are showing signs of cerebellum, brainstem, or cranial nerve compression or hydrocephalus. The mean time from the onset to diagnosis is over 30 months. Tumors with extension and enlargement of the HC may compress the nerve resulting in lose of function.

The most common initial symptom was headache. There was no characteristic of the headache that was common to all patients. Other symptoms and signs were related to intracranial pressure (ICP), such as vomiting and papilledema, as well as long tract dysfunction. Most patients with large intracranial component presented with symptoms and signs of brainstem compression or cerebellar dysfunction. As in many reports, it was

the compression symptoms of the cerebellum or brainstem rather than those related to the hypoglossal nerve that first brought the patient to a physician. These symptoms seem to be correlated closely with tumor bulk of intracranial portion. Dumbbell-shaped tumors with extension to the jugular foramen (JF) may also exhibit jugular foramen syndrome. Dysphagia or swallowing problems are the second initial symptom following cerebellar symptoms such as nausea, vomiting, unsteadiness, and vertigo. Tumors located at parapharyngeal or submandibular spaces presented with ipsilateral tongue atrophy in less than one-third of patients. The most common clinical presentation with this type of tumors was slow growing painless palpable mass at the upper neck or parapharyngeal space.

The surgical resection of hypoglossal schwannomas has been associated with high mortality in the literature before 1970s. Over half of the patients died of respiratory difficulty within 4 weeks after surgery. Because of frequent postoperative respiratory difficulties, a mandatory prophylactic tracheostomy has been recommended before 1970'. With contemporary microneurosurgical techniques with the use of adequate monitoring and improved postoperative care, this procedure is not absolutely necessary and permanent swallowing problems are rare nowadays.

Surgical Approaches

The critical element of surgical exposure for hypoglossal schwannomas is the exposure of HC as well as the internal auditory canal in the surgery of vestibular schwannomas. The adjacent structures such as the OC and JT should also be exposed. The ELITE approach can basically be divided into two types: "Dorsolateral" approach and "Anterolateral" approach (Fukushima et al., 1996; Fukushima and Nonaka, 2010). The selection of the proper approach depends upon the location, size and extent of the tumor. For intradural tumors, the "dorsolateral approach" is performed through a lazy-S incision with the patient in a lateral position. For intra- and extracranial dumbbell-shaped tumors, the "anterolateral approach" is performed through a post-auricular "Question mark shaped incision" with the patient in a supine position and the head rotated laterally (Fig. 30.1).

Dorsolateral ELITE Approach

Dorsolateral ELITE approach is divided into three subcategories. The "Limited" dorsolateral ELITE approach (opening of the foramen magnum (FM) + OC drilling without JT drilling) is used for surgery of hypoglossal schwannomas of intracranial type. The "Standard" dorsolateral ELITE approach (FM opening + OC drilling and JT drilling) is for intradural tumors with HC or JB extension. The "Extended" dorsolateral ELITE approach (FM opening + subtotal condylectomy + VA transposition) is designed for the resection of large hypoglossal schwannomas with caudal extension through the FM.

The steps involved in the dorsolateral ELITE approach are (1) a retroauricular lazy S-shaped incision; (2) anterior retraction of the sternocleidomastoid muscle (SCM); (3) inferior lateral suboccipital craniotomy; (4) identification of the vertebral sulcus in the C1 atlas; (5) exposure of extradural VA (V3 segment); (6) exposure of the FM; (7) skeletonization of the SS and exposure of the inferior retrosigmoid point; (8) drilling of superomedial one-third of the OC and exposure of the HC; (9) drilling of the JT; (10) intradural exposure.

Positioning and Skin Incision

For the dorsolateral ELITE approach, the patient is placed in the lateral position and the laterally flexed head is elevated off from the lower shoulder with the vertex extending away from the upper shoulder. The face may be rotated slightly down to elevate the ear and the mastoid to the highest position. A skin incision is made in a lazy S-shaped fashion which begins 2–3 cm behind the posterior ridge of the body of mastoid passing just over the asterion at the level of the superior auricular point. The incision courses inferiorly inside the hairline then curves gently posterior at the level of the mastoid tip.

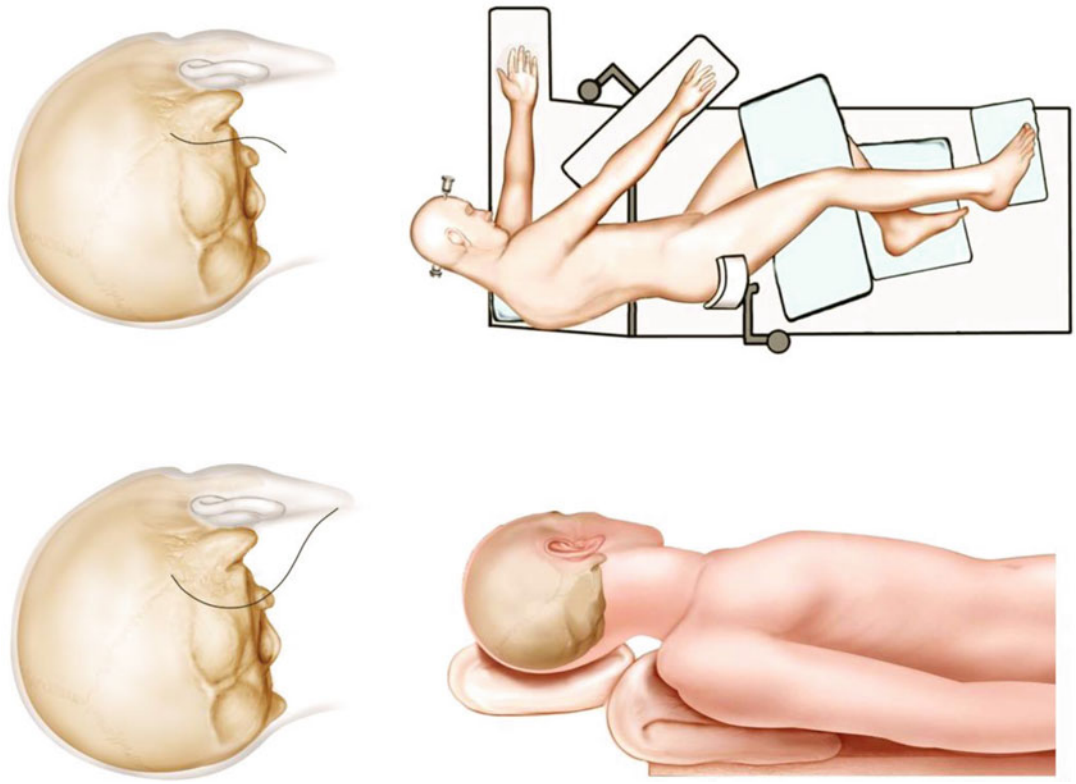

Fig. 30.1 Dorsolateral ELITE approach and Anterolateral ELITE approach illustrations demonstrating the positioning and skin incision for right side dorsolateral (*upper*) and anterolateral (*lower*) ELITE approaches

Muscle Dissection and Craniotomy

The SCM is dissected and reflected anteriorly. The splenius and longissimus capitis muscles (the middle layers) are either split or detached from the mastoid and reflected posterior. The superior oblique and rectus capitis muscles are detached at their insertions on the transverse process of C1 and reflected posteriorly. Location of the V3 segment of the VA is estimated by finger palpation or with a pencil Doppler probe. Prior to performing the suboccipital craniotomy, a partial mastoidectomy using a large diamond burr is performed to expose the inferior SS down to the inferior retrosigmoid point in a groove fashion. The posterior ridge of the mastoid body is drilled away to expose the inferior SS, then bone removal is continued inferiorly to the digastric groove. A small inferior suboccipital osteoplastic craniotomy is made following the partial mastoidectomy. Following the removal of the lateral edge of the FM, the superomedial portion of the OC and the JT, the inferior CPA and the CVJ are viewed in a straight, flat line.

Bone Removal and Drilling

Drilling of the OC is the critical component of this approach. OC removal is necessary for exposure of the HC. Usually, the posterior and superior medial one-third of the OC can be drilled away to expose the HC. This is sufficient for resecting an intracranial tumor with HC extension. Aggressive removal of the OC may cause craniovertebral instability and necessitate placement of hardware for stabilization. When the superomedial part of the OC is drilled away within the condylar triangle, the HC can be identified as an extension of the C1 dura, running almost parallel to the condylar facet, but slightly in a cephalad direction (Fig. 30.2). In cases of dumbbell-shaped tumors with enlargement of

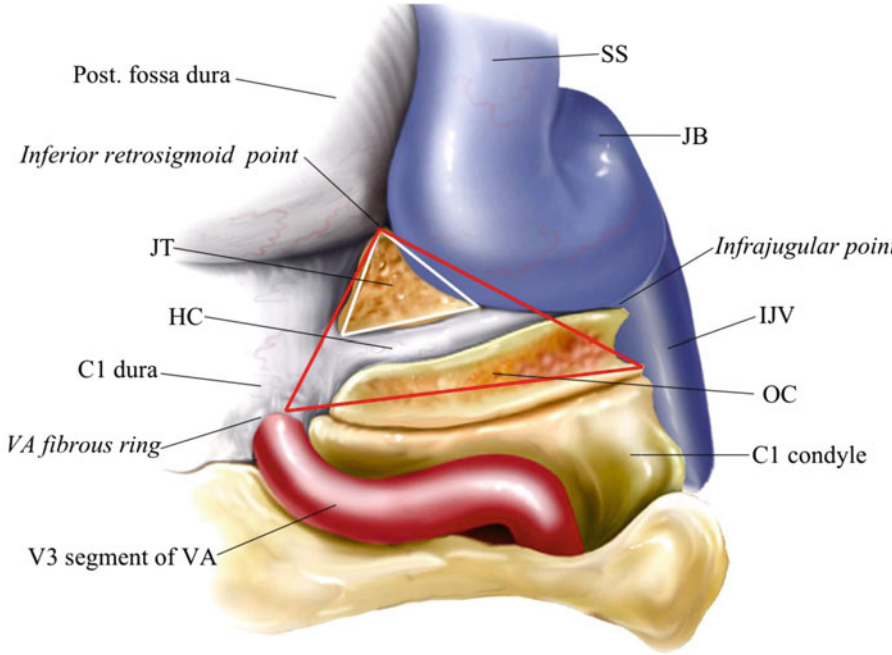

Fig. 30.2 Illustration of a coronal section demonstrating the condylar triangle (*red*) and tubercular triangle (*white*) at the level of the right hypoglossal canal. *JB* jugular bulb, *JT* jugular tubercle, *HC* hypoglossal canal, *IJV* internal jugular vein, *OC* occipital condyle, *SS* sigmoid sinus

the HC, additional drilling around the canal may provide suitable exposure of the tumor for removal of the extracranial component and result in the full exposure of posteroinferior portion of the JB and medial portion of the internal jugular vein (IJV) at the entrance of JF.

Bone removal is then directed superiorly towards the inferior aspect of the JB. At this point, the JT is already partially removed such that its posterior part resembles a triangle (tubercular triangle). The JT is a bony structure located at the junction of the clivus and condylar portion of the occipital bone which hinders surgical exposure of lesions situated at the lower clivus and premedullary areas. Drilling the JT is crucial to obtain a flat view to maximize surgical exposure without excessive cerebellar retraction. The JT should be drilled under high magnification, using a small diamond burr under constant irrigation. The JT should be hollowed out until only a thin outer rim remains. Holding the posterior fossa dura and SS by one or two self-retaining spatulas provides working space for safely drilling and allows visualization of the superomedial rim of the JT. In cases of large tumors with HC enlargement, the JT is often eroded by the tumor and easy to remove.

Dural Incision

The dural incision begins superiorly several millimeters posterior to the SS, and continues inferiorly passing just behind the VA entrance through the dura (vertebral fibrous ring) ending just above the C1 lamina. A dural ring should be preserved around the VA for a watertight dural closure. The surgeon should clearly identify the following structures: CNs XII, XI, X, IX, VII, VIII, and VI, posterior inferior cerebellar artery (PICA), anterior inferior cerebellar artery (AICA) and the vertebrobasilar junction.

The "Extended" dorsolateral ELITE approach is indicated for large tumors with caudal extension through the FM. The removal of the transverse process and hemilaminectomy of the C1 atlas allow the opening of the transverse foramen and extracranial VA (V3, V4 segments) transposition. Care must be taken during manipulating the VA

for transposition because too much dislocation may cause kinking of the vessel or a dissection. The dural incision begins posterior to the SS and ends just above the C2 lamina. If the atlantooccipital (AO) joint is already invaded by the tumor, or craniovertebral instability is noted after tumor removal, craniocervical or atlantooccipital fusion should be considered.

Anterolateral ELITE Approach

The anterolateral ELITE approach is an extended transcondylar approach with the SCM retracted posteriorly which allows a more anterior infrajugular exposure for dumbbell-shaped tumors (Liu et al., 2006; Fukushima and Nonaka, 2010). It provides multiple trajectories, both intra- and extradurally to the HC, extending to the parapharyngeal space.

Positioning and Skin Incision

The patient is positioned supine with the head laterally rotated on an ENT pillow. The skin incision for the anterolateral ELITE begins 2–3 cm behind and at the level of the superior auricular point. The incision then curves gently posteroinferiorly, passing just behind the asterion and continues anteroinferiorly passing the anterior margin of the SCM toward the submandibular angle (question mark incision). The skin is reflected with galea in the upper part and with superficial cervical fascia in the lower part. The SCM and greater auricular nerve crossing over the SCM are exposed. The nerve is carefully dissected and preserved for a distance of 2 cm so that can be utilized for grafting if necessary.

Muscle Dissection

After the SCM is detached from the mastoid body and has been reflected posteriorly, the digastric muscle is reflected anteriorly to obtain maximum exposure of the high cervical portion of the internal carotid artery (ICA), carotid bifurcation, IJV and parapharyngeal portion of lower CNs. The peripheral portion of the XIIth nerve is easily identified below the digastric muscle, just under the facial vein at the submandibular angle. The suboccipital muscles and pericranium are retracted posteriorly to expose the mastoid body and suboccipital bone.

Bone Removal and Drilling

A standard mastoidectomy is performed with decompression of the SS. Retrolabyrinthine and infralabyrinthine bone removal is performed and the Fallopian segment of the facial nerve is located. If the tumor expands toward the JB, skeletonization and anterior transposition of the facial nerve will provide additional working space and allows visualization of the anterior rim of the JB. In most cases, the semicircular canals and the basal turn of cochlea can be preserved to maintain hearing function.

After completion of the mastoidectomy, a small suboccipital osteoplastic craniotomy is performed. The exposure can be improved by performing a C1 hemilaminectomy. Drilling of the OC, exposure of the entire HC and removal of the JT are also key elements as in addition to the components of the dorsolateral ELITE. The dura is incised several millimeters posterior to the SS, continued inferiorly, passing just medial to the vertebral fibrous ring to end just above the C2 lamina.

Meticulous hemostasis should be assured after tumor resection. To prevent any postoperative cerebrospinal fluid (CSF) leak or infection, watertight dural closure with fascia, abdominal fat graft and cosmetic cranioplasty are essential. A fascial graft of the SCM or pericranium can be harvested from the postauricular area. These are utilized for the dural closure or repair of the dural tear. Abdominal rectus muscle fascia is also taken if necessary. Abdominal fat grafts are cut into multiple narrow strips and are placed into the extradural space to fill the gap and bone defects. They are reinforced with fibrin glue. Careful cosmetic cranioplasty is performed with a bone flap, micro titanium plates, titanium mesh plate and calcium phosphate or calcium carbonate bone cement. The wound is then closed in anatomic layers in the deep muscle. The muscle attachments to the bone are sutured to the bone holes or titanium plate as they put in original position to avoid muscle atrophy and deformity.

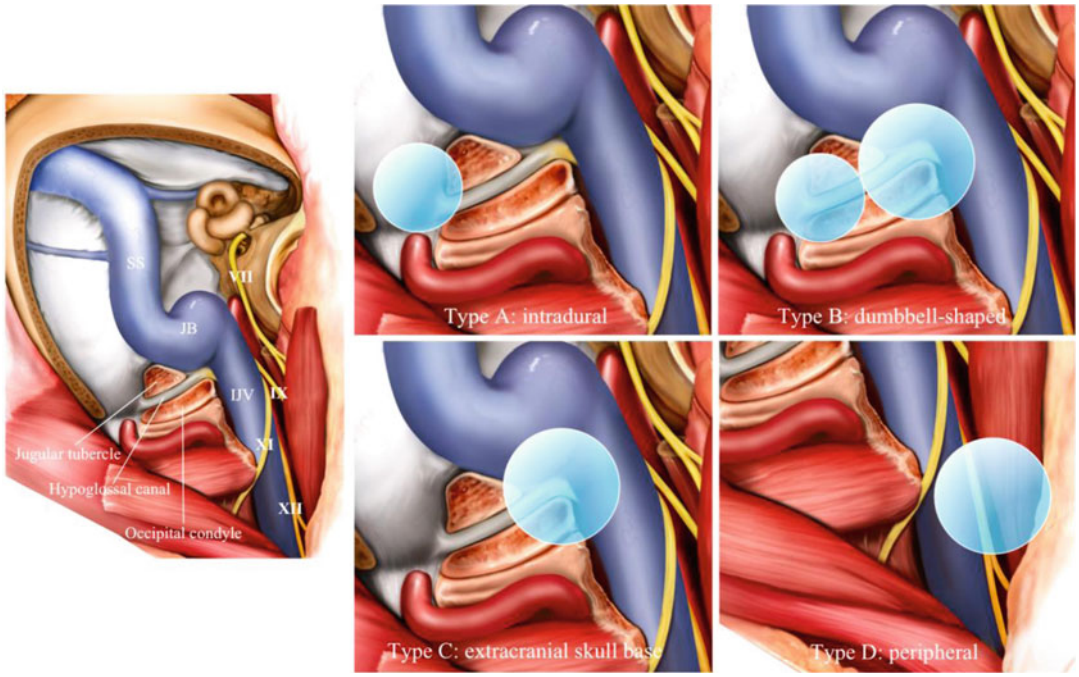

Fig. 30.3 Classification of hypoglossal schwannomas Illustration of our classification scheme for hypoglossal schwannomas. Tumor is shown in *blue*

Intraoperative monitoring consisting of bilateral somatosensory evoked potentials (SSEP), motor evoked potentials, electrophysiological monitoring of the ipsilateral cranial nerves VII–XII, and brainstem auditory evoked potentials was utilized.

Grading Scale and Tumor Classification

We presented a modified grading system for jugular foramen schwannomas and have been used the scale to determine the extent of exposure (Bulsara et al., 2008). A grading scale is useful to guide surgical management for this rare type of tumor too. Based on a review of past literature, we proposed a modified grading scale for hypoglossal schwannomas (Nonaka et al., 2011). The lesions are classified according to imaging results. As with previous grading scales of hypoglossal schwannomas, our grading system takes into account the different growth patterns of these tumors. Figure 30.3 illustrates our classification of hypoglossal schwannomas: Type A, intradural tumor; Type B, dumbbell-shaped tumor; Type C, extracranial skull base tumor; Type D, peripheral tumor without osseous involvement.

Type A tumors without HC extension can be approached via a conventional lateral suboccipital route. If there is osseous involvement, an ELITE approach with partial occipital condylectomy can be used. An OC drilling to expose HC is necessary for intracanal tumor removal. Partial mastoidectomy and high cervical exposure are added for the resection of type B tumors. A combined transmastoid/transjugular and high cervical approach and full exposure of the IJV (if necessary, SS-IJV can be ligated and removed) are used for large type B and C tumors. Type D tumors are approached by transcervical or high cervical approach without any bone removal.

Nerve Reconstruction

In most cases, severe or complete ipsilateral atrophy of the tongue is already present when the diagnosis is established. However, attention should

always be paid to the possibility of reconstruction of cranial nerve. Sural nerve graft reconstructions are an important adjunct technique for patients in whom hypoglossal nerve resection is necessary. If a proximal hypoglossal nerve stump is preserved at the brainstem, a sural nerve (external saphenous nerve) graft can be performed between that stump and distal portion of the hypoglossal nerve. Hypoglossal nerve reconstruction was performed in four patients in our series (Nonaka et al., 2011).

After tumor removal, the stump is trimmed proximally and distally. A sural nerve graft of appropriate length is harvested. It is attached so that there is no tension on the anastomosis. Since the proximal stump of the hypoglossal nerve is much smaller than the sural nerve, every single fascicle of the hypoglossal nerve is anastomosed to the sural nerve by using No. 9–0 or 10–0 monofilament nylon suture with one stitch respectively. Four interrupted sutures through the epineurium are enough for the anastomosis.

Three of the four patients that sural nerve reconstruction was performed regained satisfactory movement of the tongue by their 1 year follow-up. In those patients no identifiable nerve stump at the brainstem, tongue atrophy developed. Some of them have mild atrophy while others have severe tongue atrophy.

Recently, we fond that the greater auricular nerve is also useful as a nerve graft, especially in the anterolateral ELITE approach. In this approach, it spares the additional skin incision necessary to harvest the sural nerve graft. One of our four patients had combined nerve grafts with sural and greater auricular nerves. The idea of saphenous vein sleeve with fibrin glue that was reported by Mathiesen et al. (2009) is also very useful.

Discussion

Despite the fact that the mortality and morbidity for resecting hypoglossal schwannomas has improved, these lesions still pose a formidable challenge. Traditional surgical approaches such as lateral or midline suboccipital craniotomies may be available for only intracranial tumors in moderate size without HC extension. These approaches do not usually allow for gross total resection of tumors for these lesions without significant patient morbidity especially in large or combined intra- and extracranial tumors. Recent skull base techniques such as the far-lateral, transcondylar, supracondylar, and transcondylar fossa approaches have been advocated to access and manage lesions in this complex area. Seeger described his basic concept of the transcondylar approach as early as 1978. Gilsbach and Seeger pioneered this approach in clinical cases in the 1980s. In 1986, Heros published a detailed description of the extreme lateral inferior suboccipital approach for vertebral and vertebrobasilar artery lesions. The concept of transcondylar approach was finally established by Bertalanffy in 1991.

In 1987, Fukushima and colleagues reported the new surgical concept of ELITE approach, which entailed resection of the JT (hands-on workshop in UCLA, CA). This skull base approach basically consists of an extended lateral suboccipital craniotomy with partial removal of the OC and total removal of the JT to provide a wider view of the cerebello-medullary to medullary cisterns. The ELITE technique is suitable for vertebro-posterior inferior cerebellar artery (PICA) and vertebro-basilar (VB) junction aneurysms, lower clival and ventral foramen magnum lesions and JF or hypoglossal tumors. For the past 20 years, this technique has been developed with establishment of microanatomical surgical landmarks such as concept of condylar and tubercular triangles, morphometric analysis of HC and JT, and simple method to identify the V3 segment of the VA (Mintelis et al., 2006; Wanibuchi et al., 2009).

The reconstruction of an injured hypoglossal nerve using a sural nerve or greater auricular nerve graft may be useful to regain its function. In the rare instance that a sural nerve anastomosis cannot be performed with sutures, anatomical reconstruction using fibrin glue and a vein sleeve could be utilized (Mathiesen et al., 2009). This surgical combination was achieved to reduce the morbidity of postoperative hypoglossal nerve deficits.

When tumor recurrence is observed at follow-up, stereotactic radiation therapy may be indicated or for younger patients with under 60-year age, second surgical tumor resection is considered.

References

Bertalanffy H, Seeger W (1991) The dorsolateral, suboccipital, transcondylar approach to the lower clivus and anterior portion of the craniocervical junction. Neurosurgery 29:815–821

Bulsara KR, Sameshima T, Friedman AH, Fukushima T (2008) Microsurgical management of 53 jugular foramen schwannomas: lessons learned incorporated into a modified grading system. J Neurosurg 109:794–803

De Martel T, Subirana A, Guillaume J (1933) Los tumores de le fossa cerebral posterior: voluminoso neurinoma del hipogloso con desarrollo juxtabulbo-protuberancial. Operacionsuracion Ars Med 9:416–419

Fukushima T, Nonaka Y (2010) Exercise 10: Fukushima ELITE approach. In: Fukushima T, Nonaka Y (eds) Fukushima manual of skull base dissection, 3rd edn. AF-Neurovideo Inc, Raleigh, pp 286–301

Fukushima T, Day JD, Maroon JC (1996) Manual of skull base dissection. AF-Neurovideo Inc., Pittsburgh, pp 111–123

George B, Dematons C, Cophignon J (1988) Lateral approach to the anterior portion of the foramen magnum. Surg Neurol 29:484–490

Gilsbach JM, Eggert HR, Seeger W (1987) The dorsolateral approach in ventrolateral craniospinal lesions. In: Voth D, Glees P (eds) Diseases in the cranio-cervical junction. Walter de Gruyter, Berlin, pp 359–364

Hakuba A, Hashi K, Fujitani K, Ikuno H, Nakamura T, Inoue Y (1979) Jugular foramen neurinomas. Surg Neurol 11:83–94

Heros RC (1986) Lateral suboccipital approach for vertebral and vertebrobasilar artery lesions. J Neurosurg 64:559–562

Liu JK, Sameshima T, Gottfried ON, Couldwell WT, Fukushima T (2006) The combined transmastoid retro- and infralabyrinthine transjugular transcondylar transtubercular highcervical approach for resection of glomus jugulare tumors. Neurosurgery 59:ONS115–ONS125

Mathiesen T, Svensson M, Lundgren J, Kihlstrom L, Parisotto R, Bagger-Sjoback D (2009) Hypoglossal schwannoma-successful reinnervation and functional recovery of the tongue following tumour removal and nerve grafting. Acta Neurochir (Wien) 151:837–841

Mintelis A, Sameshima T, Bulsara KR, Gray L, Friedman AH, Fukushima T (2006) Jugular tubercle: morphometric analysis and surgical significance. J Neurosurg 105:753–757

Nonaka Y, Grossi PM, Bulsara KR, Taniguchi RM, Friedman AH, Fukushima T (2011) Microsurgical management of hypoglossal schwannomas over 3 decades: a modified grading scale to guide surgical approach. Neurosurgery 69:ons121–ons140

Seeger W (1978) Atlas of topographical anatomy of the brain and surrounding structures. Springer, Wien, pp 486–489

Wanibuchi M, Fukushima T, Zenga F, Friedman AH (2009) Simple identification of the third segment of the extracranial vertebral artery by extreme lateral inferior transcondylar-transtubercular exposure (ELITE). Acta Neurochir (Wien) 151:1499–1503

ERRATUM

Tumors of the Central Nervous System

Pineal, Pituitary, and Spinal Tumors

Edited by

M.A. Hayat

M.A. Hayat (ed.), *Tumors of the Central Nervous System, Volume 11*,
DOI 10.1007/978-94-007-7037-9, © Springer Science+Business Media Dordrecht 2014

DOI 10.1007/978-94-007-7037-9_31

Old book sub title: Pineal, Pituitary, and Spinal Tumors

New book Sub title: Imaging, Glioma and Glioblastoma, Stereotactic Radiotherapy, Spinal Cord Tumors, Meningioma, and Schwannomas

Index

M.A. Hayat (ed.), *Tumors of the Central Nervous System, Volume 11*,
DOI 10.1007/978-94-007-7037-9, © Springer Science+Business Media Dordrecht 2014

C

Q