M.A. Hayat *Editor*

Tumors of the Central Nervous System

Volume 3
Brain Tumors (Part 1)

Springer

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Volume 3

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Brain Tumors (Part 1)

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
Union, NJ, USA
ehayat@kean.edu

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"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

Preface

In this volume, as in volumes 1 and 2, the emphasis is on the diagnosis, therapy, and prognosis of brain tumors. In addition to describing strategies for advanced brain tumor treatment, this volume presents information on understanding the unique biology of the brain and its tumors. The information contained in this volume should aid in the development of tools for better diagnosis and effective treatment of brain malignancy.

The application of various imaging techniques, including MRI, MRSI, PET, and CT, for diagnosing brain tumors including peripheral nerve sheath tumors is detailed. The use of MRS modality for classifying brain tumors is presented. This volume also contains information on the passage of malignancy to brain from tumors of other organs such as female breast and lung (tumor to tumor).

The inception of both primary and secondary brain tumors is discussed. Also is included the delivery of drugs into brain tumors, considering the presence of blood brain barrier. A wide variety of treatments, such as conventional chemotherapy, electrochemotherapy, conventional resection, stereotactic radiosurgery, and magnetic resonance-guided focused ultrasound surgery in clinical practice, are explained in detail. The use of radioresponsive gene therapy for malignant brain tumors is included in this volume. The use of molecular markers as predictive and prognostic indicators in treatment decisions for individual cases are already beginning to have a significant positive effect on the clinical practice. A number of such markers are discussed in the volume. This volume also discusses pain management following craniotomy, antiepileptic drugs, and quality of life after brain tumor therapy and follow-up.

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. This volume was written by 69 authors representing 12 countries. I am grateful to contributors for their promptness in accepting my suggestions. Their practical experience highlights their writings, which should build and further the endeavors of the readers 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 subgroups: Introduction, Diagnosis and Biomarkers, Therapy, and Prognosis for the convenience of the readers.

It is my hope that the current volume will join the preceding volumes of this 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 prevention, diagnosis, treatment, and hopefully cure.

I am thankful to Dr. Dawood Farahi, Dr. Kristie Reilly, and Mr. Philip Connelly for recognizing the importance of medical research and publishing in an institution of higher education, and providing the resources for completing this project.

Union, New Jersey M.A. Hayat
December 2010

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Contributors

Giovanni Addolorato Department of Internal Medicine, Catholic University of Rome, 8 – 00168 Rome, Italy, g.addolorato@rm.unicatt.it

Birgit Agerholm-Larsen Glostrup Research Institute, Copenhagen University Hospital Glostrup, 2600, Glostrup, Denmark, Bial@heh.regionh.dk

Emilie Allard INSERM, U646, Universite d'Angers, Angers F-491000, France, emilieallardfr@yahoo.fr

Sameer A. Ansari Section of Neuroradiology, Northwestern University Feinberg School of Medicine and the University of Chicago Pritzker School of Medicine, 5841 S. Maryland Ave., Chicago, IL 60637, USA, sansari@radiology.bsd.uchicago.edu

Benjamin J. Arthurs Department of Oncology, Cancer Care Northwest and Gamma Knife of Spokane, Spokane, WA 99204, USA, barthurs@u.washington.edu

Issam A. Awad Neurovascular Surgery Program, Section of Neurosurgery, University of Chicago Pritzker School of Medicine, 5841 S. Maryland Ave., Chicago, IL 60637, USA, iawad@uchicago.edu

Surinder K. Batra Department of Biochemistry and Molecular Biology, College of Medicine, Eppley Cancer Institute, 7052 DRC, University of Nebraska Medical Center, 985870 Nebraska Medical Center, Omaha, NE 68198-5870, USA, sbatra@unmc.edu

Tommy Bergenheim Umea University Hospital, Umea, Sweden

Arthur W. Clark Department of Pathology and Laboratory Medicine, Foothills Medical Centre, Calgary, AB, Canada T2N 2T9, Arthur.clark@cls.ab.ac

Barton S. Cooke Department of Oncology, Cancer Care Northwest and Gamma Knife of Spokane, Spokane, WA 99204, USA, bo@gkspokane.com

Cristina D'Angelo Department of Internal Medicine, Catholic University of Rome, Gemelli Hospital, l.go Gemelli, 8, 00168 Rome, Italy, dangelocristina@virgilio.it

Vincenzo Antonio D'Angelo Department of Neurosurgery, IRCCS "Casa Sollievo della Sofferenza" Hospital, San Giovanni Rotondo, Italy, vincenzo.dangelo@yahoo.it

Theri Leica Degaki Department of Biochemistry, Chemistry Institute, NUCEL-Cell and Molecular Therapy Center, University of Sao Paulo, Sao Paulo 05508-900 SP, Brazil, theridegaki@gmail.com

John J. Demakas Department of Oncology, Cancer Care Northwest and Gamma Knife of Spokane, Spokane, WA 99204, USA, johndemakas@gkspokane.com

Marcos Angelo Almeida Demasi Department of Biochemistry, Chemistry Institute, NUCEL-Cell and Molecular Therapy Center, University of Sao Paulo, Sao Paulo 05508-900 SP, Brazil, marcodms@iq.usp.br

Sophie Dupont Epilepsy Unit, Clinique Neurologique Paul Castaigne, Hopital de la Salpetriere, 75651 Paris cedex 13, France, Sophie.dupont@psl.ap-hop-paris.fr

Ameer L. Elaimy Department of Oncology, Cancer Care Northwest and Gamma Knife of Spokane, Spokane, WA 99204, USA, aelaimy@hotmail.com

Johnathan A. Engh Department of Neurological Surgery, University of Pittsburgh Medical Center, UPMC Presbyterian, Pittsburg, PA 15213, USA, enghja@upmc.edu

Robert K. Fairbanks Department of Oncology, Cancer Care Northwest and Gamma Knife of Spokane, Spokane, WA 99204, USA, fairbrk@ccnw.net

Frank Floeth Department of Neurosurgery, Heinrich-Heine-University Düsseldorf, D-40225 Düsseldorf, Moorenstr. 5, floethf@uni-duesseldorf.de

Juan M. García-Gómez Informatica Biomedica, Institudo de Aplicaciones de las Technologias de la Informacion y de las Comunicaciones Avanzadas, Universidad Politecnica de Valencia, Valencia, Spain, Juanmig@ibime.upv.es

Julie Gehl Department of Oncology, Copenhagen University Hospital Herlev, 2730 Herlev, Denmark, Juge@heh.regionh.dk

Richard G. Grundy Children's Brain Tumor Research Center, Medical School D Floor, School of Clinical Sciences, Queen's Medical Centre, Nottingham, NG7 2UH, UK, richard.grundy@nottingham.ac.uk

Abhijit Guha Division of Neurosurgery, Toronto Western Hospital, Toronto, ON, Canada, Abhijit.guha@uhn.on.ca

Sheffali Gulati Division of Pediatric Neurology, Department of Pediatrics, All India Institute of Medical Sciences, New Delhi, India, sheffaligulati@gmail.com

Joerg Haier Comprehensive Cancer Centre Muenster, International Patient Management, University Hospital Muenster, 48149 Muenster, Germany, Joerg.haier@ukmuenster.de

M.A. Hayat Department of Biological Sciences, Kean University, Union, NJ 07083, USA, ehayat@kean.edu

Arend Heerschap Department of Electrical Engineering (ESAT/SISTA), K.U. Leuven, Leuven, Belgium, a.heerschap@rad.umcn.nl

Eirik Helseth Department of Neurosurgery, OSLO University Hospital, Oslo, Norway, ehelseth@ous-hf.no

Doug Hughes Department of Neurosurgery, Medical College of Georgia, Augusta, GA 30912, USA, dhughes@georgiahealth.edu

Richard Hummel Department of General and Visceral Surgery, University Hospital Muenster, 48149 Muenster, Germany, richard.hummel@ukmuenster.de

Albert J. Idema Department of Electrical Engineering (ESAT/SISTA), K.U. Leuven, Leuven, Belgium, a.idema@nch.umcn.nl

Shogo Ishiuchi Department of Radiology, University of the Ryukyus, Nishihara-cho, Okinawa 903-0215, Japan, ishogo@med.u-ryukyu.ac.jp

Helle K. Iversen Glostrup Research Institute, Copenhagen University Hospital Glostrup, 2600, Glostrup, Denmark, Heiv@glo.regionh.dk

Hanna Järnum Department of Radiology, Aalborg Hospital, Arhus University Hospital, 9000 Aalborg, Denmark, h.jarnum@rn.dk

Stephen Johnston Breast Unit, Royal Marsden Hospital, Downs Road, Sutton, SM2 5PT, UK, Stephen.Johnston@rmh.nhs.uk

Ferenc A. Jolesz Brigham and Women's Hospital, Harvard Medical School, Boston, USA, jolesz@bwh.harvard.edu

Youngmee Kim Department of Psychology, University of Miami, Coral Gables, FL 33146, USA, ykim@miami.edu

Linda Knutsson Department of Medical Radiation Physics, Lund University, Lund, Sweden, Linda.Knutsson@med.lu.se

Anne-Laure Laine INSERM, U646, Universite d'Angers, Angers F-491000, France, annelaure.laine@wanadoo.fr

Wayne T. Lamoreaux Department of Oncology, Cancer Care Northwest and Gamma Knife of Spokane, Spokane, WA 99204, USA, wayne.lamoreaux@gkspokane.com

Karl-Josef Langen Institute of Neuroscience and Medicine, Forschungszentrum Jülich, D-52425 Jülich, Germany, k.j.langen@fz-juelich.de

Elna-Marie Larsson Department of Radiology, Uppsala University, Uppsala University Hospital, SE 751 85 Uppsala, Sweden, elna-marie.larsson@radiol.uu.se

Teresa Laudadio Department of Electrical Engineering (ESAT/SISTA), K.U. Leuven, Leuven, Belgium, t.laudadio@ba.iac.cnr.it

Andre A. le Roux Division of Neurosurgery, Toronto Western Hospital, Toronto, ON, Canada, aaleroux@yahoo.com

Christopher M. Lee Department of Oncology, Cancer Care Northwest and Gamma Knife of Spokane, Spokane, WA 99204, USA, lee@ccnw.net

Peter Lindvall Umea University Hospital, Umea, Sweden, peter_lindvall_nkk@hotmail.com

Mette Linnert Department of Oncology, Copenhagen University Hospital Herlev, 2730 Herlev, Denmark, Melije01@heh.regionh.dk

Aida Loudyi Section of Melanoma, Renal Cancer and Immunotherapy, Nevada Cancer Institute, Las Vegas, NV 89135, USA, aspaladatabouka@yahoo.com

Jian-Qiang Lu Department of Lab Medicine and Pathology, 5B2.24 WCM Health Sciences Centre, University of Alberta Hospital, Edmonton, AB, Canada TG6 2B7, Jianqiang.lu@albertahealthservices.ca

Jan Luts Department of Electrical Engineering (ESAT/SISTA), K.U. Leuven, Leuven, Belgium, jan.luts@esat.kuleuven.be

Alexander R. MacKay Department of Oncology, Cancer Care Northwest and Gamma Knife of Spokane, Spokane, WA 99204, USA, gammaknife@armackay.net

Faisal Mahmood Department of Oncology, Copenhagen University Hospital Herlev, 2730 Herlev, Denmark, Fama@heh.regionh.dk

Edward M. Marchan Department of Neurological Surgery, Health Sciences Center, Charlottesville, VA 22908, USA, edmarchan@gmail.com

Ernst Martin University Children's Hospital, CH-8032 Zurich, Switzerland, Ernst.martin@kispi.uzh.ch

Akira Matsumura Department of Neurosurgery, Clinical Medicine, Graduate School of Comprehensive Human Science, University of Tsukuba, Tsukuba, Ibaraki 305-8565, Japan, a-matsumur@md.tsukuba.ac.jp

Jessica Maurer Department of General and Visceral Surgery, University Hospital Muenster, 48149 Muenster, Germany, jessica-maurer@gmx.de

Torstein Meling Department of Neurosurgery, OSLO University Hospital, Oslo, Norway, tmeling@ous-hf.no

Laurent Menard Laboratoire Imagerie et Modelisation en Neurobiologie et Cancerologie, IMNC- UMR 8165, Universita Paris Diderot 7, Paris, France, menard@imnc.in2p3.fr

Philippe Menei INSERM, U646, Universite d'Angers, Angers, F-491000, France; Centre Hospitalier Universitaire d'Angers, Angers cedex 9, F-49933, France, PhMenei@chu-angers.fr

Murielle Mimeault Department of Biochemistry and Molecular Biology, College of Medicine, Eppley Cancer Institute, 7052 DRC, University of Nebraska Medical Center, 985870 Nebraska Medical Center, Omaha, NE 68198-5870, USA, mmimeault@unmc.edu

Antonio Mirijello Department of Internal Medicine, Catholic University of Rome, 8 – 00168 Rome, Italy, antonio.mirijello@gmail.com

Sadayuki Murayama Department of Radiology, University of the Ryukyus, Nishihara-cho, Okinawa 903-0215, Japan, sadayuki@med.u-ryukyu.ac.jp

Pawel G. Ochalski Department of Neurological Surgery, University of Pittsburgh Medical Center, UPMC Presbyterian, Pittsburg, PA 15213, USA, ochalskipg@upmc.edu

Kazuhiko Ogawa Department of Radiology, University of the Ryukyus, Nishihara-cho, Okinawa 903-0215, Japan, kogawa@med.u-ryukyu.ac.jp

Naoto Oku Department of Medical Biochemistry, School of Pharmaceutical Sciences, University of Shizuoka, Shizuoka, 422-8526 Japan, oku@u-shizuoka-ken.ac.jp

Catherine Passirani INSERM, U646, Universite d'Angers, Angers F-491000, France, catherine.passirani@univ-angers.fr

Akshal S. Patel Department of Neurosurgery, Penn State Milton S. Hershey Medical Center, Hershey, PA 17033-0850, USA, apatel4@psu.edu

Richard Prayson Department of Anatomic Pathology, Cleveland Clinic Foundation, CCLCM, Cleveland, OH 44195, USA, praysor@ccf.org

Scott Y. Rahimi Department of Neurosurgery, Medical College of Georgia, Augusta, GA 30912, USA, scottrahimi@yahoo.com

Ruman Rahman Children's Brain Tumor Research Center, Medical School D Floor, School of Clinical Sciences, Queen's Medical Centre, Nottingham, NG7 2UH, UK, Ruman.rahman@nottingham.ac.uk

Siril Rogne Department of Neurosurgery, OSLO University Hospital, Oslo, Norway, sirilrogne@gmail.com

Paul Ronning Department of Neurosurgery, OSLO University Hospital, Oslo, Norway, palronning@gmail.com

Wolfram E. Samlowski 2435 Grassy Spring Pl, Las Vegas, NV 89135, USA, wsamlowski1@gmail.com

Naveen Sankhyan Division of Pediatric Neurology, Department of Pediatrics, All India Institute of Medical Sciences, New Delhi, India, drnsankhyan@yahoo.co.in

Jesse J. Savage Department of Neurological Surgery, Health Sciences Center, Charlottesville, VA 22908, USA, jjs8x@virginia.edu

Suvasini Sharma Division of Pediatric Neurology, Department of Pediatrics, All India Institute of Medical Sciences, New Delhi, India, sharma.suvasini@gmail.com

Jason P. Sheehan Department of Neurological Surgery, Health Sciences Center, Charlottesville, VA 22908, USA, Jps2f@virginia.edu

Jonas M. Sheehan Department of Neurosurgery, Penn State Milton S. Hershey Medical Center, Hershey, PA 17033-0850, USA, Jsheehan@psu.edu

Robert Shenkar Neurovascular Surgery Program, Section of Neurosurgery, University of Chicago Pritzker School of Medicine, 5841 S. Maryland Ave., Chicago, IL, 60637, USA, rshenkar@uchicago.edu

Kosuke Shimizu Department of Medical Biochemistry, School of Pharmaceutical Sciences, University of Shizuoka, Shizuoka, 422-8526 Japan, kshimizu@u-shizuoka-ken.ac.jp

Arjan W. Simonetti Department of Electrical Engineering (ESAT/SISTA), K.U. Leuven, Leuven, Belgium, arjan.simonetti@philips.com

Eefje M. Sizoo Department of Neurology, VU University Medical Center, Amsterdam, The Netherlands, e.sizoo@vumc.nl

Mari Cleide Sogayar Department of Biochemistry, Chemistry Institute, NUCEL-Cell and Molecular Therapy Center, University of Sao Paulo, Sao Paulo 05508-900 SP, Brazil, mcsoga@iq.usp.br

Andreas M. Stark Department of Neurosurgery, Schleswig-Holstein University Medical Center, Campus Kiel, 24105 Kiel, Germany, starka@nch.uni-kiel.de

Stephanie Sutherland Breast Unit, Royal Marsden Hospital, Downs Road, Sutton, SM2 5PT, UK, Stephanie.Sutherland@rmh.nhs.uk

Johan A.K. Suykens Department of Electrical Engineering (ESAT/SISTA), K.U. Leuven, Leuven, Belgium, johan.suykens@esat.kuleuven.be

Martin J.B. Taphoorn Department of Neurology, VU University Medical Center, Amsterdam, The Netherlands; Department of Neurology, Medical Center Haaglanden, The Hague, The Netherlands, m.taphoorn@mchaaglanden.nl

Hideo Tsurushima Department of Neurosurgery, Clinical Medicine, Graduate School of Comprehensive Human Science, University of Tsukuba, Tsukuba, Ibaraki 305-8565, Japan, hideo-tsurushima@md.tsukuba.ac.jp

Sabine Van Huffel Department of Electrical Engineering (ESAT/SISTA), K.U. Leuven, Leuven, Belgium, sabine.vanhuffel@esat.kuleuven.be

Dirk Vandermeulen Department of Electrical Engineering (ESAT/SISTA), K.U. Leuven, Leuven, Belgium, dirk.vandermeulen@esat.kuleuven.be

Matthias Weckesser Department of Nuclear Medicine, Münster University, D-48149 Münster, Albert-Schweitzer-Strasse 33, Germany, m.weckesser@uni-muenster.de

Chapter 1

Introduction

M.A. Hayat

Keywords Tumor · CNS · Survival rate · Prognosis · Radiation · Dose

Each year malignant tumors take a devastating toll on people, and among the most feared are brain tumors. Five-year survival rates per adults are disappointing, and mortality rates have not improved during the last 3 decades. Although overall 5-year survival rates have reached to 70% in children and mortality rates have declined 25% since 1970, prognosis is still poor for those inflicted with certain types of malignant tumors. There are manifold reasons, known and unknown, for lack of improved rates of survival. One of the main reasons is the difficulty encountered by drugs to cross the blood brain barrier that is a defense mechanism, protecting the brain from blood-born pathogens. Even when therapy is effective, its side-effects can cause serious disabilities. Another reason is that the diffuse infiltration of this neoplasm does not allow even the smallest surgical instruments to resect only the tumor cells bypassing the healthy neurons. In addition, these malignant cells are highly resistant to external radiation or systemic chemotherapy. Both radiation and chemotherapy can also have toxic effects not only on the tumor they are intended to treat but also on brain function. In other words, these treatments also kill normal brain cells. Functional deficits in patients after radiotherapy are probably more common than is currently reported. These deficits include mental retardation in patients and memory or cognitive deficits in adults. Nevertheless, radiation therapy is a major component of the treatment of many primary and metastatic brain tumors. Doses higher than 60 Gy may produce vasogenic edema and necrosis in some patients.

The 5-year relative survival rate following diagnosis of a primary malignant CNS tumor based on age is given below (CBTRUS):

Age 0–19 years: 72.1%
Age 20–44 years: 55.9%
Age 45–54 years: 30.7%
Age 55–64 years: 16.7%
Age 65–74 years: 9.6%
Age 75 or older: 5.2%

From birth, males have a 0.67% lifetime risk of being diagnosed with a primary malignant CNS tumor, and 0.48% chance of dying from this cancer (excluding lymphomas, leukemias, and tumors of pituitary and pineal glands and olfactory tumors of the nasal cavity). From birth, females have a 0.54% lifetime risk of being diagnosed with this tumor, and a 0.38% chance of dying from this cancer.

The 5-year relative survival rate following diagnosis of a primary malignant CNS tumor (including lymphomas and leukemias and tumors of pituitary and pineal glands, and olfactory tumors of the nasal cavity) is 33% for males and 37% for females. The estimated prevalence rate for all primary CNS tumors is 209/100.000. Approximately, more than 612,000 persons are living with this caner in the United States (malignant tumor: >124,000 and nonmalignant tumor: >488,000). The prevalence rate for all pediatric CNS tumors is estimated at 35.4/100,000, with more than 28,000 children living with this cancer in the United States.

M.A. Hayat (✉)
Department of Biological Sciences, Kean University, Union, NJ 07083, USA
e-mail: ehayat@kean.edu

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The above-mentioned sobering statistics clearly indicate a considerable challenge to overcome brain tumors. To respond to this challenge, various experimental therapies have been administered, including gene therepy, antisense treatment, boron neutron capture, locoregional redioimmunotherapy, ligand-toxin conjugate administration and 5-aminolevulinic acid photodynamic therapy. Methods for sensitizing glioma cells to apoptosis induction and aiming at different targets such as the coagulation system have also been tried. These efforts have failed to significantly increase the overall survival of patients. Recently, Samnick et al. (2009) have tested the efficacy of ^{131}I-IPA combined with external beam photon radiotherapy as a new therapeutic approach against malignant glioma cells. This approach is based on the finding that malignant brain tumors accumulate amino acids more avidly than do healthy brains, using PET or SPECT (Hellwig et al., 2005). This finding led to the development of amino acid-based radiopharmaceuticals for detecting brain neoplasms. The use of this approach seems to merit a clinical trial to ascertain its potential in malignant glioma patients.

Causes of Developing Brain Tumors

Although little is known regarding the causes of developing brain tumors, the following conditions may increase the risk of developing this neoplasm. Exposure to certain chemicals (e.g., vinyl chloride) and mutation of relevant genes are risk factors. Brain tumors can develop after medical radiation to the scalp or brain. Brain metastatic tumors can develop from cancer of other organs such as lung and breast. Certain viruses (Epstein-Barr virus and human cytomegalovirus) can also cause brain tumors. Diseased organ transplant can lead to primary CNS lymphoma. Genetic syndromes, such as neurofibromatosis types 1 or 2 and tuberous sclerosis, may increase the risk of developing brain tumors. Immune system disorders may also play a direct or indirect roe in developing these tumors. Some types of brain tumors tend to run in families. Although smoking, alcohol consumption, and certain dietary habits are associated with some types of cancer, they have not been directly linked to primary CNS tumors. Brain and spinal cord tumors are not contagious, and presently are not preventable. CNS tumors rarely spread outside the nervous system.

Distribution of Types of CNS Tumors

There are many types of brain and spinal cord tumors (NCI): astrocytic tumors, embryonal tumors, ependymal tumors, germ cell tumors, meningeal tumors, mixed gliomas, oligodendroglial tumors, pineal parenchymal tumors, pituitary tumors, CNS lymphomas, tumors of the seller region, and other adult brain tumors. Anaplastic astrocytomas and glioblastoma account for ~27% of brain tumors.

Tumors that start in the brain are called primary brain tumors. Often tumors found in the brain are initiated somewhere else in the body and spread to one or more parts of the brain, and are called metastatic brain tumors. Brain metastases outnumber primary neoplasms by at least 10 to 1; the latter occur in 20–40% of cancer patients. The most common primary cancers metastasizing to the brain (tumor to tumor) are lung cancer (50%), breast cancer (15–20%), melanoma (10%), colon cancer (5%), and unknown primary cancers (10–15%). Approximately, 80% of brain metastases occur in the cerebral hemispheres, 15% occur in the cerebellum, and 5% occur in the brain stem. Metastases to the brain are multiple in >70% of cases, but solitary metastases also occur. Many brain tumors recur after they have been treated, and the recurrence may occur at the same cite or in other parts of the brain.

Tumor Grading

Grading is based on the cellular make-up and location of the tumors. Tumors are graded in biopsy tissue or during surgery. The grade of a tumor can be used to indicate the difference between slow- and fast-growing types of the tumor. Grade I tumors (e.g., pilocytic astrocytoma) grow slowly, do not spread into nearby tissues, and look like normal cells. It is possible to entirely remove this type of tumor by surgery. Grade II tumors (e.g., diffuse astrocytomas) also grow slowly, but may spread into nearby tissues, may recur after treatment, and may become a higher-grade tumor.

Grade III tumors (e.g., annaplastic astrocytomas) grow rapidly, spread into nearby tissues, appear very different from normal cells, and may progress to a higher grade and become glioblastoma. Grade IV tumors (e.g., glioblastoma) grow and spread very quickly; the cells do not look like normal cells, and may show areas of dead cells.

Symptoms

The symptoms caused by a brain tumor depend on its location in the brain, functions controlled by that part of the brain, and the size and grade of the tumor (NCI). Although the following symptoms are seen in brain tumor patients, other conditions may show the same symptoms. Headaches in the morning, which go away after vomiting. Frequent nausea and vomiting are not uncommon. Problems in normal speech, vision, and hearing are common. Trouble in walking and loss of balance may also be present. Depending on the location of the tumor in the brain, weakness on one side of the body may be found. Other symptoms include seizure, and unusual sleepiness and personal behavior.

Diagnosis

Early Symptoms (mentioned elsewhere in this chapter and other chapters in this volume and in volume 1) necessitate immediate consultation with a physician. If the doctor suspects a brain tumor, a biopsy can be done to remove a sample of the tissue from the brain by removing a small part of the skull and using a needle. If a cancer is diagnosed under the microscope, the surgeon may remove as much tumor as safely possible during the same surgery or later, after detailed examination of the biopsy sample. A pathologist may check the cancer cells in the biopsy to find out the type and grade of the brain tumor and if the tumor is likely to grow and spread. An imaging modality such as computed tomography (CT) or magnetic resonance imaging (MRI) can be used to find out if any cancer cells remain after surgery. These and other imaging procedures are also used to diagnose spinal tumors.

Prognosis

Prognosis (chance of recovery) and treatment depend on a large number of factors, most of which are enumerated below (NCI).

1. The Type, grade, and location of the tumor in the brain.
2. Whether the tumor can be removed by surgery; if not, radiotherapy or chemotherapy, or both are alternate treatments.
3. Prognosis also depends on whether cancer cells remain after surgery.
4. Late or early diagnosis and whether the cancer has recurred.
5. The health and age of the patient.
6. The presence or absence of relevant gene mutations.
7. Whether there is a single tumor or more than one tumor in the brain.
8. Use of an imaging procedure to determine whether the tumor is responding to the treatment or is continuing to grow and spread.

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Chapter 2

Brain Tumor Classification Using Magnetic Resonance Spectroscopy

Juan M. García-Gómez

Abstract The systematic compilation of Magnetic Resonance Spectroscopy (MRS) has allowed the application of statistical and signal processing techniques to analyze the contribution of metabolites and other compounds in the brain tissues. The complex nature of the MR spectra and the intrinsic difficulty of the Brain Tumor (BT) classification has led researchers towards the Machine Learning discipline, as an objective, as well as practical, methodology for discovering common patterns in the MR spectra acquired from the tumor tissues. This chapter tries to introduce the reader in the classification of brain tumor using MRS. The classification of the most prevalent types of brain tumors using MRS has been largely studied by several authors. Recently, classifiers for the childhood and for a wider range of types of tumors have been also obtained. Furthermore, incremental learning is a promising solution for the dynamism of the clinical environments. During the text we will justify the necessity of agreed acquisition protocols and prospective evaluation of the automatic classifiers to improve the predictive power of the classifiers. The aim of this chapter is to give a practical perspective of the automatic classification of brain tumors using magnetic resonance spectroscopy through the development of Clinical Decision Support Systems (CDSSs) and multicenter studies.

J.M. García-Gómez (✉)
Informatica Biomedica, Instituto de Aplicaciones de las Technologias de la Informacion y de las Comunicaciones Avanzadas, Universidad Politecnica de Valencia, Valencia, Spain
e-mail: Juanmig@ibime.upv.es

Keywords Magnetic resonance spectroscopy · Pattern classification · Brain tumors · Decision support systems · Multicenter evaluation study

Introduction

MRS is an in-vivo noninvasive methodology requiring no ionizing radiation that allows a profile of the metabolites within a tissue to be obtained. The systematic compilation of MRS following agreed acquisition protocols has allowed the application of statistical and signal processing techniques to analyze the contribution of metabolites and other compounds in the brain tissues.

Since the publication of the seminal paper by Preul et al. (1996), one major challenge during the last 2 decades has been the development of objective procedures to assist radiologists in the diagnosis of brain tumors by means of automatic classification of MRS signals from the patients.

The complex nature of the MR spectra and the intrinsic difficulty of the BT classification has led researchers towards the Machine Learning discipline, as an objective, as well as practical, methodology for discovering common patterns in the MR spectra acquired from the tumor tissues.

This chapter tries to introduce the reader in the classification of brain tumor using MRS. The application of the machine learning methodology will guide the exposition of the subject, illustrating the text through examples involving multicenter datasets. Along the chapter, we will try to range the next learning objectives:

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1. The first learning objective of the chapter will be to design of a brain tumor classification study with MRS based on the machine learning methodology. This general framework will lead us through the different steps to solve the automatic classification.
2. To enumerate the pre-processing steps needed to prepare the MR spectra for a correct classification study.
3. To summarize the feature extraction techniques applied to brain tumor diagnosis with MRS and to review relevant results in multicenter studies.
4. To summarize the classification techniques applied to brain tumor diagnosis with MRS and to review relevant results in multicenter studies and trends.
5. To justify the necessity of a correct evaluation of the classification results and to review a comparative evaluation with retrospective and prospective datasets.
6. To cite secondary outcomes of the automatic classification of brain tumors to analyze the contribution of metabolites, discover heterogeneous patterns, and detect outliers in the MRS datasets.
7. To cite Clinical Decision Support Systems (CDSSs) for brain tumor diagnosis using MRS.

MRS Classification Overview

The life cycle of a Brain Tumor classification study based on MR spectroscopy mainly follows the Machine Learning methodology for solving a Pattern Recognition problem. It is composed of two main phases: the Training phase and the Recognition phase (see Fig. 2.1). During the Training phase, a set of signals following (the training corpus) a acquisition protocol is used to adapt a classification function. In this phase, a preprocessing and a features extracted from the signals are established. Afterwards, an adaptive model is fitted, selected and evaluated trying to obtain the optimal generalization for predicting new cases. Once the model is ready, it can be incorporated into a CDSS to be used for the prediction of new cases, where the preprocessing and feature extraction steps will be carried out before applying the classification function.

The rest of the chapter reviews the main techniques of each step of the Machine Learning methodology applied to Brain Tumor classification with MRS. Section "MRS Classification Overview" specifies the well-established pre-processing pipeline agreed in the eTUMOR project for normalizing MR spectra. In section "Preprocessing Magnetic Resonance Spectroscopy" the main pattern recognition techniques for extracting relevant features from MR spectra are studied. That section ends with a review of the effect of feature extraction from MRS in brain tumor classification. Section "Feature Extraction" studies the Machine Learning approach for classification, its techniques and its application to different problems of brain tumor diagnosis. The relevance of an accurate evaluation is studied in section "Peak Integration" by comparing retrospective and prospective evaluations of brain tumor classifiers. The use of the classification results to interpret of signal patterns, detect outliers, and perform quality control of MRS biobanks is presented in section "Stepwise Algorithm for Feature Selection in Classification". Before conclusions, section "Relieff Feature Selection" provides an enumeration of CDSS for brain tumor diagnosis using MRS.

Preprocessing Magnetic Resonance Spectroscopy

A spectrum acquired with a Time Echo (TE) <45 ms is usually considered a Short TE spectrum, and a Long TE spectrum otherwise. Different criteria have been argued in favor and against every option (e.g. Majos et al. (2004)), whereas the multicenter INTERPRET

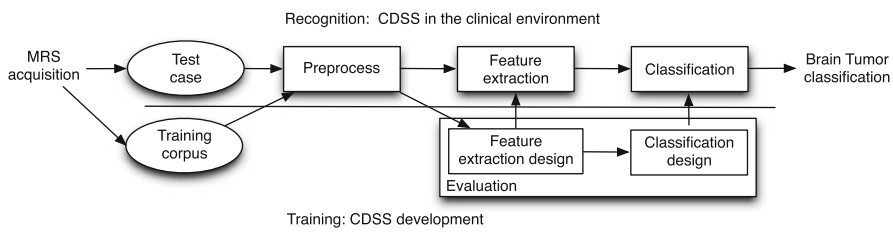

Fig. 2.1 Design of a brain tumor classification with MR spectroscopy based on the machine learning approach

and eTUMOUR projects[1] defined protocols based on the acquisition of both Short TE and Long TE spectra for the same patient.

Short TE (20–35 ms) ^{1}H MRS allows to observe several metabolites and other compounds considered useful for tumor classification: macromolecules (MM; 5.4 ppm, 2.9 ppm, 2.25 ppm, 2.05 ppm, 1.4 ppm and 0.87 ppm), myo-Inositol (mI) and Mobile Lipids (ML). However, Short TE signals are more sensible to artifacts, show a large number of overlapping peaks, and a strong MM-/ML-originated baseline. Long TE (about 135 ms) ^{1}H MRS is less informative than Short TE, because resonances with short T2 may be lost. However, lipid resonances (1.3 and 0.9 ppm) and MM will not be the dominating components at Long TE, making easier the analysis of the spectrum and possible the study of contributions from lactate (Lac, doublet at 1.33 ppm) and alanine (doublet at 1.47 ppm). BT classification requires the acquisition of homogeneous MRS. Therefore, acquisition protocols should be agreed at the very beginning of a classification study is started. As an example, data in the INTERPRET and eTUMOUR projects were acquired with Single Voxel (SV) ^{1}H MRS at 1.5 T, avoiding areas of cysts or necrosis and with minimum contamination from the surrounding non-tumoral tissue. Volume of interest size ranged between $1.5 \times 1.5 \times 1.5$ cm^3, (3.4 mL) and $2 \times 2 \times 2$ cm^3, (8 mL), depending on tumor dimensions. Long TE spectra were acquired with the PRESS sequence, and a recycling time (TR) between 1,500 and 2,020 ms, TE of 135 or 136 ms, spectral width of 1,000 or 2,500 Hz and 512 or 2,048 data points. Short TE were acquired using PRESS or STEAM sequences, with TR between 1,600 and 2,020 ms, TE of 20 or 30 ms, spectral width of 1,000 or 2,500 Hz and 512 or 2,048 data points. Before using the spectra for classification purposes, a quality control was carried out over both Long TE and Short TE spectra. Once a case is acquired following the agreed protocol, it is preprocessed to make it compatible, independent on the manufacturer and acquisition configuration. A worthy idea for consideration is that the preprocessing should be applied to each training and test case, hence, it is recommendable to be an automatic (or mostly automatic) procedure.

The next automatic pipeline was agreed within the eTUMOUR project. It has demonstrated its usefulness in multicenter studies, such as the ones carried out by Luts et al. (2008) and García-Gómez et al. (2009a). It consists of eight steps applied consecutively to the raw data file of a SV MR spectrum (Short or Long TE) from which an unsuppressed water acquisition is also available.

1. Eddy current correction is applied to the water-suppressed Free Induction Decay (FID) of each case using the Klose algorithm. An additional manual zero-order and first-order phase correction can be performed to improve the phase correction of the MR spectra, being strongly recommended for 3 T samples.
2. The residual water resonance is removed using the Hankel-Lanczos Singular Value Decomposition (HLSVD) time-domain selective filtering using 10 singular values and a water region of [4.33, 5.07] ppm.
3. An apodization with a Lorentzian function of 1 Hz of damping is applied.
4. Before transforming the signal to the frequency domain using the Fast Fourier Transform (FFT), an interpolation is needed in order to increase the frequency resolution of the low resolution spectra to the maximum frequency resolution used in the acquisition protocols. This can be carried out with the zero-filling procedure.
5. Afterwards, the baseline offset, which can be estimated as the mean value of the region [11, 9] U [–2, –1] ppm, is subtracted from the spectrum.
6. The normalization of the spectral data vector to the L2-norm is performed based on the data-points in the region [–2.7, 4.33] U [5.07, 7.1] ppm.
7. Depending on the Signal-to-Noise Ratio (SNR) and the tumor pattern, an additional frequency alignment check of the spectrum should be performed by referencing the ppm-axis to (in order of priority) the total Creatine (Cr) at 3.03 ppm or to the Choline (Cho) containing compounds at 3.21 ppm or the Mobile Lipids (ML) at 1.29 ppm.
8. Finally, the region of interest is restricted to [0.5, 4.1] ppm.

This pipeline can be adapted for the preprocessing of Magnetic Resonance Spectroscopic Imaging (MRSI) if

[1] Interpret acquisition protocols 2000. http://azizu.uab.es/INTERPRET/mrsdata/mrsdata.html. eTUMOR acquisition protocols 2003. http://www.etumour.net

we include few steps at the beginning of the process. First, a filtering of k-space data by a Hanning filter is applied. After that, a zero filling to 32×32 and a spatial 2D Fourier transformation obtain the time domain signals for each voxel.

Feature Extraction

Menze et al. (2006) defined two different approaches for feature extraction from MR spectra: (a) the quantification approach, and (b) the pattern recognition approach. The quantification approach is based on an inverse modeling of the resonance lines to infer the absolute or relative concentrations of the biochemical agents. Algorithms, such as AQSES, QUEST, AMARES, or LCModel are based on this approach.

In this chapter, we will mainly discuss about the second approach, based on feature extraction from the spectra with no assumption of an underlined model. Menze et al. (2006), Luts et al. (2008), and García-Gómez et al. (2009a) have achieved high-accurate results in brain tumor classification with pattern recognition-based techniques, whereas Opstad et al. (2007) and Weis et al. (2010) have argued in favor of quantification methods based on LCModel. The feature extraction methods based on pattern recognition can be applied directly to the spectra, with no case-specific parameter to be tuned. Hence, pattern recognition approach is considered to offer a good tradeoff between usability of the technique and reproducibility of the results.

Different methods have been applied for obtaining relevant features for brain tumor classification using MRS. Luts et al. (2008) examined the effect of feature extraction methods, mainly from the pattern recognition approach, prior to automated classification based on MRS for BT diagnosis. In that study, Peak Integration (PI) on selected metabolite resonance regions, peak height of typical resonances (PPM), Principal Component Analysis (PCA), Independent Component Analysis (ICA) and Wavelet (WAV) transformation, among others were compared on MRS and MRSI real data. Additionally, García-Gómez (2009a) evaluated these methods on multicenter prospective datasets. Several studies have included the simple PPM method to extract the maximum height values of the resonance peaks (Table 2.1) of the metabolites as inputs of the classification.

Table 2.1 Typical PPM of metabolite/molecule resonances and other molecules observed in short TE and the interval of integration used in PI

Resonance	Resonance frequency (ppm)	Region (ppm)
L2	0.92	0.15
L1	1.29	0.15
LAC	1.31	0.15
ALA	1.47	0.15
NAA	2.01	0.15
Cr	3.02	0.15
Cr2	3.92	0.15
Cho	3.21	0.15
Gly	3.55	0.15
Glx	2.04	0.15
GLx2	2.46	0.15
mI/Tau	3.26	0.15
mI2	3.53	0.15
Tau2	3.42	0.15
ALA2*	3.78	0.15

*ALA and others alpha-CH from amino-acids (e.g. Glx)

Peak Integration

Peak Integration (PI) is a simply form of estimating a quantity relative to the metabolite concentration, assuming that the amplitude of a metabolite resonance is proportional to the integral of its corresponding peaks in the spectrum. A precise estimation of the peak integrals is difficult due to several factors, including nonzero baseline, peak overlap, noise and also the discrete nature of the spectrum. In contrast, Peak Integration (PI) is a good choice when an accurate estimation of the metabolites is the objective of the study.

The areas of the regions around the resonance frequencies of the metabolites can be estimated by the trapezoidal rule. Let $(x(f_1), \ldots, x(f_l))$ be a discretized sample of the function $x(f)$ from which the integral with respect to f in a the range $(f_1, \ldots, f_l)$ is wanted to be approximated $I = \int_{f_1}^{f_l} x(f)df$. In practice, the trapezoidal integration is computed as:

$$\Delta f = (f_2 - f_1, \ldots, f_l - f_{l-1})$$

$$x' = \left(\frac{x(f_1) + x(f_2)}{2}, \ldots, \frac{x(f_{l-1}) + x(f_l)}{2} \right)$$

$$I = \Delta f \cdot x'$$

For each selected metabolite resonance the area under the frequency peak in the magnitude spectrum is calculated. Several studies have used fifteen ranges for Short TE spectra integrated within a window of 0.15 ppm around the expected chemical shift of the main resonances of the metabolites (Table 2.1).

Stepwise Algorithm for Feature Selection in Classification

StepWise (SW) is one of the most extended algorithms for solving the feature selection task. SW consists in a greedy hill climbing approach where the subset of features with the highest performance measure will be selected in each step and modified in the next step by the addition or deletion of one variable in the model. To select the next model, the algorithm compares the visited models by a measure over a validation dataset. Garczarek (2002) defined measures of the performance, such as, the Ability to Separate (AS) to check the unlike the classes are after the transformation carried out by the model, by means of the euclidean distance between the true posterior probability, $p(c|\mathbf{x})$, and the posterior probability of the model $p(c|\mathbf{x};\boldsymbol{\Theta})$.

Relieff Feature Selection

ReliefF is a feature selection method based on how well features distinguish between instances that are near to each other. In classification problems, the quality of each variable is calculated by the accumulation of the distance between randomly selected instances and their k-nearest neighbors of a different class minus the distance to the k neighbors of the same class. To make comparable the variables, the distance is normalized by the range of the feature. For neighbors of different classes, a large distance for a variable will substantially increase the quality of the variable, whereas for neighbors of the same class, a large distance for a variable will substantially decrease its quality. As a result, a discriminative variable will have a large distance with samples of other classes and a short distance with samples of the same class.

Principal Components Analysis (PCA)

PCA is a well-known projection method for studying the variability in multivariate data.Consequently, when applied to MR spectra, we will assumed the case x in frequency domain as a D-dimensional space of variables $(x_1, \ldots, x_D)$. PCA searches in the observational D-dimensional space those p directions (called principal components) where data have the highest variability. Each principal component $i = 1, \ldots, p$ defines one direction of variability by means of a loading vector $\mathbf{w}_i$, and for each case $\mathbf{x}$, the principal component score z_i is given by $z_i = \mathbf{w}_i^T \cdot \mathbf{x}$, assuming zero empirical mean. PCA finds the loading vector $\mathbf{w}_1$ that maximizes the variance of the principal component scores z_i, i.e. $\mathbf{w}_1 = \arg\max_{||\mathbf{w}_1||=1} Var(z_1)$, subject to the constraint $||\mathbf{w_1}|| = 1$. The second (or a higher) principal component is defined is the same way, but also constrained to orthogonality to the first (other) component(s), $\mathbf{w}_1 \cdot \mathbf{w}_2 = 0$. The transformation matrix W, composed by the loading vectors $\mathbf{w}_p$ is usually computed by means of the eigenvalue decomposition of the covariance matrix of the original cases. Once principal components are obtained, it is usual to represent each case by means of a vector of the p-firsts z-scores.

Functional Data Analysis

The MR spectrum can be seen as a function defined on time, $x(t)$, or on frequency, $x(f)$, composed by the contributions of a mixture of resonances of metabolites. Pattern Recognition (PR) methods for classification and clustering are usually applied on data of finite-dimensional spaces, but they cannot be directly applied to infinite-dimensional space (such as a function, a temporal series, or a curve). Although the previous methods are based on the discretization of the frequency interval of interest, they have been successfully applied for MRS classification in previous studies. Nevertheless, the space resulting from this multidimensional approach results in highly correlated high-dimensional data that should be taken into account when estimating the predictive models. Therefore, regularization techniques or dimensional reduction should be applied to avoid overfitting.

The alternative proposed by Ramsay and Silverman (2002) consists in fitting the curve of each spectrum to a linear combination of l basis functions $x(f) = \sum_{i=1}^{l} \alpha_i \upsilon_i(f)$, such as cubic splines, or wavelets. This can be carried out by the minimization of a least squares fitting criterion with a regularization term over the roughness of the second derivative of the fit. Then, the resulting l-vector $\boldsymbol{\alpha}$ of coefficients can be the input of the classifiers as a finite-dimensional representation of the spectrum.

In the functional version of PCA, each eigen vector $\mathbf{w}_i$ of the multivariate data $\mathbf{x}$ now corresponds to a eigen function $\xi_i(f)$ and the i eigen component score is $z_i = \int \xi_i(f)x(f)$. In fact, functional Principal Component Analysis (fPCA) finds the eigen functions $\xi_i(f)$ that maximizes the variance of the principal component scores z_i, subject to the constraint $\int \xi_i^2(f)df = 1$ and the orthogonality to all the previous principal components. As a result, we can represent each function $x_i(f)$ (MR spectrum) by a vector of scores z_i obtained by fPCA.

Wavelet Transform and Multi-resolution Analysis

The wavelet transform consists in carrying out translations and scale transformations of a prototypical wavelet function ψ in order to adjust the shape of a signal and to successively obtain a linear expansion of it with coefficients $\gamma(s, \tau)$. Mathematically this can be expressed as:

$$x(t) = \iint \gamma(s,\tau)\psi_{s,\tau}(t)d\tau ds,$$

where $x(t)$ is the signal and the variables s and τ are referred to the translation and scale dimension. Each scaled and translated wavelet $\psi_{s,\tau}(t)$ is called *child wavelet* and is generated from a common *mother wavelet* $\psi(t)$ by $\psi_{s,\tau}(t) = \frac{1}{\sqrt{s}}\psi(\frac{t-\tau}{s})$.

The wavelet is defined as a finite length or fast decay wave with the *admissibility* and the *regularity conditions*. These properties imply that the Fourier transform of $\psi(t)$ tends to zero for low frequencies and therefore their behavior is similar to a band pass filter. Using this wavelet transform and taking into account the filter behavior of the *wavelet* and *scaling* functions, the signal can be divided into different resolution levels. As a result, each MR spectrum can be represented by the parameter-space composed by the $\gamma(s, \tau)$ coefficients. Afterwards it can be applied some feature selection procedure (such as SW in 3.2) to obtain an optimal input vector for classification.

Independent Component Analysis

The motivation to apply ICA to a set of MR spectra is due to the presence of partial volume effects. Partial volume effects result in the fact that a signal from a specific voxel can contain components of different tissue types. The input for the ICA method is the full region of interest of the real spectrum.

Given n MR spectra $(x_1(t), \ldots, x_n(t))$, each one composed as a linear combination of n independent sources, $x_i(t) = \sum_{j=1}^{n} a_{ij}s_j(t), \forall i = 1, ..., n$, ICA attempts to un-mix the sources $s_j(t)$. Let $\mathbf{X} = \{x_i(t_k)\}_1^n$ the $m \times n$ matrix of the discretized cases $x_i(t)$, such as, $\mathbf{X} = \mathbf{SA}$, where $\mathbf{S}$ contains the independent sources and $\mathbf{A}$ the linear mixing coefficients. ICA estimates the un-mixing matrix $\mathbf{W}$ that makes $\mathbf{XW} = \mathbf{S}$.

Due to the Central Limit Theorem, ICA assumes that the generative model $\mathbf{X}$ tends to be more Gaussian than the sources $\mathbf{S}$. As a consequence, the optimal $\mathbf{W}$ is such that maximizes the non-gaussianity of the sources. Once ICA is obtained for the training dataset, coefficients in the $\mathbf{S}$ basis for a new case $x^*(t) = (x^*(t_1), \ldots, x^*(t_m))$ it can be easily computed as $(\mathbf{S}^T\mathbf{S})^{-1}\mathbf{S}^T x^*(t)$. Most ICA algorithms start with a pre-whitening step, based on a PCA of the observations. After pre-whitening, a dimensionality reduction is obtained in the source signal subspace.

Feature Extraction for Brain Tumor Classification Based on MR Spectra

Several studies have investigated the effect of feature extraction for brain tumor classification based on MR spectra. Despite of the simplicity of PI, García-Gómez et al. (2009a) obtained high performances in several pairwise and multi-class classification tasks