Spinal Cord Tumors

Kenan I. Arnautović
Ziya L. Gokaslan
Editors

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Editors

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I dedicate this book to the memory of my parents, Azijada and Ibrahim, who always taught me human decency and to aim for perfection with whatever I do; to my family, Sanja, Aska, and Alisa, with limitless love; to my mentors Professors Yasargil, Al-Mefty, de Oliveira, Boop, Samii, and Krisht who still keep me on my toes; and to my patients with spinal cord tumors with utmost appreciation for putting their trust, life, and function in my hands.

—Dr. Kenan I. Arnautović

I dedicate this book to the memory of my father Ibrahim and my mother Gonul; my siblings, Husnu, Tunc, and Nadide, who have been an inspiration and wonderful role models in my life; to my wife, Ayse Gul; to my children, Aaron and Hannah, for their unconditional love, understanding, and support; and to my mentors Drs. Robert Grossman, Raymond Sawaya, Henry Brem, Paul Cooper, Thomas Errico, Gordon Engler, as well as the many wonderful colleagues, residents, fellows, and staff from each I learned a tremendous amount; and most importantly, to my patients with spinal cord tumors and their loved ones for their incredible trust and most humbling bravery.

—Dr. Ziya L. Gokaslan

Foreword

"The brain may be forgiving, but the spinal cord is not" is an axiom that generations of neurosurgeons have inherited and passed on to accentuate the seriousness of spinal cord surgery. With their relative rarity, available literature dedicated to spinal cord tumors has been sparse and collective expertise has been missing. Many advances have taken place toward the improvement of diagnosis, treatment, and outcomes of these otherwise dreadful diseases. Drs. Arnautović and Gokaslan are to be commended for their effort to bring together a comprehensive text that covers all aspects of spinal cord tumors in a scholarly and expert manner. Like all the beneficiaries of this work, patients and physicians alike, I am deeply grateful for their endeavor and congratulate them for their excellent contribution. Knowing them personally, I would not expect anything less than superb work, and I say that with a sense of pride.

Although advances in imaging, rehabilitation, monitoring, and radiation have markedly improved the outcomes of patients with spinal cord tumors, it remains that an overwhelming number of these lesions are treated surgically with the expectation of cure. Hence, surgical technique is the most crucial factor in treatment, and subsequently, microsurgical techniques are indispensable in tackling these tumors and paramount for success.

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Foreword

Aside from metastases to the vertebral column, spinal neoplasms are relatively rare in the average neurosurgeon's practice. That being said, spinal cord lesions can be challenging to manage surgically and devastating to a patient's quality of life, if inadequately and/or poorly treated. To produce this book, Drs. Arnautović and Gokaslan have assembled an international cast of neurosurgeons and affiliated specialists with expertise in the management of spinal neoplasms. The result is an opus that provides a comprehensive and contemporary overview of their treatment. I congratulate the authors for producing a volume that is informative while remaining quite readable. For neurosurgeons—both resident and graduate—looking for a comprehensive overview of the topic, I highly recommend this book.

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Contents

1 History of Spinal Surgery and Surgical Treatment of Spinal Intradural Tumors 1
Bruno Splavski

2 Epidemiology of Spinal Cord Tumors 31
Yusuf Şükrü Çağlar and İhsan Doğan

3 Spinal Cord Anatomy 43
David B. Choi, Gahie Nam, Darren M. Groh, Sohail Syed, Jared S. Fridley, and Ziya L. Gokaslan

4 Diagnostics and Differential Diagnostics of Spinal Cord Tumors 55
Zulejha Merhemic and Majda M. Thurnher

5 Neuropathology of Spinal Cord Tumors 71
Stephanie Livingston and Blazej Zbytek

6 Neurological Aspects of Spinal Cord Tumors 91
Tania Hassanzadeh, Sushma Bellamkonda, Sajid S. Suriya, Farzad H. Adl, Andrei V. Alexandrov, and Martin M. Mortazavi

7 Intraoperative Neurophysiology during Surgery for Spinal Cord Tumors 109
Vedran Deletis and Kathleen Seidel

8 Neuro-Anesthesiology Considerations in Spinal Cord Tumors 127
Zana Borovcanin, Vijay Ramaiah, and Jacob Nadler

9 Spinal Meningiomas 147
Roberto Delfini, Benedetta Fazzolari, and Davide Colistra

10 Spinal Schwannomas 161
Madjid Samii and Mario Giordano

11 Management of Intradural and Extradural Spinal Schwannomas . . . 171
Alvin Y. Chan, Andrew K. Chan, Catherine A. Miller, Line G. Jacques, and Praveen V. Mummaneni

12 Spinal Cord Tumors in Neurofacomatosis 187
Frederick A. Boop, Jimmy Ming-Jung Chuang, and Chenran Zhang

13 Spinal Cord Astrocytomas 211
Mirza Pojskić and Kenan I. Arnautović

14 Spinal Cord Hemangioblastomas 243
Nickalus R. Khan, Aqsa Ghazanfar, Nitin Patel, and Kenan I. Arnautović

15 Myxopapillary Ependymomas 273
Ibrahim Omerhodžić, Mirza Pojskić, and Kenan I. Arnautović

16 Pediatric Spinal Cord Tumors: Diagnosis and Management 301
Jaafar Basma, Jimmy Ming-Jung Chuang, and Frederick A. Boop

17 Spinal Cord Ependymomas 325
Tom Kosztowski, Jared S. Fridley, and Ziya L. Gokaslan

18 Malignant Intramedullary Spinal Cord Tumors 337
Nir Shimony, Sara Hartnett, Brooks Osburn, Mari Groves, and George I. Jallo

19 Intradural-Extramedullary and Intramedullary Spinal Metastases 365
Alan Siu, Michael LaBagnara, Kenan I. Arnautović, and Jason A. Weaver

20 Sacral Spinal Tumors 381
David B. Choi, Sanjay Konakondla, Sean M. Barber, Jared S. Fridley, and Ziya L. Gokaslan

21 Rare Spinal Cord Tumors 397
Nir Shimony, Brooks Osburn, Sara Hartnett, Mari Groves, and George I. Jallo

22 Dumbbell Tumors of the Spine 433
Mirza Pojskić and Kenan I. Arnautović

23 Instrumented Fusion after Spinal Cord Tumor Resection 457
Michael A. Galgano, Jared S. Fridley, and Ziya L. Gokaslan

24 Radiosurgical and Radiation Considerations for Residual, Recurrent and Malignant Spinal Cord Tumor 467
Jason Weaver

25 Complications in Treatment of Spinal Cord Tumors and Prevention Surgical Strategies 485
Marko Kovacevic, Bruno Splavski, and Kenan I. Arnautović

26 Rehabilitation of Patients with Primary Intradural Tumors of the Spinal Cord 511
Philippines Cabahug, Alba Azola, and R. Samuel Mayer

Correction to: History of Spinal Surgery and Surgical Treatment of Spinal Intradural Tumors C1

Correction to: Epidemiology of Spinal Cord Tumors C3

Index 529

Introduction

Since the start of my neurosurgical career some 30 years ago, I was fascinated by spinal cord tumors and their treatment. These tumors occur in a very limited space of spinal cord and spinal nerves (<10 mm anterior-posterior and <15 mm transverse diameters); they extend into adjacent and similarly limited subarachnoid, subdural, and spinal canal spaces within functionally numerous, extremely tight, high value central nervous system (CNS) "real estate" with a relatively limited blood supply. They are probably at the top of most challenging CNS tumors to treat. Fortunately (or not), they are predominantly benign lesions, histologically.

As I looked closer, I realized and learned that it takes an average of 2 years from the first appearance of symptoms to diagnose spinal cord tumors. Furthermore—and as I talked to my mentors, all fathers of micro-neurosurgery—I found out that none of them have significantly focused on those lesions for unclear reason, perhaps due to their rare occurrence (<15% of all CNS tumors). I then wondered, to whom do these tumors belong? To micro-neurosurgeons, to spine surgeons, or to pediatric neurosurgeons? And I still do not have an answer. Finally, when I look in the neurosurgical literature, I always found these types of tumors buried at the end of the tumor or spine section, seemingly neglected and underestimated. Similarly, books regarding the subject are scarce at best. As I significantly increased my experience in treating spinal tumors, I respected them even more and realized how difficult is it to treat them. Finally, unlike any other neurosurgical pathology, there is a very limited number of authors who have significant series of several dozens or very unlikely hundreds of cases in the literature.

The goal of this book is to provide an in-depth, contemporary review of all—or at least most—aspects of treatment of spinal cord tumors by experienced authors and their teams. The attempt is to include as many figures as possible, and even some video clips, to illustrate the text in the best way possible. We can only hope that many neurosurgeons will find help and guidance reading this book in preparation for their surgeries or at least get inspired to pursue an interest in this ever-fascinating part of our beloved specialty.

Memphis, TN, USA — Kenan I. Arnautović

Despite my 3 decades of experience in treating spinal neoplasms as a surgeon, I am truly humbled by how challenging treating patients with spinal cord tumors can be. Perhaps no other pathology in our field is a better reminder of how privileged we are as neurosurgeons to be trusted in this way and how brave and inspiring our patients are in placing their well-being, hopes, and dreams in our hands. It is a responsibility I know that we—as neurosurgeons—take incredibly seriously.

The risks of surgical intervention in the spinal cord are very high and the consequences of surgery to our patients are very significant and life altering. Thus, not only surgical resection of these tumors remains to be a technical feat but even the decision of when and on whom to operate can be very difficult.

I was taught from the very early days of my residency training by my senior mentors that the brain can be forgiving, but the spinal cord is "very expensive real estate"; hence, it needs to be treated with utmost respect and care. There is no question that, over the past several decades, imaging, surgical techniques and magnification, operative tools, electrophysiological monitoring, and postoperative ICU care have all dramatically improved. Many neurosurgeons and other specialists have contributed to the improvement of surgical outcomes in patients with spinal cord tumors.

This book is an attempt to compile current information in the literature, summarize recent advances in the field, and try to communicate the collective wisdom, experience, and lessons learned over the years in a practical format.

I hope we have achieved this objective at the end and that you remain committed to contributing to the advances in the field, but are also always reminded, humbled, and inspired by how our patients with spinal cord tumors deal with the challenges they face on a daily basis.

Providence, RI, USA Ziya L. Gokaslan

Abbreviations

AA	Anaplastic astrocytoma
ABC	Aneurysmal bone cyst
AD	Axial diffusivity
ADC	Apparent diffusion coefficient
ADL	Activity of daily living
AFO	Ankle, foot orthosis
AGG	Anaplastic ganglioglioma
AION	Anterior ischemic optic neuropathy
AIS	America Spinal Injury Association Impairment Scale
ASA	American Society of Anesthesiologists
AVMs	Arteriovenous malformations
BART	Blood Conservation using Antifibrinolytics in a Randomized Trial
BCR	Bulbocavernosus reflex
BED	Biologically effective dosages
BSCB	Blood-spinal cord barrier
Bx	Biopsy
cfDNA	Cell-free deoxyribonucleic acid
CMAP	Sphincter compound muscle action potential
CNS	Central nervous system
CRAO	Central retinal artery occlusion
CSF	Cerebrospinal fluid
CST	Corticospinal tract
CT	Computed tomography
CTA	Computed tomography angiography
CUSA	Cavitron ultrasonic surgical aspirator
DAs	Diffusely infiltrating astrocytomas
DLT	Double lumen endobronchial tube
DNA	Deoxyribonucleic acid
DRAP	Dorsal root action potentials
DSA	Digital subtraction angiography
DTI	Diffusion tensor imaging
DTT	Diffusion tensor tractography
DVT	Deep venous thrombosis
DWI	Diffusion-weighted imaging

EAS	External anal sphincter
EBRT	External beam radiation therapy
ECOG	Eastern Cooperative Oncology Group
EEG	Electroencephalogram
EGFR	Epidermal growth factor receptor
EMA	Epithelial membrane antigen
EMG	Electromyography
EUS	External urethral sphincter
EVN	Extraventricular neurocytoma
FA	Fractional anisotropy
FDA	Food and Drug Administration
fEMG	Free run electro-myography
FEV_1	Forced expiratory volume in 1s
FIM	Functional Independence Measure
FISH	Fluorescence in situ hybridization
FLAIR	Fluid-attenuated inversion recovery
GBM	Glioblastoma
Gd-DTPA	Gadopentetic acid
Gd-MRI	Gadolinium-enhanced magnetic resonance imaging
GFAP	Glial fibrillary acidic protein
GTR	Gross total resection
HIF-1α	Hypoxia-inducible factor 1-alpha
HK2	Hexokinase 2
ICF	International Classification of Function
IDH	Isocitrate dehydrogenase
IESCT	Intradural-extramedullary spinal cord tumor
IMRT	Intensity-modulated radiation therapy
IMSCT	Intramedullary spinal cord tumor
IOM	Intraoperative neurophysiological monitoring
ION	Ischemic optic neuropathy
IONM	Intraoperative neurophysiological monitoring
ISCT	Intramedullary spinal cord tumor
ITI	Inter-train interval
IV	Intravenous
KAFO	Knee, ankle, foot orthosis
KPS	Karnofsky Performance Score
LC	Local control
LE	Lower extremity
LGSI	Low-grade astrocytoma, subtype indeterminate
LMN	Lower motor neurons
LMNOP	Location of disease, mechanical stability, neurological risk, oncological parameters, preferred treatment
LMWH	Low molecular weight heparin
LOH	Loss of heterozygosity
MAC	Minimal alveolar concentration

MAP-2	Microtubule-associated protein-2
MAPK	Mitogen-activated protein kinase
MEN	Multiple endocrine neoplasia
MEP	Motor evoked potential
MGMT	Methylguanine-DNA methyltransferase
MIOM	Multimodality intraoperative monitoring
MIS	Minimally invasive surgery
MLS	Myxoid liposarcoma
mMEP	Muscle motor evoked potentials
MMP	Matrix metalloproteinase
MPE	Myxopapillary ependymoma
MPNST	Malignant peripheral nerve sheath tumor
MRA	Magnetic resonance angiography
MRI	Magnetic resonance imaging
MTOR	Mechanistic target of rapamycin
n/a	Not applicable
NAP	Nerve action potentials
NF1	Neurofibromatosis 1
NF2	Neurofibromatosis 2
NIH	National Institutes of Health
NMB	Neuromuscular blockade
NOMPS	Neurologic, Oncologic, Medical, Pain and Support
NOMS	Neurological, oncological, mechanical and systemic evaluation
NOS	Not otherwise specified
NSAID	Nonsteroidal anti-inflammatory drug
NSE	Neuron-specific enolase
NST	Nerve sheath tumors
OLIG2	Oligodendrocyte transcription factor
OS	Overall survival
PAs	Pilocytic astrocytomas
PCR	Polymerase chain reaction
PDGFR	Platelet-derived growth factor receptor
PDH	Phosphorylation of pyruvate dehydrogenase
PDK1	Pyruvate dehydrogenase kinase 1
PDS	Polydioxanone sutures
PE	Pulmonary embolism
PET	Positron emission tomography
PFS	Progression-free survival
PHD	Phosphorylation of pyruvate dehydrogenase
PION	Posterior ischemic optic neuropathy
PMAs	Pilomyxoid astrocytoma
PNET	Primitive neuroectodermal tumor
PNST	Peripheral nerve sheath tumors
PR	Progesterone receptor
PSO	Primary spinal oligodendroglioma

RANKL	Receptor activator of nuclear factor κ-B ligand
Ras-MAPK	Ras-mitogen-activated protein kinase
RCC	Renal cell carcinoma
RD	Radial diffusivity
RNA	Ribonucleic acid
ROI	Regions of interest
ROM	Range of motion
RT	Radiotherapy
SBP	Solitary bone plasmacytoma
SBRT	Stereotactic body radiotherapy
SCA	Spinal cord astrocytoma
SCD	Spinal cord dysfunction
SCE	Spinal cord ependymoma
SCG	Spinal cord germinoma
SCI	Spinal cord injury
SCSE	Spinal cord subependymoma
SCT	Spinal cord teratoma
SEC	Spine extraosseous chordoma
SEER	Surveillance, Epidemiology, and End Results
SINS	Spine Instability Neoplastic Score
SRS	Stereotactic radiosurgery
SRT	Spinal radiotherapy
SSEP	Somatosensory evoked potential
SSRS	Stereotactic spinal radiosurgery
STGC	Syncytiotrophoblastic giant cells
STR	Subtotal resection
SYN	Synaptophysin
TAO	Temporary arterial occlusion
tEMG	Triggered EMG
TES	Transcranial electrical stimulation
TIVA	Total intravenous anesthesia
TP53	Tumor suppressor protein 53
TSC	Tuberous sclerosis complex
TXA	Tranexamic acid
UE	Upper extremity
UK	United Kingdom
UMN	Upper motor neuron
VAE	Venous air embolism
VEGF	Vascular endothelial growth factor
VHL	Von Hippel-Lindau syndrome
VMAT	Volumetric modulated arc therapies
VPL	Ventral posterolateral nucleus
VS	Vestibular schwannomas
VTE	Venous thromboembolism
WHO	World Health Organization

History of Spinal Surgery and Surgical Treatment of Spinal Intradural Tumors

1

Bruno Splavski

1.1 Introduction

Neurosurgery may be one of the oldest medical professions and surgical disciplines. There is a proof that trephining was practiced by Neolithic people during prehistoric times. However, neurosurgery and spinal surgery as we know them today did not develop until the second half of the nineteenth century when a select few general surgeons in a handful of medical centers started to perform an assortment of brain and spinal surgical procedures. In particular, the history of spinal intradural tumor and spinal cord surgery remained relatively obscured and small in comparison to those of other parts of nervous system, including the spine. This type of surgery developed slowly and sporadically, gaining its prominence only recently, in the last few decades.

Surgical treatment of spinal intradural tumors has always been a demanding and challenging task for neurosurgeons worldwide because of the distinctive clinical and histopathological characteristics of these tumors, as well as their specific surgical anatomy. Because of that, the practice of spinal surgery and spinal cord surgery did not emerge as a separate specialty until the beginning of the last century. Hence, up-to-date and state-of-the-art diagnostics, surgical techniques, and tools only developed during the last few decades due to the expansion of operative microscopy and endoscopy, as well as intraoperative neurophysiology and systems for image-guided surgery, which provide the foundation for contemporary spinal intradural tumor and spinal cord surgery. Such techniques and armamentariums enabled not only the most accurate and precise tumor identification, but also the safe removal

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of tumors and satisfactory patient recovery, considerably diminishing the rate and scope of postoperative complications.

In this chapter, historical issues concerned with surgical treatment of spinal intradural tumors, as well as the timeline of spinal cord surgery development and improvements, will be discussed and explained.

1.2 Spinal Surgery in Antiquity

Due to its complexity, operating on spine and spinal cord was a heavy burden for ancient surgeons, who tried to avoid it. The scarce knowledge of spinal anatomy was only gained from sporadically observing spinal trauma cases.

The evidence of spinal disorders was limited and obscured. However, tuberculous spondylitis—which causes permanent spinal deformity—has been found in Egyptian mummies dated to 4000 BC, making it one of oldest diseases for which the evidence exists. It has also been documented in spinal remains from Iron Age Europe as well. Furthermore, a possible description of the successful use of spinal traction-reduction used to reverse a paralyzing cervical spine injury from circa 3000 BC may be the oldest neurosurgical procedure ever recorded [1].

1.2.1 Edwin Smith Papyrus

The earliest described experience-based examples of anatomical dissections were mentioned by ancient Egyptians during the fourteenth century BC, but medical practice of that time was grounded in superstition and magic rather than scientific knowledge, which was mainly nonexistent. Despite of that, ancient Egyptian surgeons recognized spinal trauma as a grave injury that resulted in poor outcome and typically death. The evidence of this can be found in the famous Edwin Smith papyrus from 1700 BC, which is one of the most valuable medical manuscripts ever discovered [2]. The scroll was purchased by an American Egyptologist, Edwin Smith (1822–1906) in Luxor, Egypt in AD 1862 and translated from the hieroglyphics and published in 1930 [3]. The text described six trauma cases of the cervical spine, including two obvious injuries to the spinal cord. It is the oldest description of spinal cord injury and infection with the first ever treatment management recommendations in the history of medicine [4]. Accordingly, the first traces of rudimental spinal surgery dated back to 1550 BC, making it one of the oldest surgical procedures known.

It was likely that the ancient Assyrians had some idea of the consequences of spinal cord injury, too, based on a famous relief from 650 BC found in Nineveh in modern-day Iraq. It depicted a dying lioness injured by arrows in the back and trying to crawl while struggling to move her paralyzed lower limbs, indicating spinal cord damage [5].

1.2.2 Alexandrian School

It may be said that the intellectual underpinnings of spinal surgery originated with the ancient Greeks in 300 BC, indebted to the illustrious Alexandrian school and based on Hippocratic writings that contained anatomic descriptions and descriptions of early spinal injury practice and conservative management. The ancient Greeks understood spinal cord injury with urinary incontinence to be a severe injury with a[1] particularly devastating prognosis. Hence, Alexandrian school surgeons were reluctant to pursue aggressive surgery on the spine or spinal cord. The main representative of that school, Herophilus (335–280 BC) (Fig. 1.1)—who was the most distinguished scholar and accomplished physician of the time—also avoided direct surgery on the spine. He was the first ancient physician to name the spinal cord as a caudal prolongation of rhombencephalon [7], and observed that damage to motor nerves may induce paralysis. Herophilus and his co-scholar Erasistratus (304–250 BC) performed human dissections for medical research for the first time in history, which became the main source of Greek anatomic knowledge. Both Herophilus and Erasistratus provided an outstanding early appreciation of the separate neural spinal cord pathways responsible for sensory and motor control [8].

Fig. 1.1 A sketch of Herophilus redrawn from an original painting by Joseph F. Doeve. Reprinted with permission from the collection of the Houston Academy of Medicine-Texas Medical Center Library

[1] It is known that Hippocrates (460–375 BC) himself provided specific evidence that was concerned with the clinical implications of spinal cord damage [6].

1.2.3 Galen of Pergamon

During the first century AD, Galen of Pergamon (AD 129–200) was the chief advocate of Hippocratic and Alexandrian medicine, but he contested Hippocrates' reference to the brain as merely a gland. Galen assigned control of voluntary action and sensation to the brain, which was carried through the medulla downward. He was the first surgeon to define the dural and pial coverings of the spinal cord [2]. He recognized also that spinal injury might result in neurological deficits, including motor weakness of the limbs, and that complete medullar transection was responsible for the loss of function below the level of cord damage [8]. He was also the first physician to propose the removal of compressive bone fragments from the vertebral canal in case of vertebral body fracture. Regrettably, following Galen's demise, there was no competent supplementary research of the nervous system's surgery for more than a millennium. But his remarkable scientific achievements, as well as several of his errors and misinterpretations, are still responsible for the great majority of the relevant medical texts from antiquity. His surgical competence and vast scientific knowledge made him a celebrated contributor to neuroanatomy in general and neurosurgery in particular.

1.3 Spinal Surgery in the Middle Ages, the Renaissance, and Beyond

Although Galen's outstanding accomplishments were still venerated by Arabic scholars and physicians of the middle ages, spinal surgery was mostly regarded as hopeless during this time. The academic centers of medicine and surgery moved to the Arabic and Byzantine controlled cities, which served as protectors of ancient medical teachings, as well as dogma.

1.3.1 Avicenna (Ibn Sina)

The finest representative of Arabic school was Avicenna (AD 980–1037), a prominent philosopher, academic, and physician from Persia whose encyclopedic writings enormously expanded ancient medical knowledge. Within his texts, one can find useful discussions of various types of spinal injuries that both evaluate their usually bleak outcomes and prognoses and justify non-surgical treatment.

1.3.2 Dogmatic Scholasticism

Following the decline of the Arabic schools, a transition to mediaeval dogmatic scholasticism occurred in Europe (AD 700–1500), characterized by unavoidable academic decline in every aspect of medical knowledge. Consequently, a deficiency of proper anatomical expertise—caused by the Catholic Church forbidding body

dissections—was responsible for poor outcomes of surgical management. Surgeons were unable to perform spine and spinal cord surgery, which remained virtually absent throughout the next few centuries.

Despite of that, the contributions of Mondino de Liuzzi (circa 1270–1326), a key anatomist of the late Middle Ages from Bologna, Italy should not be forgotten. He was credited as the restorer of anatomy after he wrote a manual for anatomic dissection for the first time in medical history [9].

At the same time, Guy de Chauliac (1300–1368), practicing in Montpellier and Avignon, France, publish his book *Chirurgia Magna* in 1363. De Chauliac was the most influential European surgeon of the fourteenth century, and his book became a standard medical reference for surgery for several subsequent centuries. It has also been regarded one of the most influential medical texts originated from the Middle Ages, which collated medical knowledge from ancient Greek and Arabic sources. Considering the circumstances and the backwardness of medicine in the European Middle Ages, his work was very innovative and astonishingly progressive for its time.

1.3.3 Andreas Vesalius

The sudden transfer from scientifically dormant medieval times to the open-minded and creative period of the Renaissance enabled the early groundwork of the present-day neurosurgery. As the new dawn for science and arts emerged, Andreas Vesalius (1514–1564), a physician and teacher who is considered the predecessor of neuroscience, published his masterpiece *De humani corporis fabrica* in 1543, establishing anatomy and body dissection as scientific disciplines. The books contributed enormously to the understanding of spinal anatomy as Vesalius was the physician to describe and illustrate the spinal cord and devised the names for every particular spinal level (cervical, thoracic, lumbar, sacral, and coccygeal). In fact, much of the terminology used for the spine today can be attributed to him [10]. Vesalius was one of the most distinguished medical scholars of his time and his influence on medical knowledge is still relevant today, more than 500 years later. His groundbreaking ideas and methods helped to free medicine in general and neuroscience in particular from the limitations imposed by the Middle Ages, moving it forward up to the modern era [7].

Vesalius's observations of the anatomy of the spinal cord were updated by the renowned Dutch anatomist Gerard Blasius (1625–1692). In 1666, Blasius clearly illustrated the cross-section of the medulla for the first time, identifying the distinction between the gray and white matter of the cord, as well as the spinal nerve roots, which increased the knowledge of neuroanatomy meaningfully in his era [2, 11].

The first classic clinical description of tuberculous spondylitis, leading to grave progressive and permanent spinal deformity with consecutive possible spinal cord compression, was given in 1782 by Percival Pott (1714–1788), a famous English surgeon and one of the founders of orthopedic surgery. Tuberculous spondylitis became known as Pott's disease in honor of this distinguished clinician who was generally regarded as one of the greatest surgeons of the eighteenth century [12].

1.4 The Beginnings and Evolution of Modern Spinal Surgery

Surgical methods, neuroscience, and neurosurgery developed unevenly and sporadically throughout the time, due to the lack of proper diagnostic strategies and appropriate instruments. Accordingly, spinal surgery also saw no major progress due to its complex mechanical procedures. It did not advance in the West until the beginning of the industrial revolution at the start of nineteenth century. Afterwards, it followed a general advancement in modern medicine and surgery, steadily but slowly.

It was during the beginning of the modern era in surgery during the nineteenth century that inhalation agents for general anesthesia were first used. In addition, the germ theory of infection was both recognized and accepted in conjunction with principles of antisepsis. The introduction of ether anesthesia not only released patients from pain during surgery but also allowed more extensive surgical procedures. The technique was first demonstrated in 1846 by an American dental surgeon William Morton (1819–1868) at Massachusetts General Hospital in Boston. A year later, chloroform for general anesthesia was introduced with absolute success in Edinburgh by James Young Simpson (1811–1870), a Scottish obstetrician, which soon became the widespread anesthetic of choice.

In the mid-nineteenth century, Louis Pasteur (1822–1895), a French microbiologist, observed and explained the relationship between bacteria and infectious diseases. From 1867, Joseph Lister (1827–1912)—a British surgeon and a pioneer of antiseptic surgery—was the first physician to promote the principles of antisepsis and the idea of sterile surgery [13]. Lister, practicing at Glasgow Royal Infirmary in Glasgow, UK applied Pasteur's theory to wound sepsis, introducing the technique of antisepsis, which brought about subsequent decrease in the mortality rate from postoperative wound infections. Thereafter, other antiseptic techniques followed, such as the use of surgical masks, operating gowns, hats, and latex gloves. Finally in 1886, Ernst von Bergmann (1836–1907), a physician from the University of Berlin, Germany who devoted a large part of his career to the surgery of neurological diseases [14], introduced the concept of asepsis by steam sterilization of instruments, which was another major breakthrough in reducing the rate of infection and improving postoperative outcomes. He also used heat sterilization of wound dressing material.

A pioneer in bacteriology, a German physician and scientist Robert Koch (1843–1910), demonstrated in 1877 how bacteria could be successfully isolated and cultivated, imposing the theory that infectious diseases were caused by microorganisms and summarizing his postulates on the etiology of wound infection. Following recognition of the germ theory of infection, a stream of antimicrobial innovations followed, providing the means to minimize, abolish, and treat surgical infections.

Further improvements in knowledge of spinal cord functional anatomy were developed by Charles Edouard Brown-Séquard (1817–1894), a French neurophysiologist, who pioneered advancement in neuroscience through experimental physiological observation. In 1846, he explained spinal cord injury as the cause of pain, temperature, and light touch sensation loss occurring at the opposite side of the damaged cord, while loss of motor function, vibration, position, and deep touch remained at the injured side of the cord itself because of the decussation of the fibers

carrying different features of sensation throughout the medulla (i.e., syndrome of cord hemi-section, characterized by ipsilateral hemiplegia and hypesthesia and contralateral analgesia—Brown-Séquard Syndrome) [2, 15].

The evolution of neurosurgery as a distinctive surgical discipline followed, happening step-by-step as a result of the personal interest in this field by a small number of talented professionals. Antony Chipault (1866–1920) from France, Ernst von Bergmann (1836–1907) and Fedor Krause (1857–1937) from Germany, and William Macewen (1948–1924) from Scotland all performed cranial and spinal procedures as well as general surgery. Simultaneously, William Keen (1837–1932) from Philadelphia in the United States was the first surgeon in the Americas to successfully remove a benign brain tumor in 1887.

French neurosurgical pioneer Antoine Chipault was the first surgeon in France to devote his practice on the surgery of neurological affections. He was also the first to use laminectomy in operative treatment of Pott's paraplegia in 1896.

1.4.1 William Macewen

The first cranial surgeries were done by a William Macewen (Fig. 1.2), who operated on a brain abscess in 1876, and resected his first cranial tumor in 1879 [16]. He also advanced spinal surgery by successfully operating on hematomas of the spine,

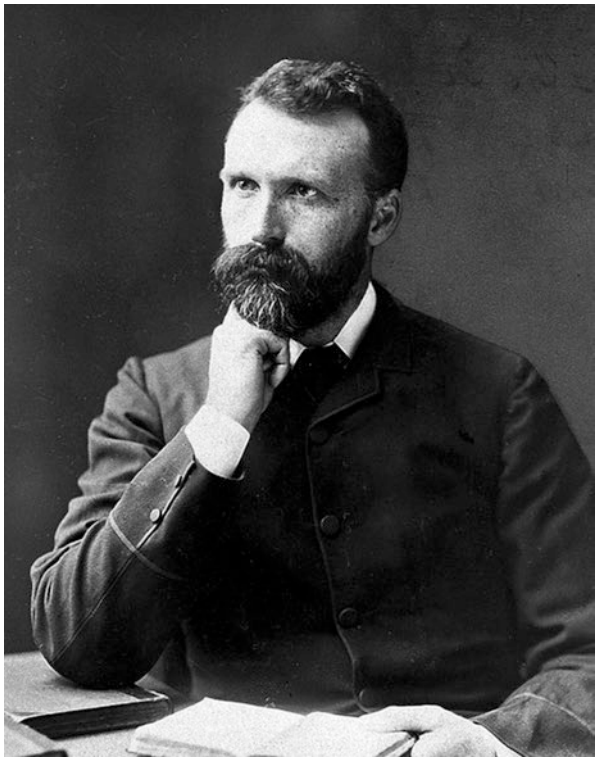

Fig. 1.2 William Macewen. Credit: "Sir William Macewen. Photograph" from the Wellcome Collection (https://wellcomecollection.org/works/qd7exx4c). CC BY (https://creativecommons.org/licenses/by/4.0/)

soon becoming a leading British surgeon and the first proponent of neurosurgery. His milestone study about pyogenic diseases of the brain and spinal cord was the first scientific description of the subject ever published [17]. Consequently, he was highly acclaimed for his endeavor and managed to succeed his mentor, Joseph Lister, to the Chair of Surgery in Glasgow, UK.

1.4.2 Elective Surgery on the Central Nervous System

The period from the 1880s to 1914 was an epoch marked by the development of new elective surgical methods for the central nervous system. The primary scientific participants were celebrated physicians, and pioneering neurologists and surgeons like John Hughlings Jackson (1835–1911), David Ferrier (1843–1928), William Gowers (1845–1915), and Victor Horsley (1857–1916), all of whom worked at the National Hospital at Queen Square, in London, UK (Fig. 1.3). Their concepts and ideas had a deep influence on further advancement of the field. Experimentation on animal models and a comprehensive interest in clinical practice resulted in fast progress in understanding detailed nervous system function.

However, it was not until the introduction of the exact localization of neural structures and lesions by clinical observation and examination that neurosurgery in general—as well as spinal surgery in particular—developed into a separate branch

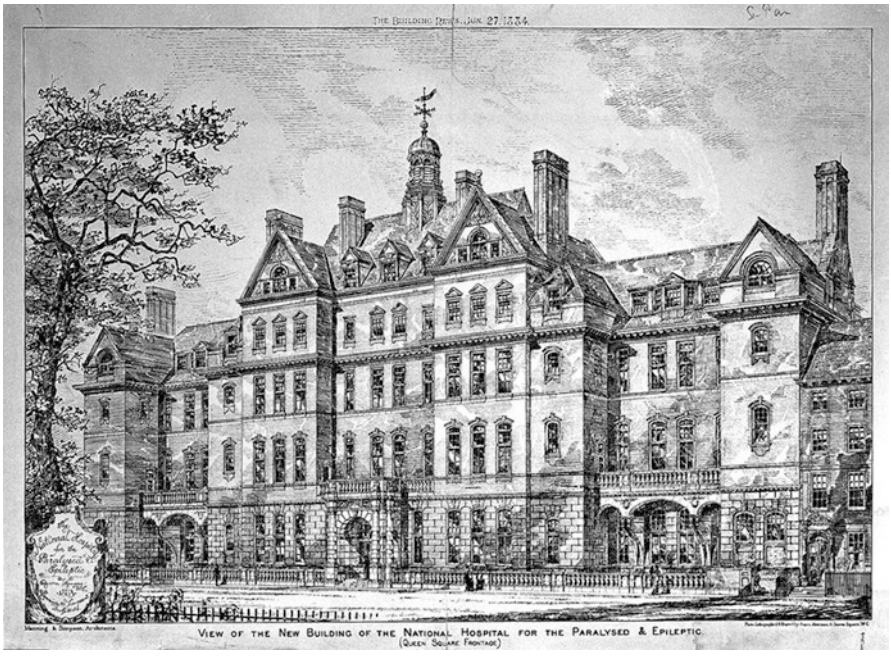

Fig. 1.3 National Hospital, Queen Square, London. Credit: "'National Hospitals for the Paralysed and Epileptic" from the Wellcome Collection (https://wellcomecollection.org/works/phmgcn3g). CC BY (https://creativecommons.org/licenses/by/4.0/)

of modern neuroscience. At the same time, skilled operative techniques together with precise experimental physiology created a framework for the further development of neurological surgery. Renowned British neurologist William Gowers (1845–1915), from National Hospital in London, introduced clinical examination, including patient history and physical signs and symptoms, making the exact localization of neural structures and lesions crucial in the diagnosis of neurologic disorders. His accurate observations of spinal cord structures enabled the first clinical identification of a removable intradural spinal tumor in 1887 [18].

1.4.3 Victor Horsley

Victor Horsley (1857–1916) was the first to encourage surgical removal of brain and spinal tumors following the exact localization and identification by neurologists (Fig. 1.4). In 1886 when he was only 28 years old, Horsley was the first surgeon appointed to a hospital post to perform neurological surgery at the National Hospital for Neurology and Neurosurgery, Queen Square, London [19] (Fig. 1.5). He furthered the understanding of what was possible in neurosurgery to a great extent. He was a multi-talented and multilingual polymath who produced a large number of articles covering many subjects of interest to neuroscience, including anatomy, physiology, pathology, and surgery [20].

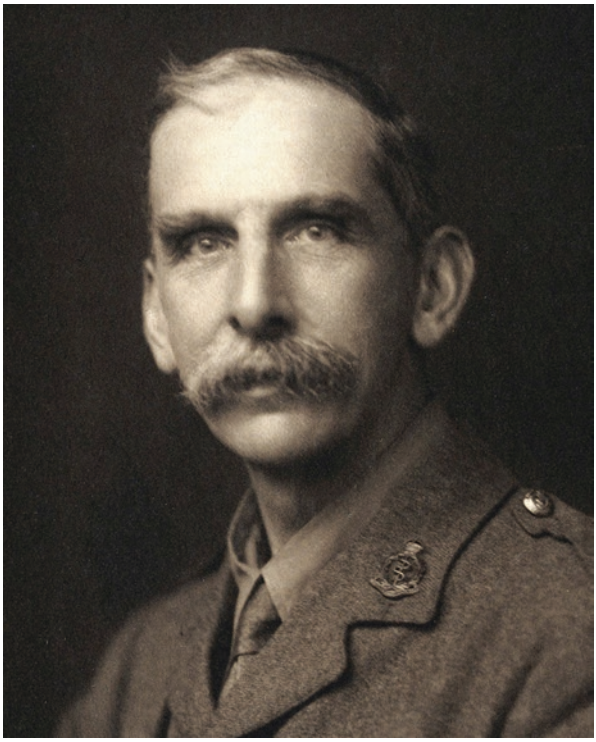

Fig. 1.4 Victor Horsley. Credit: "'Sir Victor Horsley. Photograph by G.C. Beresford" from the Wellcome Collection (https://wellcomecollection.org/works/ct2bex5p). CC BY (https://creativecommons.org/licenses/by/4.0/)

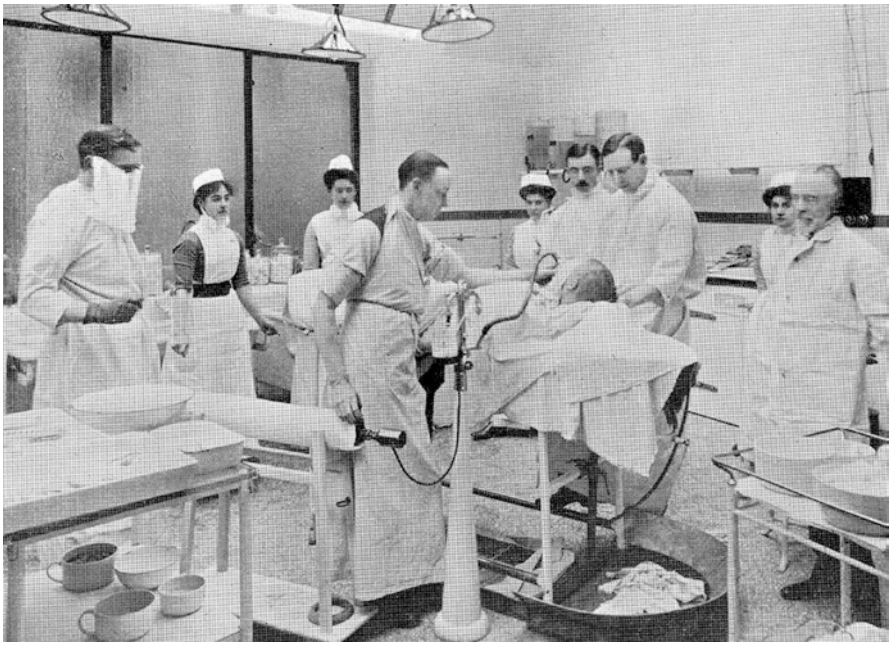

Fig. 1.5 Operating theater, the National Hospital for Neurology and Neurosurgery, Queen Square, London. Credit: "S. Paget: Sir Victor Horsley … Life and Work" from the Wellcome Collection (https://wellcomecollection.org/works/yk2uawfd). CC BY (https://creativecommons.org/licenses/by/4.0/)

Horsley was also the first surgeon to successfully resect an intraspinal extramedullary tumor in June of 1887. This surgery was performed on an Army officer with spinal meningioma, who was in substantial pain, almost paralyzed, and incontinent. Within a year, the patient had practically recovered ambulation completely [20]. Charles Ballance (1856–1936), the second pioneer of British neurosurgery, assisted Horsley during the procedure (Fig. 1.6). Horsley was about to abandon the surgery, due to difficulties identifying the proper tumor location, but Ballance advised the removal of one lamina higher and the tumor was discovered and removed. Ballance, who became the first president of the Society of British Neurological Surgeons in 1927, was known as a scrupulously slow but delicate and meticulous surgeon [21]. On the contrary, Horsley was fast, ambidextrous and decisive, which enabled him to achieve excellent surgical outcomes for the time.

In 1908, Horsley invented the stereotactic frame, which was possibly his most important contribution to neurosurgery [22], which has anticipated much of the contemporary neurosurgical practice of neuronavigation, making him by far the most important neurosurgeon in the world at his time. He was the first physician to dedicate his attention and practice to diseases of the central nervous system entirely.

Other substantial contributions during this time came from Anton von Eiselberg (1860–1939), Fedor Krause (1857–1937), and Wilhelm Conrad Röntgen (1845–1923). Anton von Eiselberg (Fig. 1.7) from Vienna founded neurosurgery in the Austro-Hungarian Empire and wrote the first detailed description of a successful resection of primary intramedullary tumor in a 27-year-old woman with a complete

Fig. 1.6 Charles Ballance. Credit: "Paleozoic examples of pathology" from the Wellcome Collection (https://wellcomecollection.org/works/datc54z7). CC BY (https://creativecommons.org/licenses/by/4.0/)

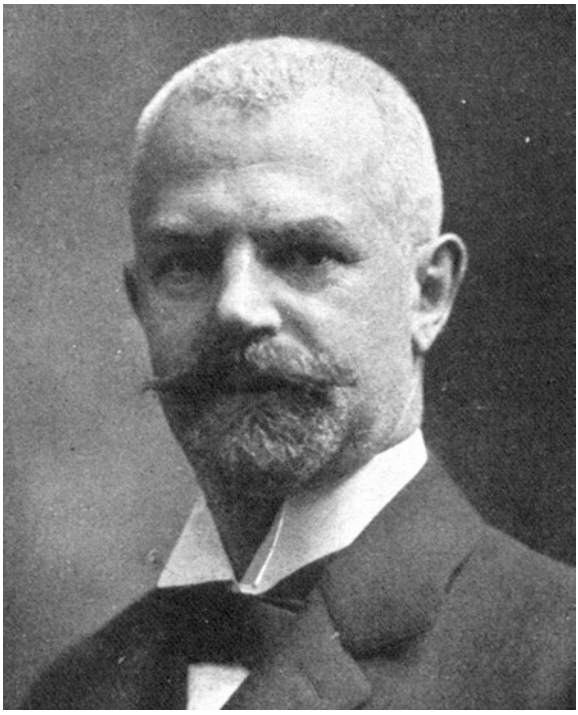

Fig. 1.7 Anton von Eiselberg (Public domain photograph: https://en.wikipedia.org/wiki/Anton_Eiselsberg#/media/File:Prof._Dr._Baron_Eiselsberg_1917_L._Grillich.png)

postoperative functional recovery which appeared in 1907 [23, 24]. Fedor Krause from the University of Berlin was the father of German neurosurgery and developed distinctive operative techniques for tumors of the brain and spinal cord. He reported first surgical series of spinal tumors in 1908 [25]. Finally, a dramatic evolution in diagnostics followed due to the discovery of X-rays by Wilhelm Conrad Röntgen in 1895, and the discovery of radium and radioactivity by Pierre Curie (1859–1906) and Marie Curie (1867–1934) in 1898. Above all, Röntgen's discovery profoundly altered neurosurgery by facilitating more precise diagnosis.

1.4.4 Charles Elsberg, a Pioneer of Spinal Cord Surgery

A practicing neurosurgeon at the New York Neurological Institute, New York, Charles A. Elsberg (1871–1948) was one of the true pioneers of spinal cord surgery [26] (Fig. 1.8). Elsberg carried out the successful removal of an intramedullary spinal cord tumor in 1909. Few years later, he described two-staged intramedullary tumor spinal cord surgery in 1911 when he was forced to stop an initial surgery due to patient's hemodynamic instability [27]. The first-stage procedure consisted of a posterior midline myelotomy and non-dural closure only [28]. A week later when performing the

Fig. 1.8 Charles A. Elsberg. Reprinted with permission from the US National Library of Medicine

second-stage surgery, he discovered that the tumor had expressed itself throughout the previously completed myelotomy. Assuring better outcome, the procedure had become to be known as extrusion of intramedullary tumors. In a subsequent book from 1916, he described the two-step technique as his innovative recommended method for operating on such tumors [29]. Moreover, the diagnosis and treatment of spinal cord tumors were detailed in his seminal publication from 1925 [30].

Charles Elsberg succeeded in spinal cord surgery at a time when cerebrospinal fluid (CSF) tests and plain spine X-rays were the only addition to a clinical neurological examination. He emphasized the role and importance of careful neurological assessment, assisted by spinal manometric determinations, to find out the presence and location of intraspinal masses [30, 31]. In 1914, he completed the first successful operation of spinal cord vascular malformation [29]. Therefore, for his enormous contributions to the field, Elsberg may well be considered the father of spinal cord surgery [26].

Between 1910 and 1926, Byron Stookey (1887–1966), a neurosurgeon from the New York Neurologic Institute and Elsberg's associate and successor, operated on eight cases of pediatric intraspinal tumors [32] (Fig. 1.9). The New York Neurological Institute was founded in 1909 as the first hospital in North America exclusively devoted to the care of patients with neurological diseases; the first Department of Neurological Surgery was established there in 1915 (Fig. 1.10).

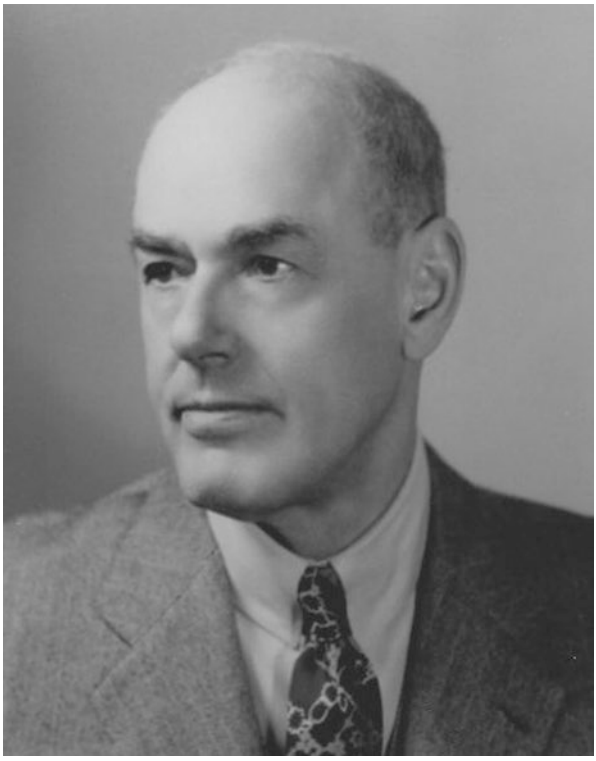

Fig. 1.9 Byron Stookey. Reprinted with permission from the Department of Neurosurgery, Columbia University

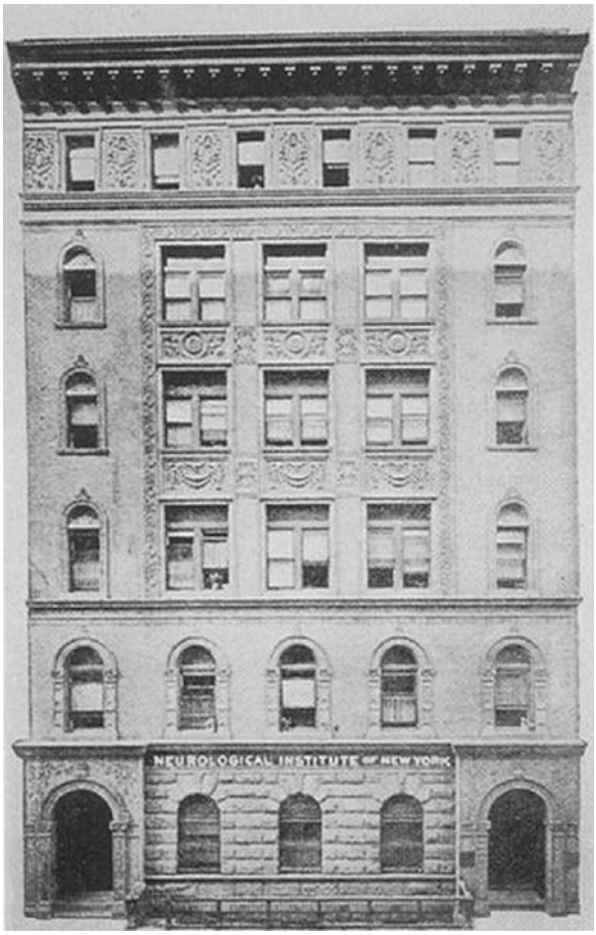

Fig. 1.10 New York Neurological Institute, New York, US. Reprinted with permission from Oxford University Press

Since the pioneer works of Krause from Germany in 1912 [25] and Elsberg in 1916 [29], several authors have contributed to spinal cord surgery to a great extent, including Cooper [33], Epstein [34], Guidetti [35], McCormick [36], Malis [37], Stein [38], Brotchi [39], Samii [40], and others. Following this, not many surgeons initially reported favorable outcomes for the next few decades. Poor diagnostic equipment and operative instrumentation slowed better intraspinal tumor outcomes, since high mortality and morbidity were frequently associated with surgical procedure.

The important step forward in radiologic diagnostics of neural structures happened in 1918 and 1919 with the introduction of ventriculography and pneumoencephalography [41], as well as the explanation of CSF circulation by Walter Dandy (1886–1946) from Johns Hopkins Hospital in Baltimore, MD. Dandy predicted the development of air myelography for spinal intradural tumors and lesions, which was first performed by Hans Christian Jacobaeus (1879–1937), a Swedish internist from Stockholm in 1921 [42].

Additionally, in 1922 Charles Elsberg analyzed the efficacy of lipiodol myelography aided by intrathecal injection of a non-absorbing iodinated contrast substance [43], which had been introduced in 1921 by Jean-Athanase Sicard (1872–1929), a French neurologist and radiologist [44].

Myelography then remained the only valuable diagnostic method available for analyzing structures of the spinal canal until the end of 1960s. With this method, the soft tissue contents of the spinal canal were outlined via fluoroscopy when appropriate radiographs were taken. Initially, it utilized air and different iodized oil-soluble non-absorbable contrasts injected intrathecally. Ionic water-soluble contrast agent, which has less neurotoxicity, was first used in 1931 and resulted in enhanced filling of the nerve root sheets with better pathoanatomical visualization compared with oily contrast media. However, it was not absorbable and was irritating to the leptomeninges and commonly produced arachnoiditis as a consequence of the procedure [45]. To solve this problem (according to Almen in 1969 [46]), a non-ionic water-soluble contrast agent of low osmolality was devised in 1976, which was tolerated well by patients undergoing the procedure. The neurotoxicity of these novel monomeric/dimetric compounds was notably lower than that of previous contrast media, which made them capable for investigating the entire spinal canal. Myelography provided visualization of the spinal cord contours, revealing a spinal mass as a complete or partial block in the flow of the intrathecal contrast material. Accordingly, the historic classification of spinal tumors was based on myelography findings with three main tumor groups identified: extradural tumors, intradural extramedullary tumors, and intradural intramedullary tumors. The so-called "cup sign" describing the silhouette of the lesion against the opacified CSF became typical of intradural extramedullary lesions compressing the spinal cord. However, a complete myelographic block may occur with larger lesions occupying the entire spinal canal.

1.4.5 Harvey Cushing and Developments between the Two World Wars

After World War I, neurosurgical specialization became the paradigm for decisive and meticulous surgical methods. Harvey Cushing (1869–1939), considered the father of neurosurgery, graduated from Yale University and attended Harvard medical school. Although he was more interested in cranial surgery than spinal surgery, he brought critical modifications in pre-operative preparation and surgical technique. His own surgical technique, promoted at John Hopkins Hospital in Baltimore, Maryland and then prevalent in the US, was slow, time-consuming and methodical, but achieved extremely successful outcomes, which consisted of accurate anatomical dissection, gentle handling of tissues, and meticulous control of bleeding, and soon became the overwhelmingly accepted surgical standard. This standard originated from his mentor, William Halsted (1852–1922), who is largely recognized as the father of modern surgery in the Western Hemisphere.

Cushing did not appreciate Victor Horsley's surgical manner, as it was entirely in contradiction with his own training, operative philosophy, and technique. Stunned by Horsley's fast and unscrupulous surgical method, he proclaimed: "There was nothing of modern neurological surgery that could be learnt from Horsley" [20].

In 1926, Cushing and William Bovie (1882–1958), a Harvard physicist, developed an efficient electrocautery system—the unipolar [47]. In 1928, they reported the use of radio frequency electrical currents (i.e., loop electrode) to better control bleeding and facilitate the removal of intracranial tumors [48]. Cushing's utilization of electrocautery stemmed from his guiding principle of avoiding neural tissue lesion by maintaining meticulous hemostasis throughout surgical procedure. Certainly, by the 1930s, the Cushing school entirely dominated world neurosurgery, which continued well into the second half of the twentieth century.

In 1929, Walter Dandy, another acclaimed neurosurgical technician from Johns Hopkins Hospital, was the first to recognize the true nature of herniated intervertebral discs as a herniation of intervertebral cartilage rather than a tumor [49]. He also described its association with sciatica and a consecutive neurological deficit, detailing the spinal surgical pathology most accurately. At the same time, Franc Ingraham (1898–1965), a gifted pediatric neurosurgeon and one of Cushing's disciples, established the first pediatric neurosurgical unit in the world at Boston Children's Hospital in 1929 [50]. Between 1918 and 1938, he reported 16 cases of surgically treated intraspinal tumors in children [51]. In 1933 W. Gayle Crutchfield (1900–1972) first described skeletal traction, providing a way to maintain better alignment of the injured cervical spine [52]. In 1939, another key accomplishment in spinal cord surgery was achieved when Horrax and Henderson reported total resection of an ependymoma occupying the entire spinal cord length [53]. The tumor was successfully removed by consecutive surgeries bearing satisfactory recovery [53].

During the 1940s, James Greenwood, Jr. (1907–1993) introduced electrosurgery with bipolar coagulation at Methodist Hospital in Houston, Texas [54]. Aided by the implementation of magnifying loupes, he successfully developed the technique of total intramedullary spinal cord tumor resection [55, 56]. He has made many other contributions to neurosurgery, including surgery of cervical spondylosis, and the use of bipolar coagulation in removal of intramedullary tumors (ependymoma) of the spinal cord [54, 57].

1.4.6 Developments in the 1950s

Spinal surgery in the early 1950s still consisted of a limited number of procedures and diagnostic tools. Almost all surgeries were performed by the large posterior approach to the spine and a huge laminectomy. Plain X-rays vertebrograms and lumbar myelography remained the only diagnostic tools available, but were less reliable than physical examination itself. However, a few successful series advocated increased aggressiveness of spinal cord tumor surgeries [58, 59]. Anterior cervical discectomy for cervical spine degenerative disease was first performed by Cloward [60] and Robinson and Smith [61], while trauma surgery for spinal injuries was mainly developed from experiences gained during war and military conflicts.

During the same decade, Isadore Tarlov (1905–1970) from the Montreal Neurological Institute contributed to the study of the anatomy and pathology of spinal nerves, and the arachnoid space. He also described sacral nerve root

cysts—which bear his name—for the first time, and introduced the use of fibrin glue to spine surgery [62, 63].

In 1957, Theodore Kurze (1922–2002) from the University of Southern California, Los Angeles described the first neurosurgical use of operative microscope for the resection of an acoustic neurinoma [64]. However, microsurgery was not employed for spinal cord pathology prior to the 1970s.

Leonard Malis (1919–1995) substantially modified the electrosurgical concept, devising bipolar coagulation forceps at Mount Sinai Hospital, New York, which became commercially available in 1955. He effectively applied this technique to spinal cord tumor surgery [37, 65]. The introduction of bipolar coagulation forceps was an essential move in promoting adequate perioperative hemostasis, permitting spine surgeons to become true microsurgeons [66–68]. It soon became the standard neurosurgical instrumentation of today.

1.4.7 Developments in the 1960s and 1970s

During the 1960s, when technological progress significantly decreased surgical morbidity, many surgical advances followed, including the introduction of instrumented lumbar fusion [69–71]. Paul Harrington (1911–1980) introduced a system of distraction and compression rods and hooks, which was adapted to the treatment of spinal fractures and dislocations [69, 72]. In the meantime, management protocols that tried to avoid the risk of increasing postoperative neurological deficit for spinal cord tumors—decompressive laminectomy, tumor tissue biopsy, and adjuvant radiation therapy—became the surgical standard [73, 74]. However, diagnoses were still frequently established late in the clinical course of the patient's condition.

In 1966 M. Gazi Yasargil (b 1925) started experimental works on canine cerebral arteries, which many consider the birth of microneurosurgery [75]. A year later, Yasargil implemented the microneurosurgery method in Zürich, Switzerland [76]. His ingenuity in developing microsurgical techniques has transformed outcomes in patients whose medical conditions were previously inoperable [77]. He conceived microsurgical instruments and the floating operative microscope, as well. Yasargil and his team also showed much improved results with the help of the operative microscope and bipolar coagulation in facilitating the surgical approach to the spinal canal and its neural structures [78]. He also described the treatment of spinal cord vascular malformations by microsurgical excision [78–80]. Therefore, it can be said that virtually every neurosurgical procedure performed today, including surgery of the spinal cord, has been affected by his ingenuity.

During the same decade, noteworthy advances were also made with the advent of spinal angiography, which generated better visualization and further understanding of normal spinal vasculature and the pathophysiology of intradural spinal tumors and malformations.

The existing surgical treatment of spinal intradural tumors did not develop before the 1970s due to previously narrow visualization and technical possibilities, as well

as the imminent peril of infections [81]. In 1971, Godfrey Hounsfield (1919–2004), an English electrical engineer, invented the CT scanner, which was introduced into practice with a successful scan on a cerebral cyst patient at Atkinson Morley Hospital in Wimbledon, London [82, 83]. Multiplanar computerized spine imaging has soon become one of the most valuable radiological tools in diagnosing spine disorders. During the same decade, Paul Lauterbur (1929–2007), an American chemist, and Peter Mansfield (1933–2017), a British physicist, developed magnetic resonance imaging (MRI). Raymond Damadian (b 1936), an American physician and medical practitioner, constructed the first commercial MRI scanner for medical practice in 1977. Magnetic resonance imaging soon become the most powerful and reliable diagnostic tool in the history of medicine [84]. The operative microscope was fully employed for spinal cord pathology during the same decade facilitating precise and safe tumor removal.

Minimally invasive spinal surgery also advanced in the same decade, including the first percutaneous discectomy and the use of the anterior approach to the lumbar spine [85, 86]. The advantage of minimally invasive surgery was a reduced recovery time, resulting from less muscle and tissue manipulation [85]. In addition, it kept skin and muscle incisions small, reduced the exposure to possible infection, and enabled the operative wound to heal faster. Some procedures may be performed in local anesthesia on a very short hospital stay and/or on an outpatient basis.

The use of endovascular therapy in the management of vascular intraspinal tumors also gradually evolved during the 1970s [87, 88].

In the subsequent years, a handful of neurosurgeons reported their thriving experience with spinal intradural tumors in children, too [2, 89–92].

1.4.8 Introduction of Imaging and other Technological Advances in the 1980s

The first report of modern radiological body imaging and scanning employment in diagnostics of spinal issues appeared in 1980, which was dramatically improved by mid-decade, particularly with regular employment of spinal MRI, which enabled considerable advances in tumor identification and localization compared with the previous diagnostic modalities. The first series describing MR imaging of the spinal cord in 17 patients was published in 1984 [84]. By the end of the decade, the MRI became the diagnostic tool of choice for the spinal cord. In assessing patients with potential cord compression in whom MRI was contraindicated, water soluble low ionic contrast enhanced CT myelography was successfully applied [46].

In the same decade, other technological advances moved spinal surgery forward. Intraoperative ultrasound was introduced in the early 1980s, being first used for cranial surgery and the spinal surgery shortly thereafter [93]. It has permitted optimization of surgical exposure and precise positioning of the myelotomy [94, 95].

Cavitron ultrasonic surgical aspirator (CUSA) was used for controlled tumor tissue removal without adversely affecting the surrounding healthy tissue. The CUSA is a device that generates mechanical energy of high frequency ultrasonic waves to

produce tissue cavitations [96]. This instrument was first applied for the removal of dental plaque in 1947. Since 1967, an ophthalmologic procedure for cataract removal was successfully developed, which prompted attempts to adapt it to neurosurgical procedures [96–99].

In 1916, the British physicist and Nobel Prize laureate John W. Strutt (1842–1919) first discovered the effect of cavitation, which is defined as the process of formation of the vapor phase of a liquid when it is subjected to reduced pressures at constant ambient temperature. Strutt concluded that a small jet stream of water may be responsible for the structural damage of the surrounding matter. Justifying a similar principle, high-speed mechanical waves can be used in non-elastic media, such as water, to create a cavitation effect. If this phenomenon is applied to water-rich tissues, such as neural tumor, the final effect is the destruction of all tumor cells while preserving structures rich in collagen and low in water, such as healthy neural tissue, blood vessels, and nerves.

The CUSA was initially used in spinal cord surgery in 1982 as described by Fred Epstein (1937–2006) from New York, a pediatric neurosurgeon credited for the development of this operative technique suitable to treat children with spinal cord tumors that were once thought to be incurable because of their location [100–102]. He also reported a pediatric series of intradural spinal tumors managed by surgery alone [34].

Further regular employment of MRI in daily diagnostics and the incorporation of an operative microscope and ultrasonic aspirator in neurosurgical routine have made spinal intradural tumor surgery more accurate and secure.

The treatment of spinal intradural tumors and vascular malformations was further expanded with the regular use of interventional neuroradiology [87]. These lesions were embolized either as a primary treatment option or prior to open microsurgical procedure. Although embolization and intramedullary microsurgery were established as the methods of management choice for spinal arteriovenous malformations (AVMs), the difficulty of totally removing intramedullary lesions without endangering spinal cord function was still a problem during the 1980s [79, 80].

Frameless stereotaxy was first proposed in the 1980s for cranial surgeries [103], even though it would be a number of years until the technology was fully implemented for spinal surgery.

1.4.9 Developments in the 1990s

With further improvements in operative and endovascular techniques, the number of patient series subsequently increased in the 1990s, but management protocols still varied significantly. The concept of total tumor resection was increasingly becoming accepted. The satisfactory results presented by Brotchi [39], Jallo [59], and Nadkarni and Rekate [104] supported this opinion. McCormick published a large surgical series demonstrating excellent long-term outcomes for surgery of spinal ependymomas, establishing a clinical grading system for these tumors [36]. Klekamp and Samii reported a series of 782 spinal tumors, concluding that MRI has shortened the

time until diagnosis, and made it possible to perform surgery before severe deficits have occurred, but did not have a major impact on postoperative results [105, 106]. In spite of that, some authors still emphasized the role of adjuvant oncological therapies, including chemotherapy and partial surgical tumor resection, arguing that intact neurological function should be maintained at all costs [107].

1.4.10 Current Innovators in the Field

Volker Sontag (b 1944) from Barrow Neurological Institute, Phoenix, AZ has improved complex spinal surgery of tumors and fractures, including advanced bone fusion techniques, which were previously an exclusive domain of orthopedic surgeons. The methods soon became broadly accepted standard neurosurgical procedures. His scientific contributions consist of more than 450 published peer reviewed articles, mainly concerned with spinal neurosurgery [108].

Another leader to gain prominence in the field, Edward Benzel (b 1948) from Cleveland Clinic, Cleveland, OH focused on spinal disorders, including cervical spondylosis and syringomyelia, complex spine instrumentation, and spine tumors. He also contributed greatly to better understanding of spinal biomechanics and dynamics for spinal tumor and degenerative diseases [109]. He and his team paid particularly close attention to dorsal approaches to intradural extramedullary tumors of the craniovertebral junction [110].

During the 1990s, preoperative tumor embolization was regularly applied and was considered both safe and beneficial in reducing intraoperative blood loss and operating time. Endoscopic, video-assisted minimally invasive spinal surgery techniques were also perfected during 1990s, gaining various diversifications in their clinical practice [111]. In 1995, Hamilton et al. firstly described the possibility of linear-accelerator based stereotactic radiosurgery for spinal tumor treatment [112].

The probability of harmless tumor removal was greatly advanced with the implementation of intraoperative motor evoked potential monitoring [113]. In 1998, Kothbauer et al. confirmed improved postoperative motor function in patients undergoing surgery for intramedullary spinal cord tumors when intraoperative neurophysiological monitoring was used [114].

1.5 Contemporary Spinal Surgery of the Twenty-First century and Future Perspectives

Since the beginning of twenty-first century, the number and scope of intradural spinal tumor and spinal cord surgeries multiplied immensely, having decreasing morbidity and close to zero mortality, as well as increasing favorable management outcomes (The timeline of major events in the history of spinal surgery and surgical treatment of spinal intradural tumors is depicted in Table 1.1).

Table 1.1 Timeline of major events in the history of spinal surgery

Date	Event
Circa 3000 BC	Egypt: Spinal traction was successfully used to reverse a paralyzing cervical spine—The oldest neurosurgical procedure recorded.
Circa 1700 BC	Edwin smith papyrus: Spinal injury was recognized as the gravest one, bearing a poor outcome which was typically fatal.
First century BC	Hippocrates (460–375 BC) provided evidence concerned with clinical implications of spinal cord damage.
First century AD	Galen of Pergamon (AD 129–200) proposed the removal of compressive bone fragments from the vertebral canal in case of vertebral body fracture.
First century AD	Avicenna (AD 980–1037) discussed on various ranges of spinal injuries evaluating their outcomes and prognosis.
1538	Andreas Vesalius (1514–1564) contributed to the understanding of the spinal cord, describing and illustrating it, devising the names for every spinal level.
1846	Implementation of inhalation agents for general anesthesia.
1867	Introduction of Listerian principles of antisepsis.
1870s	William Macewen (1848–1924) advanced spinal surgery, successfully operating on hematomas of the spine.
1877	Recognition of the germ theory of infection.
1887	Introduction of the exact localization of neural structures and lesions.
1887	Victor Horsley (1857–1916), the first surgeon to successfully resect an intraspinal extramedullary tumor.
1907	Anton von Eiselberg (1860–1939), the first detailed description of a successful resection of primary intramedullary tumor.
1909	Charles Elsberg (1871–1948) carried out successful removal of intramedullary spinal cord tumor.
1919	Walter Dandy (1886–1946) predicted the development of air myelography for spinal intradural tumors and lesions
1926	Harvey Cushing (1869–1939) and William Bovie (1882–1958) developed an efficient electrocautery system for hemostasis—The unipolar.
1940s	James greenwood, Jr. (1907–1993) introduced electrosurgery with bipolar coagulation and implemented magnifying loupes.
1950s	Isadore Tarlov (1905–1970) introduced the use of fibrin glue to spinal surgery.
1955	Leonard Malis (1919–1995) devised bipolar coagulation forceps for better control of perioperative hemostasis.
1957	Theodore Kurze (1922–2002) described the first neurosurgical use of operative microscope.
1967	M. Gazi Yasargil (b 1925) introduced microneurosurgery in routine neurosurgical practice.
1971	Godfrey Hounsfield (1919–2004) invented the CT scanner, soon becoming one of the most valuable radiological tools in the diagnostics of spine disorders.
1977	Raymond Damadian (b 1936) constructed the first commercial MRI scanner for medical practice.
1980s	Intraoperative ultrasound introduced in the early 1980s, permitting optimization of surgical exposure and precise positioning of myelotomy.
1982	Fred Epstein (1937–2006) initially used the Cavitron ultrasonic aspirator (CUSA) in the spinal cord surgery.

(continued)

Table 1.1 (continued)

Date	Event
1990s	Preoperative tumor embolization became regularly applied in reducing intraoperative blood loss and operating time.
1990s	Endoscopic and video-assisted minimally invasive spinal surgery techniques perfected.
1990s	Intraoperative neurophysiological monitoring implemented.
1990s	Stereotactic radiosurgery introduced for spinal tumor treatment.
Future perspectives	Image-guided surgery, virtual reality and robotic surgery supported by regenerative medicine and nanotechnology.

The expansion of advanced imaging software and hardware has definitely improved the possibility to visualize intradural and spinal cord structures noninvasively. Contemporary spinal angiography was improved, including digital subtraction angiography and magnetic resonance/computed tomography-based techniques for noninvasive imaging of spinal blood vessels. Spinal multi-slice, multi-detector CT angiography and paramagnetic contrast enhancement on a 3.0 T magnetic resonance angiography (MRA), which are both fast and safe methods, can clearly show the extent, location, and vasculature of intraspinal lesions.

Based on the data collected between 1980 and 2012 from the spinal cord database (n = 1317 patients with tumors of the spinal canal), it is concluded that intramedullary tumors should be surgically treated as soon as neurological symptoms appear. Considerable surgical experience is required also to achieve high rates of total tumor resection and to limit rates of permanent morbidity [105].

Modern surgical strategies have been profoundly modified and diversified, mainly with the introduction of state-of-the-art devices like high-field MRI, 3-dimensional (3D) CT and MR spinal angiography, CUSA, and preoperative/perioperative neurophysiology like somatosensory evoked potential (SSEP) and motor evoked potential (MEP) in everyday practice. Intraoperative neurophysiological monitoring is becoming routinely used to monitor intraoperative neural tissue manipulation and postoperative recovery [113].

Three-dimensional printing allows for custom-made manufacturing of spinal components to reconstruct the spine or produce personalized spine models, allowing for better and more accurate tumor resection and spinal reconstruction planning [115]. Simultaneously, Foley et al. [116], described virtual fluoroscopy and its successful use in various spinal surgical methods, which minimize paravertebral tissue trauma without compromising the quality of spinal procedure. At the same time, Ziya Gokaslan et al. markedly improved the surgical treatment of spinal tumors and complex spinal reconstructions, developing novel surgical methods to treat some of the most difficult tumor types, including spinal metastases, paying special attention to spinal instrumentation after tumor resection [117–119].

Precise and detailed neural lesion localization aided by the availability of the most modern diagnostic tools has become the normal part of the everyday neurosurgical protocol when intraspinal tumors are concerned. The whole discipline of

stereotactic spinal neuronavigation was introduced to the neurosurgical routine, directing a great deal of neurosurgeons' actual practice today.

Radiotherapy of spinal cord tumors, which have more infiltrative growth than other tumors of the spinal canal, may be given as a definitive treatment or more commonly as an adjuvant therapy. Advancements in the technology have made the delivery of high precision radiotherapy like 3-D conformal radiotherapy, intensity modulated radiotherapy, and stereotactic radiosurgery feasible and safe [120]. In general, completely resected spinal cord tumors do not require any adjuvant radiotherapy. However, subtotally resected tumors, due to a significant risk of recurrence and progression, should be considered for postoperative radiotherapy to improve outcomes [35], and avoid radiation myelopathy [120]. The only situation in which emergency radiotherapy may be considered without surgery and histopathological tumor identification is imminent spinal cord compression not amenable to surgery due to medical contraindications [120].

Recent advances in technology enable stereotactic radiosurgery to be extended to intraspinal lesions. Robotic, frameless stereotactic radiosurgery offers a precise non-invasive radiation treatment option for spinal tumor patients who are unable to undergo surgery because of tumor location or other factors. The sophisticated software is designed to pinpoint a spinal tumor's exact location in real time, allowing for more precise, selective radiation delivery while reducing the surrounding sensitive spinal cord tissue damage.

Contemporary management protocol of intramedullary spinal cord tumors involves radical tumor resection with adjuvant radiation and/or chemotherapy, depending on the tumor's histopathological type and grade. However, despite advances in surgical therapy, this protocol still carries considerable morbidity [119].

The concept of image-guided surgery signals the emergence of a completely new era in intradural and spinal cord surgical treatment based on replacing direct visualization with radiographic visualization. Image-guided surgery has enabled more precise manipulation, and a reduction in surgical exposure, duration, as well as decreased perioperative blood loss, assuring a better prognosis. Concurrently, it appears to herald a thrilling prospect in which virtual reality and robotic surgery supported by regenerative medicine and nanotechnology will emerge as modern spinal techniques of the future.

1.6 Conclusion

Spinal surgery and spinal cord operative procedures developed occasionally and disproportionally throughout the ages, mostly due to lack of knowledge and evidence, as well as a lack of proper diagnostics and appropriate instruments. Accordingly, it saw no major progress and seldom advanced until the beginning of the nineteenth century. Afterwards, spinal surgery concurrently followed the slow but steady general advancement in modern medicine and surgery.

Spinal surgery has recently proceeded from decompression procedures to complex spinal reconstruction and meticulous neural tissue handling because of

broad-based technological advances, beginning with the advent of operative microscope, and spinal CT and MRI as the most accurate diagnostic tools.

Modern spinal surgical techniques and strategies are a result of increased understanding of the anatomy, biomechanics, and physiology of the spine, spinal cord, and the central nervous system. The technological progress of spinal surgery has coincided with a simultaneous increase in the number of innovative surgeons and researchers, academic institutions, and government public health agencies, and the rise of medical industry. Consequently, better surgical training of operative personnel is broadly achieved, supported by telementoring and virtual operative simulation as teaching methods of the future.

More thorough imaging studies of clinical findings, improved image-guided surgical techniques, intraoperative electrophysiological monitoring, and enhanced knowledge of tumor molecular biology will undoubtedly result in more advanced and successful surgical management of patients with intradural spinal tumors, leading to major functional recovery.

Knowledge and understanding of intradural spinal tumors is necessary to devise suitable management protocol and to achieve the best possible patient outcomes. Careful operative technique and the use of particular surgical armamentarium and accessories are vital to carrying out proper tumor removal, lessen tumor recurrence, reduce postoperative complications, and maintain neurologic function. Therefore, contemporary surgical management protocol should be grounded on tumor type, molecular biology, volume, and location, which is highly individualized for each and every patient. Regardless of major progress in diagnostics and operative techniques, surgical management of such tumors still requires detailed clinical understanding and mandates subtle caution during surgical procedure.

Using a surgical course for intradural spinal tumors has not been fully achieved despite the generally widespread tendency toward more aggressive microsurgical procedures. Nevertheless, the question of whether spinal cord tumor patients with minor clinical signs and symptoms should be candidates for more aggressive surgical management is still open to discussion. This may be resolved in the upcoming years utilizing new concepts of virtual reality and robotic spinal surgery.

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Epidemiology of Spinal Cord Tumors

2

Yusuf Şükrü Çağlar and İhsan Doğan

2.1 Introduction

Primary spinal tumors are a group of tumors which originate from the spinal cord (intradural) or the vertebral column (extradural). In contrary, the metastatic tumors of these regions constitute the secondary tumors of the spine which metastasis or extend to these spinal compartments from a long-distance via hematogenous way or from close surrounding structures. The primary tumor group includes a wide range of neoplasms that can be encountered throughout the spine. Primary tumors of the spine commonly originate from cartilaginous, osseous, neural, and perineural structures. Although, these tumors differ significantly from each other in terms of origin and location, improper use of the correct terminology related to the spinal tumor classification and its subtypes can be found in the literature. To eliminate this confusion, and for the ease of understanding, clarification of the relevant definitions of these terms is of great importance and priority. The terminological contradiction is commonly found between the terms "spinal tumor" and "spinal cord tumor." These two terms are sometimes used interchangeably. Even when it does not originate from the spinal cord, any pathology affecting the spinal cord—whether it is a metastatic or primary vertebral column tumor—can be misnamed as spinal cord tumor without considering its origin.

The term "spinal tumor" is a general term and includes both intradural and extradural pathologies (Table 2.1). Spinal tumors are broadly categorized according to their origin, and include both "spinal cord tumors" and "vertebral column tumors."

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Table 2.1 Spinal Tumors

Vertebral column tumors (Extradural)	Spinal cord tumors (Intradural)
Primary	*Primary*
Malignant tumors	Intramedullary tumors
Osteosarcoma	Astrocytoma
Chondrosarcoma	Ependymoma
Fibrosarcoma	Dermoid tumor
Malignant fibrosis histiocytoma	Epidermoid tumor
Ewing's sarcoma	Teratoma
Multiple myeloma	Lipoma
Lymphoma	Hemangioblastoma
Chordoma	Ganglioglioma
	Oligodendroglioma
Benign tumors	
Osteoid osteoma	Extramedullary tumors
Osteoblastoma	Meningioma
Osteochondroma	Neurofibroma (nerve sheath tumor)
Enchondroma	Schwannoma (nerve sheath tumor)
Chondroblastoma	
Chondromyxoid fibroma	Dumbbell tumors
Fibroma	
Giant cell tumor	*Secondary*
Hemangioma	Metastatic tumors
Aneurysmal bone cyst	
Eosinophilic granuloma	
Secondary	
Metastatic tumors	

Vertebral column tumors originate from osseous and cartilaginous structures and can be primary or metastatic. Spinal cord tumors primarily originate from the cellular elements of the spinal cord and are thus termed as "intradural-intramedullary tumors." Nevertheless, entire intradural-extramedullary pathologies, even if they do not originate from the spinal cord, can be evaluated under the title of primary spinal cord tumor, such as meningiomas. Intradural tumors can either be intramedullary, extramedullary, or both. Extramedullary tumors originate from peripheral nerve roots (or meninges) and are not part of the essential nature of spinal cord, whereas intramedullary tumors originate from glial and support cells in the spinal cord. In this chapter, the term "spinal cord tumor" will be used to express entire intradural pathologies.

Primary spinal cord tumors constitute between 4 and 16% of all tumors of the central nervous system (CNS) in adults (Table 2.2). Total age-specific incidence rate is 0.74–2.5 per 100,000 persons [1–4]. Primary spinal cord tumors are less common than their cranial counterparts, although they are histopathologically similar. Some tumors may be in multiple compartments and are called dumbbell tumors. These are intradural-extramedullary tumors and constitute 54% of all primary spinal cord tumors, whereas intradural intramedullary tumors and dumbbell tumors constitute 18% and 22%, respectively [5].

Table 2.2 Primary Spinal Cord Tumors

Lesion	Decade of life peak occurrence	Spinal region location	Frequency (%)	Gender ratio (M/F)	Tumor type breakdown
Ependymoma	3rd–4th	Thoracic Cervical Lumber	8–14	3/2	72–75% intramedullary tumors 10–12% Intradural-extramedullary tumors
Hemangioma	6th–7th	Thoracic Cervical	4–5	1/1	55–70% intramedullary tumors
Hemangioblastoma	3rd–4th	Thoracic Cervical	2–5	2/1	83–90% intramedullary tumors
Schwannoma	5th–6th	Lumbar Thoracic Cervical	49–57	3/2	66–70% Intradural-extramedullary tumors 28–30% dumbbell tumors
Meningioma	6th–7th	Thoracic Cervical	11–17	1/3	90–95% Intradural-extramedullary tumors

There is no definite symptom or neurological finding that is pathognomonic for these tumors. Spinal cord tumors have characteristics that are related to the compression of neural structures. The clinical presentation of these tumors can include a wide spectrum of symptoms from insignificant sensation complaints to severe motor deficits.

The incidence of spinal tumors at different frequencies in many populations has been demonstrated in various case series. In a study of 678 patients, Hirano et al. reported 55.6% male 44.4% female frequency (male/female ratio, 1.25). Of the total tumors studied, 18.1% were intramedullary, 54.7% were intradural extramedullary, 4.1% were epidural, and 22.9% were dumbbell tumors. The pathological diagnoses included schwannomas (57.2%), meningiomas (11.6%), ependymomas (8.0%), hemangiomas (4.0%), hemangioblastomas (3.4%), neurofibromas (3.4%), and astrocytomas (1.3%) during the 2000–2009 period [5, 6].

Duong and colleagues reported that among 11,712 primary spinal tumor incidents diagnosed between 2004 and 2007, 2576 (22.0%) were malignant, and 9136 (78.0%) were nonmalignant (62.4% benign and 15.6% borderline) [3, 7]. Wu et al. reported that out of 184 patients, 82 (44.6%) had metastatic tumors and 102 (55.4%) had primary tumors; 5.9% patients had intramedullary tumors, 60.8% patients had intradural extramedullary tumors, 13.7% patients had epidural tumors, and 19.6% patients had dumbbell tumors during the 2002–2013 period [8].

2.2 Genetic Factors

Several genetic factors are associated with intramedullary spinal cord tumors [9]. Genetic mutations give information about tumor diagnosis and prognosis, and also connects spinal tumors with lesions that occur elsewhere in the body. Diseases related to clinical syndromes include neurofibromatosis 1 (NF1), NF2, and Von Hippel-Lindau (VHL) syndrome [10]. Neurofibromas are comprised of multiple cell types and are associated with NF1.Meningiomas and schwannomas are benign

tumors and can also be associated with NF2 [11]. Some of hemangioblastomas are associated with von Hippel–Lindau disease [4].

2.3 Histological Type of Tumors

Schwannomas, meningiomas, and gliomas are the most commonly reported spinal cord pathologies in the literature [12–14]. However, there are limited data on spinal cord tumor incidence rates; the patient population in each case series is inadequate to determine the correct distribution of these pathologies, according to their epidemiologic features. Besides, the tumor groups in current studies are heterogeneous and contain various pathologic subtypes incompatible with the proper histopathologic classification.

In general, approximately 70% of primary spinal cord tumors are non-malignant pathologies [15]. In contrast to adult tumors, more than half of childhood spinal cord tumors are malignant. In large series, the most common site of origin for the spinal cord tumors is reported differently and at various frequencies.

2.3.1 Ependymoma

Ependymomas are the most common intramedullary tumors [16] (Fig. 2.1). These tumors are thought to arise from ependymal cells of the central canal and are considered intramedullary. Furthermore, the pathology can also be located extramedullary in the filum terminale. As previously highlighted, both types are categorized under primary spinal cord tumor and are 1.5 times more common in males. Seventy-two to Seventy-five of ependymomas are intramedullary; 10% are intradural extramedullary [5] (Fig. 2.2). They are most commonly located in the thoracic region. Cervical and lumbar distributions are similar. They are diagnosed after 20 years of age and peak incidence is in the third and fourth decades of life. Approximately 65% of these tumors are associated with syrinx formation [17]. Various histologic subtypes of ependymomas exist. The most common intracranial subtype is the cellular variant, or the "typical" form. In contrast, these tumors arise in the spinal cord as the myxopapillary variant, which is classified as a World Health Organization (WHO) Grade 1 tumor. Less common variants of this tumors in the spinal cord are tanycytic ependymoma (WHO Grade 2), anaplastic ependymoma (WHO Grade 3), and subependymoma (WHO Grade 1) (Video 2.1) [15].

2.3.2 Hemangioma

Distribution of hemangioma among males and females is similar to ependymoma. Seventy percent of hemangiomas are intramedullary tumors. The remaining 30% are extramedullary and very few are diagnosed as dumbbell tumors. They are frequently located in thoracic and cervical regions and are usually diagnosed after 50 years of age [5].

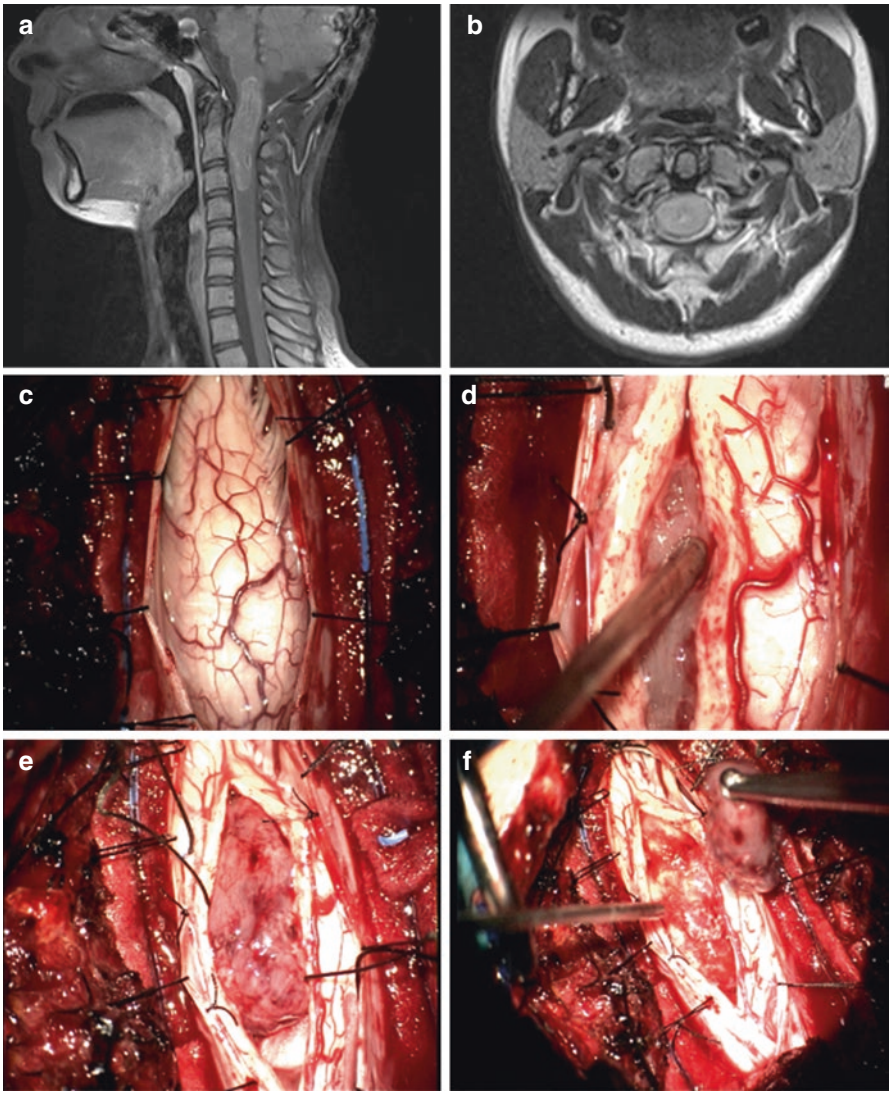

Fig. 2.1 (**a**) Preoperative T2-weighted MRI of a cervical-intramedullary ependymoma on sagittal T1 section. (**b**) T1-axial non-contrast T2-weighted MRI revealing an intramedullary lesion. (**c**) Intraoperative view of the enlarged spinal cord following midline dural incision. (**d**) Intraoperative view of an intramedullary ependymoma following myelotomy. (**e**) Following tenting of the dura and the pial membrane, general view of the tumor with its superior and inferior poles. (**f**) Total removal of the tumor and the resulting tumor cavity

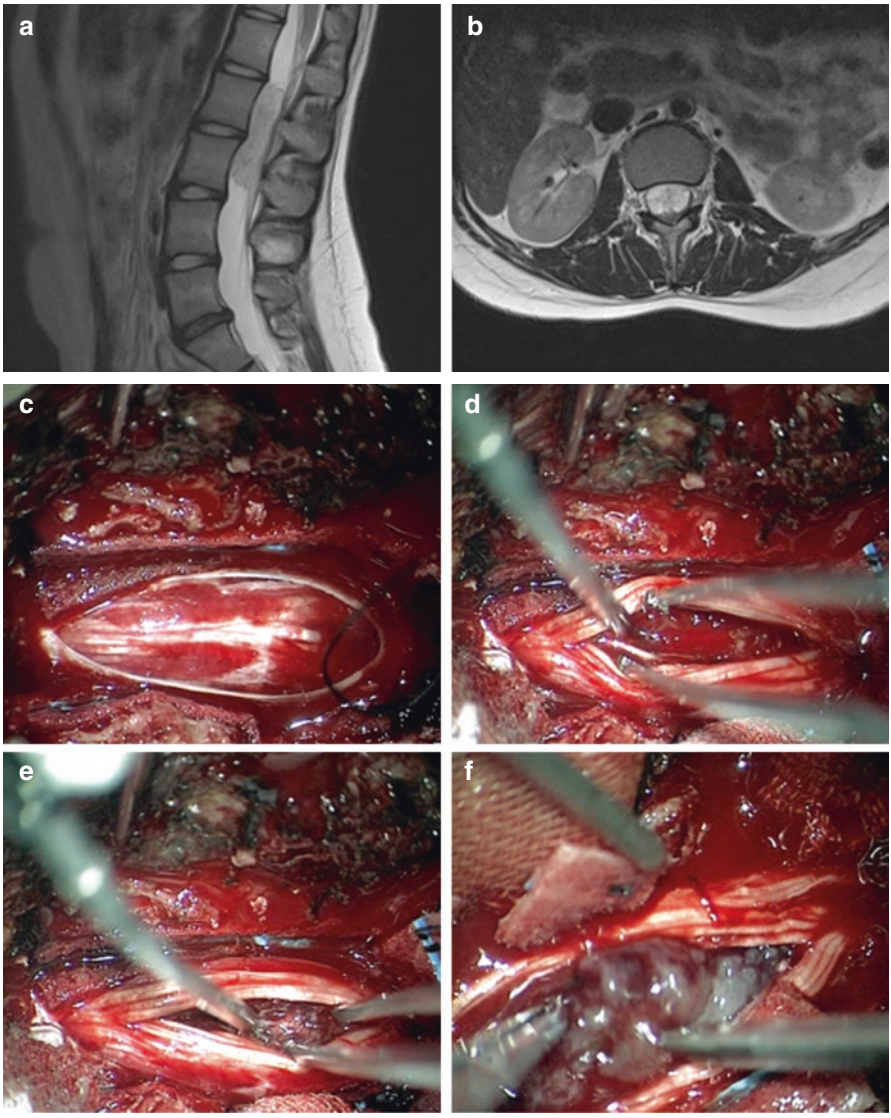

Fig. 2.2 Sagittal T2-weighted post contrast (**a**) and axial T2-weighted (**b**) MRIs of an intradural-extramedullary conus ependymoma. Dural opening (**c**) exposing the filum terminale and conus medullaris. Intraoperative view of the tumor at the level of the conus medullaris (**d**) and filum terminale (**e**). Removal of the tumor (**f**), which is highly adhesive to the rootlets and vasculature

2.3.3 Hemangioblastoma

Hemangioblastomas are twice as common in males than females [3]. Approximately 83–90% of these tumors are intramedullary. Forty percent of patients with hemangioblastoma are also diagnosed with Von Hippel Lindau Syndrome. The most common location they occur is in the thoracic region, followed by the cervical region.

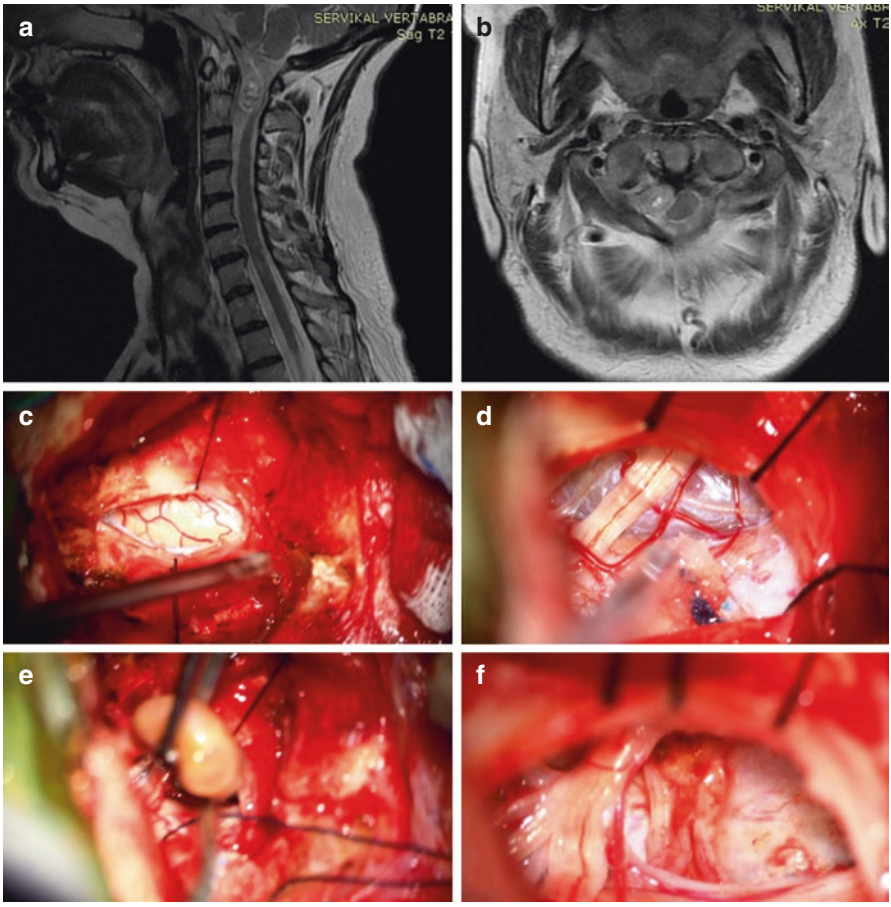

Fig. 2.3 (**a**) Preoperative post-contrast T1-weighted sagittal MRI showing cervical schwannoma. (**b**) Preoperative T1-weighted post-contrast axial MRI of the right-sided cervical schwannoma compressing and dislocating the spinal cord. (**c**) Intraoperative view after midline dural incision. (**d**) Intraoperative view of the tumor, which illustrates the close relationship of the schwannoma with the cervical vasculature and rootlets. (**e**) Safe and total removal of the tumor with preservation of neurovascular anatomy. (**f**) Surgical cavity following tumor removal

Hemangioblastomas are usually diagnosed after 20 years of age and peak incidence is in the third and fourth decades of life.

2.3.4 Schwannoma

Schwannomas arise from nerve roots originating from the spinal cord [11] (Fig. 2.3). They are 1.5 times more common in males. Approximately 66–70% of schwannomas are intradural-extramedullary, 28–30% are dumbbell tumors, and very few of them are extramedullary. Schwannomas frequently occur at the dorsal root and can arise within the intradural space [11]. It is found in the lumbar,

thoracic and cervical regions of the spine and is typically diagnosed after age 30. The peak incidence for Schwannomas is in the fifth and sixth decades of life (Video 2.2).

2.3.5 Meningiomas

Meningiomas occur in the membranes surrounding the spinal cord [7] (Fig. 2.4). They are three times more common in females than in males [18]. About 90–95% of meningiomas are intradural-extramedullary [5], and intradural or dumbbell tumor appearance is quite uncommon. The most commonplace of occurrence is the thoracic region, followed by the cervical and lumbar regions. Meningiomas are usually diagnosed after the age of 50 years and the peak incidence is in the

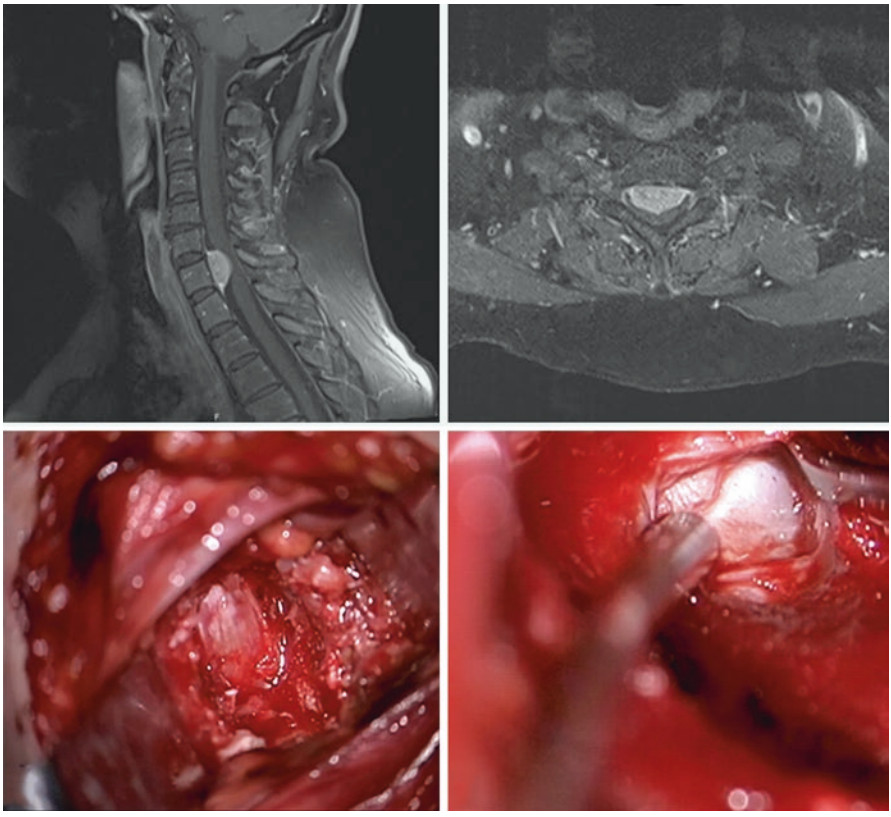

Fig. 2.4 (**a**) Preoperative sagittal MRI of an intradural meningioma which is located anterior to the spinal cord. (**b**) The T2 axial contrast-enhanced MRI revealing a broad-based extramedullary mass lesion which is compressing spinal cord posteriorly. (**c**) Intraoperative view that is showing the dural protrusion anteriorly following C7 corpectomy and removal of anterior longitudinal ligament. (**d**) Intraoperative view of the meningioma following dural opening

sixth and seventh decades of life. Meningiomas have many subtypes. Typical meningiomas are classified as WHO Grade 1, atypical meningiomas are classified as WHO Grade 2, and anaplastic meningiomas are classified as WHO Grade 3 [15].

2.3.6 Neurofibroma

Neurofibromas arise from nerve root originating from the spinal cord [2]. Distribution of male and female patients is similar. Fifty percent of neurofibromas are intradural-extramedullary; 50% are dumbbell tumors. They are most commonly located in the cervical region of the spine, followed by the thoracic region. Half of patients with neurofibromas are also diagnosed with Von Recklinghausen syndrome. Diagnoses are typically make after age 10 years [4].

2.3.7 Astrocytoma

Astrocytomas arise from cells of tissue that supports nerve cells [19] (Fig. 2.5). Their frequency in males and females are equal. Astrocytomas comprise 1% of spinal tumors. They are commonly located in the cervical region of the spine and often involve multiple spinal segments. Nearly 20% of such lesions are associated with syrinx formation [17]. Malignant degeneration develops in 25% of adult astrocytomas [16]. There are many histopathological subtypes of astrocytomas. Pilocytic astrocytomas and subependymal giant cell astrocytomas are classified as WHO Grade 1, pleomorphic and diffuse astrocytomas are classified as WHO grade 2, and anaplastic astrocytomas are classified as WHO grade 3 [15].

2.3.8 Lipoma

Lipomas are congenital tumors that constitute 1% of spinal tumors. They are commonly found in the cauda equina and conus medullaris. Lipomas are the most common dysembryogenic pathology and are in juxtamedullary locations. They are different than other tumors due to their subpial location [5].

2.4 Clinical Features

Spinal cord tumors are usually symptomatic with motor loss, sensory defects and urinary incontinence [19]. Neurogenic bladder and total incontinence of the bladder sphincter are observed in patients with intramedullary tumors of the spinal cord. Sphincter disturbances may be non-specific and the perianal reflex may be absent. Upper or lower motor neuron examination findings can

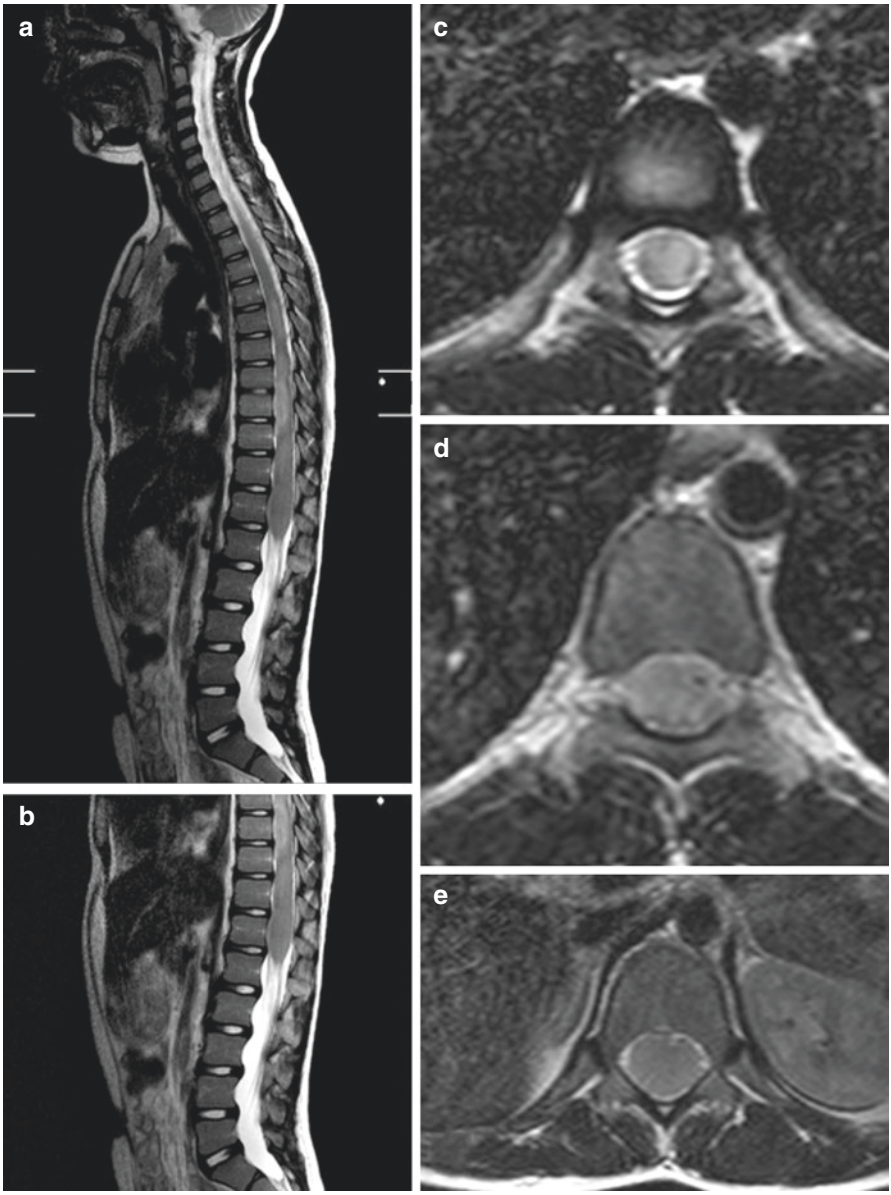

Fig. 2.5 (**a**) Sagittal T2-weighted MRI of spinal cord that is diffusely infiltrated by astrocytoma. (**b**) Diffuse involvement and enlargement of the spinal cord by highly aggressive and infiltrative intramedullary spinal cord astrocytoma. Axial T2-weighted MRIs of the spinal cord at the mid-thoracic (**c, d**) and lower thoracic (**e**) level that are revealing the totally infiltrated by the tumor

be seen according to the tumor location. Increased deep tendon reflexes, spasticity, atrophy, and fasciculation may provide insight into the location of the tumor. Magnetic resonance imaging (MRI) and computed tomography (CT) are primarily used for diagnosis. Different methods, such as surgery, medical and radiosurgery, are applied for treatment depending on the patient and their characteristics.

2.5 Conclusion

There is no clear consensus on classification and proper terminology of spinal tumors. Although, the correct histopathologic subtypes for primary spinal cord tumors should include the pure intramedullary tumors, it should be known that tumors originating from extramedullary structures, such as the dura and nerve sheath, are categorized as spinal cord tumors. Spinal cord tumors should be considered in differential diagnoses when the symptoms and clinical findings of patients with spinal complaints are also associated with findings of upper neuron disease. The lack of the consensus on a single classification scheme and proper terminology is an important factor for correct epidemiologic knowledge of primary spinal cord tumors.

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Spinal Cord Anatomy

3

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3.1 Overview of the Spine

The spinal cord is a cylindrical structure located within the vertebral canal bordered anteriorly by the posterior vertebral body, laterally by the pedicles, and posteriorly by the lamina. The bony spinal column consists of 33 total vertebrae: 7 cervical, 12 thoracic, 5 lumbar, 5 sacral, and 4 coccygeal vertebrae.

The spinal cord begins at the foramen magnum of the skull as a direct continuation of the medulla oblongata and terminates as the conus medullaris at the level of either the lumbar L1 or L2 vertebral body, although variations in termination level do exist [1–3]. Caudal to the conus medullaris, there is no longer spinal cord, but rather free-floating nerve roots collectively known as the cauda equina, corresponding to the lumbar, sacral, and coccygeal nerve roots. Only during early embryologic development does the spinal cord span the entire spinal column. Due to development and growth, the cord appears to terminate in the upper lumbar spine.

On gross examination of surface anatomy, one cannot appreciate the transition from spinal cord to cauda equina due to the uniform tubular contour created by the dura mater, of which only one layer envelops the spinal cord. Dura mater overlying the brain consists of two layers: an outer periosteal layer and an inner meningeal layer. The periosteal layer is adherent to the inner surface of the skull and does not extend beyond the foramen magnum. Therefore, the inner meningeal layer is the only dural layer overlying the spinal cord. The dura mater from the brain continues to the spinal cord and terminates in the second sacral vertebra where it joins the pia mater to taper into a filament known as the coccygeal ligament, anchoring the spinal cord to the coccyx [1].

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3.2 Embryology

Development of the spinal cord begins as early as the second week of gestation, and occurs as three stages: gastrulation, primary neurulation, and secondary neurulation [2]. During gastrulation, the embryo differentiates into three distinct germ cell layers: ectoderm, mesoderm, and endoderm. Ectodermal epiblast cells on the dorsum of the embryo migrate to the midline to form the primitive streak and primitive groove [4]. The primitive node lies at the edge of the primitive groove and forms the notochordal process, a tube-like structure of mesoderm cells that remains ventral to the ectodermal cells. The overlying ectodermal cells form the neural plate, which will play an important role in the next stages of development. Additional epiblasts migrate to the interior of the embryo via the primitive streak in a process known as ingression to form the ventral endoderm. The notochord is a transient embryologic structure that eventually becomes the nucleus pulposus within intervertebral discs. Gastrulation abnormalities can result in anterior meningocele and split cord malformations.

The next two steps in spinal cord development are primary and secondary neurulation, the processes by which the neural plate edges fold and join to form the neural tube. Primary neurulation begins around post-ovulation day 16. This stage marks the formation of cervical, thoracic, lumbar, and first two sacral segments. The edges of the neural plate elevate to form neural folds, beginning in the cervical region [4]. Neural plate formation and folding, as well as fold fusion, occurs during this time. The neural tube openings, or neuropores, at the anterior and posterior ends close on post-ovulation days 25 and 27, respectively. Open neural defects occur because of abnormalities at this stage.

Secondary neurulation begins around post-ovulation days 25 to 27. Undifferentiated ectodermal cells at the caudal end of the neural tube form the tail bud, or caudal cell mass. The tail bud ultimately forms the central canal, which spans the entire length of the neural tube. The caudal portion of the tail bud regresses to form the filum terminale. The remaining sacral segments also form during this stage. By the fortieth week of gestation, the conus can be found at lumbar levels L1 or L2.

Once the neural tube closes, three distinct layers can be identified: matrix, mantle, and marginal layers. The matrix layer surrounds the central canal and gives rise to neuroblasts, which migrate via radial migration [5]. Neuroblasts also originate from neuroepithelial cells on the wall of the neural tube. These neuroblasts form the mantle cell layer, which will become the gray matter of the spinal cord. The marginal layer becomes white matter [4]. The ventral mantle layer forms the basal plates, which will become the motor horn, while the dorsal mantle layer forms the alar plates, which will become the sensory horn. The basal and alar plates are separated by the lateral sulcus limitans.

3.3 Organization of the Spine

3.3.1 Nomenclature of Spinal Cord Levels

The designation of spinal cord levels is an artificial concept but helps clinicians to reliably communicate clinically significant findings. A solid understanding of the

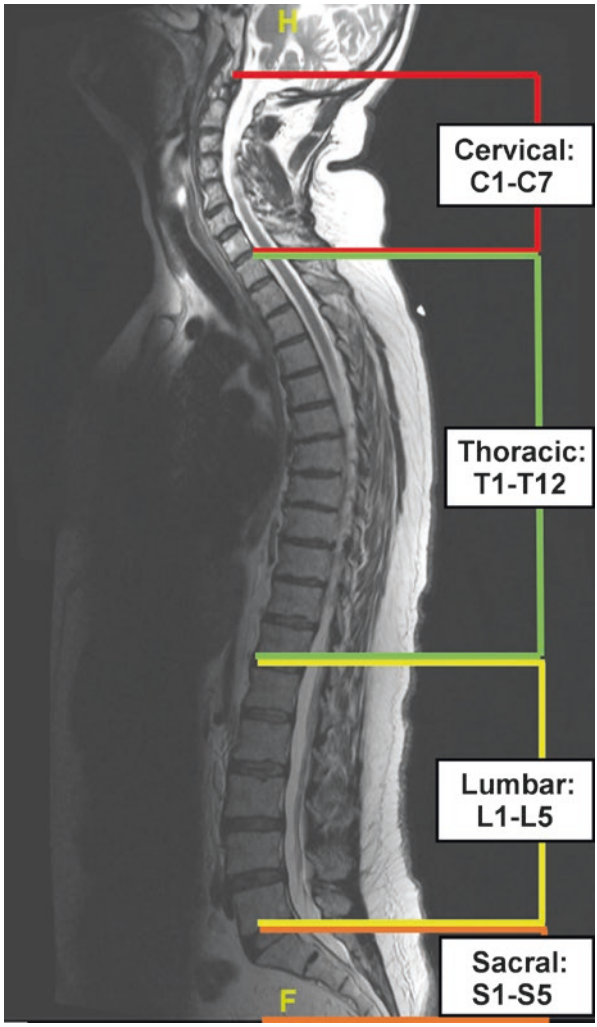

Fig. 3.1 Sagittal MRI of the spine spanning cervical, thoracic, lumbar, and sacral regions

fundamental cord nomenclature, therefore, is necessary. Although the spinal cord itself is a single, contiguous entity, discrete axial cross-sectional levels of the cord can be identified and organized relative to the bony anatomy of the spine.

The cervical spinal cord corresponds to cervical vertebrae C1–C7 (Fig. 3.1). The thoracic spinal cord spans from thoracic vertebrae T1–T12. The spinal cord terminates as the conus medullaris, usually at T12 or L1, below which the cord becomes the cauda equina, corresponding the lumbar vertebrae L1–L5. The sacrum consists of five segments, while the coccyx consists of four segments.

3.3.2 Nomenclature of Spinal Nerves

A total of 31 paired nerves originates from the spinal cord: 8 cervical, 12 thoracic, 5 lumbar, 5 sacral, and 1 coccygeal pairs. Paired nerves exit the spinal cord

bilaterally and traverse inferior to the pedicles and laterally through the neural foramina, or intervertebral foramina. In the cervical spinal cord, there are eight nerves, but only seven vertebrae. Therefore, the nomenclature of the cervical nerves is unique in that a given nerve exits above its corresponding numbered cervical vertebra. For example, the C2 nerve exits above the C2 vertebral body, while the C3 nerve exits below the C2 pedicle. The C8 nerves exit below the C7 pedicles.

In the thoracic and lumbar spines, the numbering of corresponding nerves is more straightforward because the number of nerves equals the number of vertebral bodies. A given nerve exits below the pedicle of its corresponding level. For example, the T12 nerve exits below the T12 pedicle, while the L5 nerve exits inferior to the L5 pedicle.

3.4 Gross Anatomy of the Spinal Cord

In axial cross sections, the cervical spinal cord is oval in shape, with the transverse diameter longer than the anterior-posterior diameter [5]. The spinal cord at the C1–2 region is smaller than in the subaxial (C3–7) cervical spine [6]. The subaxial spinal cord has a wider diameter due to segmental fibers that supply motor and sensory function to the arms and hands via the brachial plexus. This portion is known as the cervical enlargement. Maximal spinal cord diameter in the cervical cord occurs at C5–6, with a transverse diameter of approximately 13 mm, and an anterior-posterior diameter of 7.5 mm [5].

The thoracic and lumbar segments take a rounder shape. The smallest diameter throughout the spinal axis occurs in the thoracic cord, measuring approximately 6.4 mm. The lumbar spine contains another enlargement due to the lumbosacral plexus, measuring 9 mm in the transverse direction and 7 mm in the anterior-posterior direction.

Surface anatomy of the cord helps to distinguish dorsal and ventral structures, as well as laterality (Fig. 3.2). The anterior median fissure and posterior median sulcus occur along the midline and bisect the cord into symmetric right and left halves. On either side of the anterior median fissure lie the anterolateral sulci. Along the posterior aspect of the spinal cord lie the posterolateral and posterior intermediate sulci.

3.5 Vasculature

Blood supply to the spinal cord are provided by three main vertically-oriented arteries. The anterior two-thirds of the spinal cord are supplied by the anterior spinal artery, which originates from the vertebral arteries and join together at the midline at the level of the medulla [5]. A branch of the anterior spinal artery, the sulcal artery, supplies the gray matter. The posterior spinal cord is supplied by a pair of posterior spinal arteries. These arteries arise from the posterior inferior cerebellar artery in 75% of cases, and from the vertebral arteries in 25% of cases.

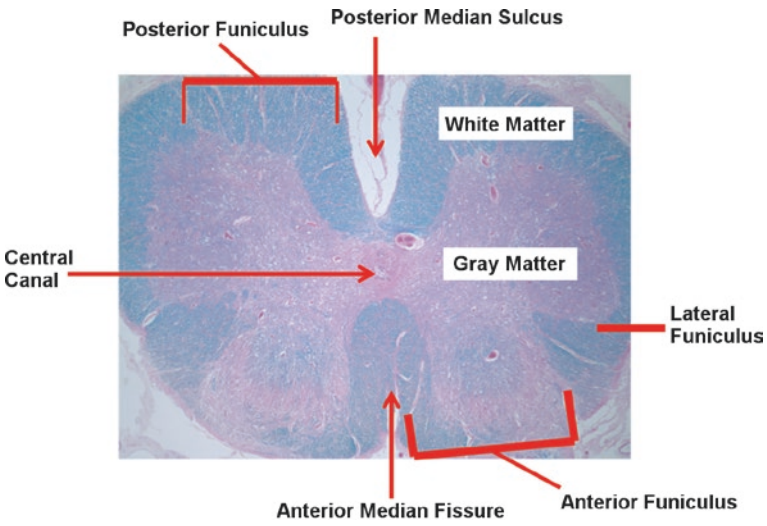

Fig. 3.2 Axial cross-section of spinal cord, histologic hematoxylin and eosin stain, demonstrating surface anatomy and organization of central gray and peripheral white matter

Smaller arteries also supplement the three main arteries. The arterial vasocorona are anastomoses between the anterior and posterior spinal arteries and supply the lateral aspect of the spinal cord. Segmental medullary arteries originate from various branches, dependent upon the spinal level: vertebral, ascending cervical, deep cervical, posterior intercostal, lumbar, and lateral sacral arteries [7]. These vessels supply the spinal cord, as well as the vertebral bone. The largest medullary artery is the artery of Adamkiewicz, which originates from an intercostal artery, arising from the aorta, in the lower thoracic spine at levels T8–T12. This artery also occurs more often on the left side.

Spinal veins follow a similar course as the arteries. The anterior and posterior spinal veins drain the interior of the spinal cord. Radicular and spinal veins then carry blood to the internal vertebral venous plexus, which lies in the epidural space in the spinal canal [7]. The intervertebral and basivertebral veins connect the internal plexus with the external venous plexuses, which then ultimately drain into the azygos system.

3.6 Blood–Spinal Cord Barrier

There is a blood-spinal cord barrier (BSCB)—like the blood-brain barrier—that helps to protect the spinal cord parenchyma [8]. The BSCB is composed of non-fenestrated capillary endothelia, capillary pericytes, and astrocytic foot processes. Capillary endothelia in the spinal cord, unlike those of the peripheral circulation, are non-fenestrated, which limits free transcellular diffusion of molecules. Tight junctions between endothelial cells further ensure restricted diffusion.

Pericytes are cells associated with capillary vessel walls, separated from the endothelium by the basal lamina. These cells communicate with endothelial cells via gap junctions. Pericytes play a role in endothelial cell proliferation, migration, and differentiation [8]. They are also believed to contribute in the synthesis of basal lamina components, such as proteoglycans.

Astrocytes surround the surface of capillaries, and instead of providing mechanical protection of the spinal cord, physiologically manage secretory patterns of capillaries. For example, astrocytic foot processes express aquaporin 4 and potassium channel Kir4.1, which help to regulate ion and volume concentrations within the cord [8].

3.7 Functional Anatomy

On axial cross section views of the spinal cord, gray matter is located centrally, while white matter lies in the periphery. The gray matter forms a butterfly-like shape within the spinal cord, and the "wings" constitute dorsal and ventral horns, which mediate sensory and motor functions, respectively.

3.7.1 Gray Matter: Internal Organization

The gray matter of the spinal cord is organized into 10 laminae, or nuclei, labeled I–X. This arrangement was first described by Bror Rexed in 1952 [9] (Fig. 3.3).

- Lamina I is the marginal nucleus or posteromarginal nucleus, located along the apex of the dorsal horn of gray matter. Neurons receive input from Lissauer's tract and process information regarding pain and temperature.

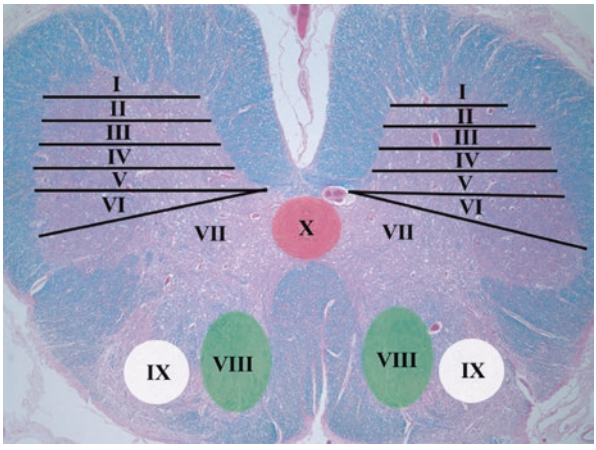

Fig. 3.3 Rexed laminae

- Lamina II is the substantia gelatinosa of Rolando. This layer appears gelatinous due to a low concentration of myelinated fibers. First-order neurons of the spinothalamic tract synapse at this nucleus, involved in pain reception. C fibers terminate at this layer and conduct poorly localized pain. There are also A delta fibers that terminate at this layer, which are involved in relaying fast, localized pain sensations [10].
- Laminae III and IV are known as the nucleus proprius. These nuclei are the first synapse of the spinothalamic tract, which relays pain and temperature sensation [11].
- Lamina V neurons process sensory information from cutaneous, muscle and joint, and visceral nociceptors.
- Lamina VI is located at the base of the dorsal horn of the gray matter. It is responsible for the flexion reflex, prompting withdrawal of extremities from a painful stimulus.
- Lamina VII is the intermediolateral nucleus, located in the thoracic and upper lumbar spine. This nucleus mediates sympathetic innervation to the body via preganglionic fibers (general visceral efferents).
- Lamina VIII contains motor interneurons.
- Lamina IX, located in the ventral portion of the gray matter, contains the phrenic and spinal accessory nuclei in the cervical spinal cord, and Onuf's nucleus in the sacral segments, which is involved in urinary and bowel continence. The neurons within this nucleus are the origin of the pudendal nerve [12]. This lamina was described by Bronislaw Onuf-Onufrowicz in 1899 [13].
- Lamina X circumferentially surrounds the central canal. The function of this layer is not fully understood.

3.7.2 White Matter: Descending Tracts

The descending tracts within the spinal cord are classified into two categories: pyramidal and extrapyramidal tracts. The two pyramidal tracts are the anterior and lateral corticospinal tracts. The pyramidal tracts are the anterior and lateral corticospinal tracts. The four major extrapyramidal tracts are the rubrospinal, reticulospinal, tectospinal, and vestibulospinal tracts. (Fig. 3.4).

Corticospinal Tract. There are two corticospinal tracts: the anterior corticospinal tract and the larger lateral corticospinal tract. Fibers of both tracts do decussate, but at distinct levels within the central nervous system. The anterior corticospinal tract is responsible for axial and proximal limb movement and is composed of descending fibers originating in the motor cortex of the brain. These neurons synapse with second-order neurons within the anterior column of the spinal cord, decussating in the anterior horn, ultimately synapsing on the target motor end plate.

The lateral corticospinal tract is the largest descending tract, controlling limb movements. Its first-order neurons originate in the premotor and primary motor cortex of the brain. These neurons decussate at pyramids within the medulla oblongata, giving rise to second-order neurons. The tract then runs along the lateral column of the cord, medial to the dorsal spinocerebellar tract. Almost half of these

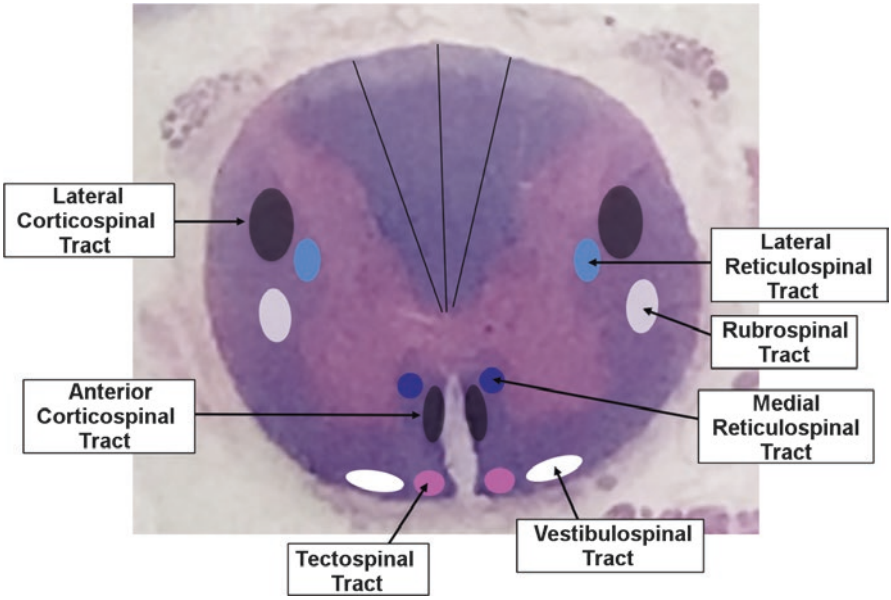

Fig. 3.4 Descending tracts of the spinal cord

axons synapse in the cervical spinal cord. Fibers mediating the upper extremities are located medially, while lumbar and sacral fibers are located laterally [5, 14].

Rubrospinal Tract. The rubrospinal tract mediates voluntary muscle movements. Most fibers terminate within the cervical spinal cord, suggesting that the rubrospinal tract is more involved with the upper limbs rather than the lower limbs. This tract originates in the magnocellular red nucleus within the midbrain. Neurons cross to the contralateral side within the midbrain and descend to the spinal cord, where the tract travels within the lateral funiculus, ventrolateral to the lateral corticospinal tract.

Reticulospinal Tracts. The reticulospinal tracts originate in the reticular formation in the brain, diverging onto two separate paths: the medial and lateral reticulospinal tracts. The reticulospinal tracts are involved in volitional motor, fine motor, and postural control. The medial reticulospinal tract activates extensor muscles and works in conjunction with the vestibulospinal tract to provide postural control. It lies posterior to the anterior corticospinal tract. The lateral reticulospinal tract inhibits axial extensor muscles and also modulates automatic breathing. It lies medial to the lateral corticospinal tract.

Tectospinal Tract. The tectospinal tract originates in the superior colliculus of the midbrain, crossing to the contralateral cervical cord. This tract helps to coordinate eye and head movements in response to visual stimuli. This tract lies in the anteromedial cord, lateral to the anterior median fissure.

Vestibulospinal Tract. The vestibulospinal tract, which lies in the anterior horns of the spinal cord, consists of two components: the medial and lateral vestibulospinal tracts. These tracts help to maintain head and eye coordination, as well as postural

balance. Medial vestibulospinal tract fibers originate in the medial vestibular nucleus, which lies within the medial longitudinal fasciculus, terminating in the cervical spinal cord. This tract helps to activate neck muscles that act in concert for coordinate head and eye movements. The lateral vestibulospinal tract relays signals to activate antigravity muscles, which help to maintain an upright posture.

3.7.3 White Matter: Ascending Tracts

The ascending tracts in the spinal cord convey sensory information from the body to the brain, and can be organized into two major categories: tracts conveying conscious and unconscious information [5]. The pathways involved in conscious information processing are the dorsal column and spinothalamic tracts. The spinocerebellar tracts are involved in unconscious information processing. (Figs. 3.5 and 3.6).

Dorsal Column/Medial Lemniscus. The dorsal column pathway of the spinal cord carries sensory information to the somatosensory cortex of the brain. Touch, vibration, and proprioception are relayed along this tract [15, 16]. First-order neurons originate from the peripheral nerves and ascend to the medulla oblongata. Neurons from the lower limbs travel in the fasciculus gracilis, or the medial portion of the dorsal column. The upper limb neurons travel in the fasciculus cuneatus, or the lateral portion of the dorsal column [17]. Second-order neurons begin in the cuneate or gracilis nuclei, and these fibers decussate in the medulla oblongata,

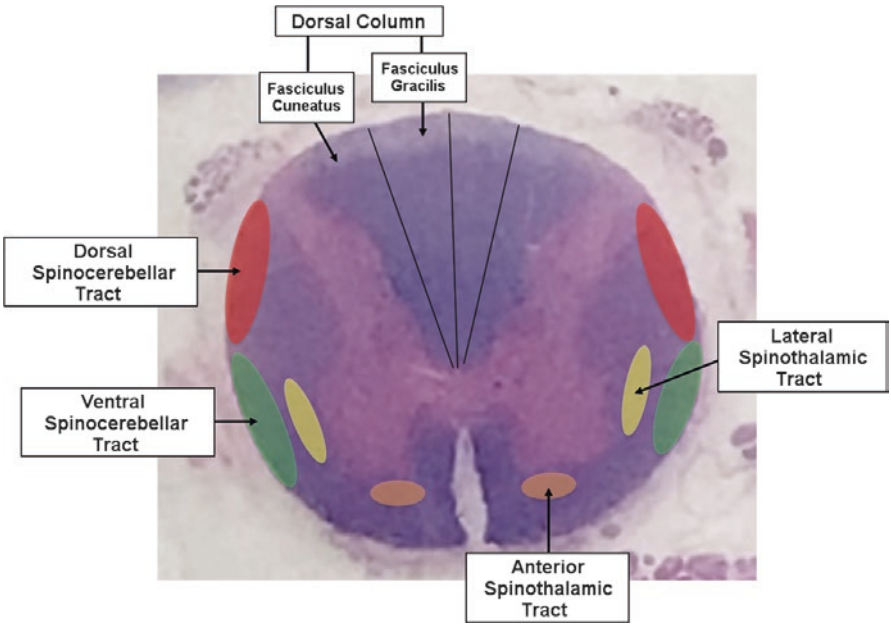

Fig. 3.5 Ascending tracts of the spinal cord

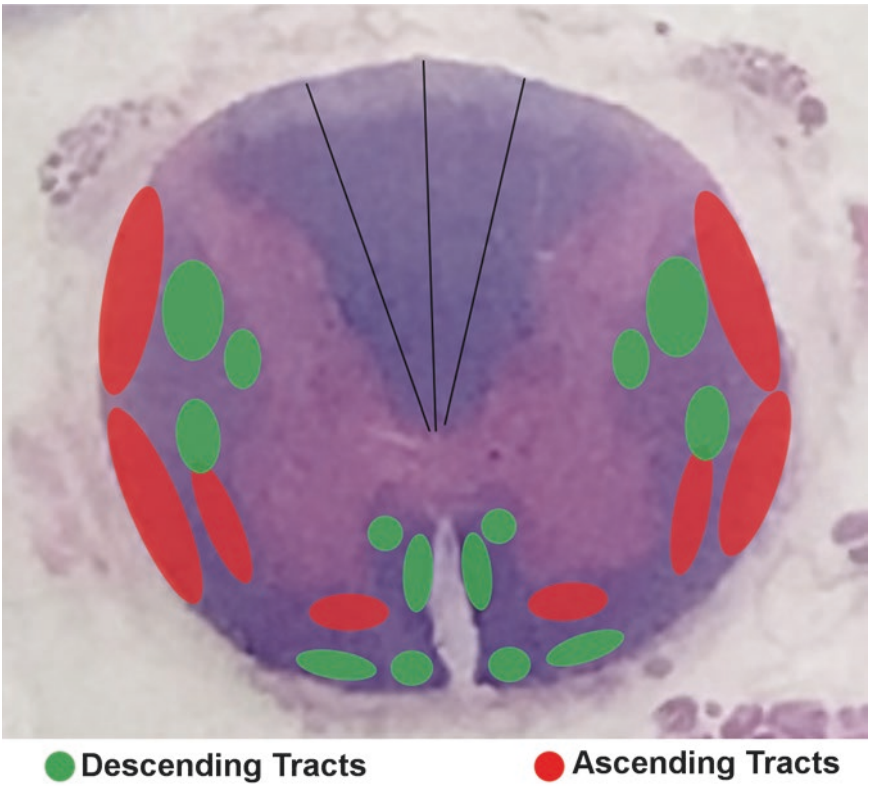

Fig. 3.6 Compilation of descending and ascending tracts of the spinal cord

terminating in the thalamus. Third-order neurons originate from the ventral posterolateral nucleus (VPL) of the thalamus, traveling as the medial lemniscus, via the internal capsule and terminating in the primary sensory cortex.

Spinothalamic Tracts. The spinothalamic tracts are comprised of two adjacent pathways with two distinct functions: the anterior spinothalamic tract conveys crude touch and pressure sensation, and the lateral spinothalamic tract conveys pain and temperature sensation. The points of origin are the same for these two tracts, peripheral sensory receptors, and they diverge at the level of second-order neurons.

First-order neurons originate in peripheral sensory receptors, and in the spinal cord, ascend one or two vertebral levels, and synapse in the substantia gelatinosa (Rexed lamina II). Second-order neurons decussate within the spinal cord, via the anterior white commissure, and then give rise to either the anterior or lateral spinothalamic tract. The fibers have a somatotopic organization, with cervical segments lying medially and sacral segments in the lateral portion of the tract. The spinal cord is the only point at which spinothalamic fibers decussate to the contralateral side. These fibers ascend to the thalamus in the brain. Third-order neurons from the VPL of the thalamus then travel through the posterior limb of the internal capsule and terminate in the sensory cortex [17].

Spinocerebellar Tracts. The anterior spinocerebellar tract conveys proprioceptive information from the lower extremities to the cerebellum. Fibers decussate twice, and therefore, the tract terminates in the ipsilateral cerebellum [18]. The posterior spinocerebellar tract directly conveys proprioceptive information from the lower extremities to the ipsilateral cerebellum. These fibers do not decussate. The rostral spinocerebellar and cuneocerebellar tracts convey proprioceptive information from the upper extremities to the ipsilateral cerebellum.

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Diagnostics and Differential Diagnostics of Spinal Cord Tumors

4

Zulejha Merhemic and Majda M. Thurnher

4.1 Introduction

Spinal cord tumors are rare tumors with nonspecific clinical symptoms; they occur usually in the late stage of the disease, resulting in delayed diagnosis. Radicular symptoms and other symptoms, such as back pain, slowly progressive neurologic deficits, or skeletal deformities (such as kyphoscoliosis), are commonly observed in children. Spinal cord tumors amount to between 20 and 30% of all primary intradural spinal tumors. About 70–80% of the remaining primary intradural tumors are located in the intradural-extramedullary compartment [1].

Magnetic resonance imaging (MRI) is the method of choice for detecting and evaluating spinal cord tumors. The imaging protocol should be composed of sagittal and axial T1-weighted and T2-weighted sequences. Those sequences should include contrast enhanced T1-weighted sequences in the sagittal, axial, and coronal planes. Short-TI Inversion Recovery (STIR) must be added for spinal cord tumors, as well as for the detection of bone abnormalities. Recently, some advanced techniques, such as diffusion-weighted imaging (DWI) and diffusion tensor imaging (DTI), have been described being increasingly used in the spinal lesions evaluation [2].

New techniques—including DTI and fiber tractography (FT)—have potential usefulness in preoperative diagnosis and postoperative follow-up of spinal cord tumors. These techniques are more sensitive than conventional MRI because they provide a more detailed picture of the white matter tracts in relation to space-occupying lesions. Exploiting tractography in these cases is helpful in predicting the nature of the lesion preoperatively and in surgical intervention planning [3].

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DTI and diffusion tensor tractography (DTT) enable assessment of spinal cord changes caused by neoplastic disease, both in cases of intramedullary and extramedullary tumors. DTI, and especially DTT, may be useful in preoperative evaluation of spinal cord tumors. DTT provides good visualization of the displacement and deformation of the spinal cord tracts at the tumor's level in ependymomas or astrocytomas (Fig. 4.1), as well as deformation and disruption of the fibers in metastatic lesions. Thus, DTT may be valuable in the evaluation of the tumors' resectability, suggested that DTI of adult intramedullary spinal cord neoplasms can differentiate astrocytomas from ependymomas [4]. In adults, infiltrative astrocytomas are more common than in the pediatric population, while ependymomas tend to be well circumscribed. These tumors can be characterized by using DTI and DT-FT to evaluate the structural integrity of the white matter tracts, which could be a way to decrease the need for biopsy of the adult spinal cord tumor. Because of the discrete nature of most pediatric intramedullary spinal cord neoplasms, DTI is less likely to differentiate astrocytoma from ependymoma in children compared with adults [5].

Myelography and computed tomography (CT)-myelography are only used for spinal cord tumors diagnose when MRI cannot be performed (for example, when a patient has an implanted pacemaker or internal defibrillator). Analyzing the cerebrospinal fluid (CSF) may help the surgeon decide on a differential diagnosis with an inflammatory disease.

Further angiography can be performed to demonstrate the vascularization of hypervascular lesions and presurgical interventions, such as the embolization [6]. In order evaluate intramedullary lesions, particularly for tumors with high-grade

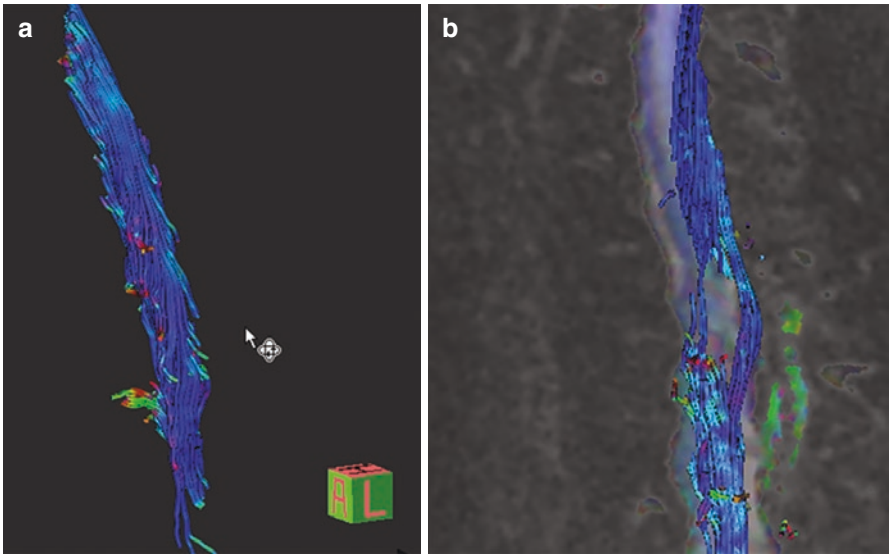

Fig. 4.1 DTI-tractography. (**a**) Astrocytoma: diffusely infiltrating fibers infiltrated but preserved. (**b**) Ependymoma: more central location; fibers displaced laterally

Table 4.1 Tumor comparisons

Ependymoma	Astrocytoma	Ganglioglioma
Central localization	Eccentric localization	Central localization
Well circumscribed	Pure circumscribed	Well circumscribed
Cervical> thoracic	Cervical>thoracic	Cervical, thoracic spine
3–4 segments	5–6 segments	1 segment
"Cap sign"-hemosiderin	± cyst	± cyst
Homogeneous	Inhomogeneous enhancement	Variable (minimal-to-marked)
Adult most common	Children-most common	Children
M < F	M > F	
NF2	NF1	

malignancy, Spinal positron emission tomography (PET)/CT using fludeoxyglucose or 11(C) methionine was used. Differentiation of tumors with low-grade malignancy from non-neoplastic lesions may still prove challenging [7].

Table 4.1 compares ependymomas, astrocytomas, and gangliogliomas of the spinal cord.

4.2 Ependymoma

The most common primary spinal cord tumor in adults is ependymoma (60% of all primary spinal cord neoplasms) with range age at presentation of 35–45 years. It is the second-most common primary spinal cord tumor in children. Ependymomas are slow growing tumors originating from the ventricle wall or from the ependyma lining of the spinal cord central canal. There are four histologic ependymoma subtypes: cellular, myxopapillary, tanycytic, and clear-cell. The World Health Organization (WHO) currently classifies ependymomas into three grades: Grade I tumors, including myxopapillary ependymomas and subependymomas; Grade II tumors, including classic ependymomas; and Grade III tumors, including anaplastic ependymomas [8]. These grade classifications may be helpful in making treatment decisions, but the prognostic value is still controversial. Ependymoma may be associated with neurofibromatosis type 2 (NF2). In NF2, most ependymomas are WHO Grade II and, rarely, WHO Grade III (anaplastic ependymoma).

Cellular ependymomas are located mostly in the cervical and thoracic spinal cord and have a slight female predilection. They are well-defined (they may even be encapsulated masses) and span up to four segments [9]. The "cap sign" (hemosiderin on cranial or caudal margin) due to hemorrhage strongly suggests cord ependymoma. They have cystic presentations in 50–90% of cases, and cysts usually have CSF intensity. The solid portion of the tumor is isointense or mildly hypointense on T1-weighted images, hyperintense on T2-weighted images and STIR, and always enhances after contrast administration [9]. Syrinx is also a common finding (Fig. 4.2).

Myxopapillary ependymoma is mostly a tumor of the conus medullaris or the filum terminale, originating from ependymal cells of the filum terminale.

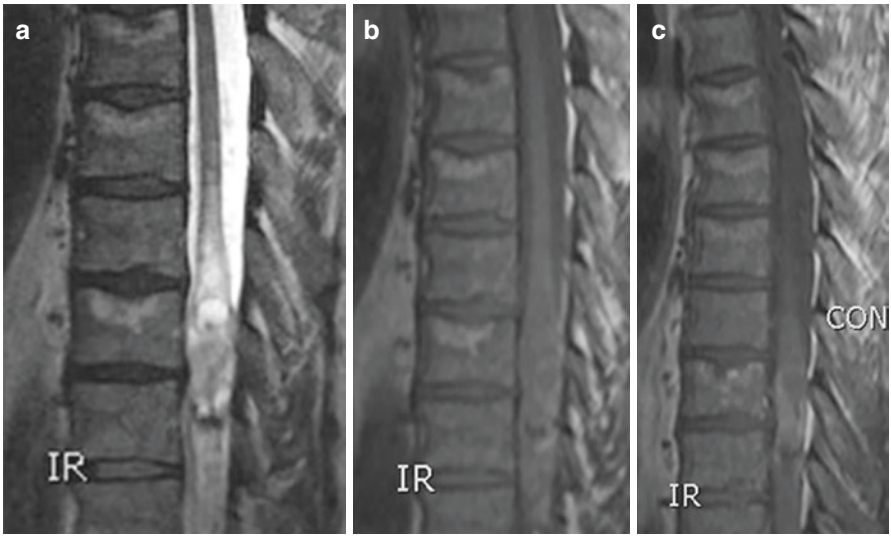

Fig. 4.2 Cellular ependymoma MRIs. Sagittal T2-weighted (**a**), sagittal T1-weighted (**b**), sagittal contrast enhanced T1-weighted (**c**) MRIs showing intramedullary mass in the thoracic spinal cord with hemosiderin deposits on caudal margin "cap sign" and cyst formation on the cranial part of tumor. Enhances after contrast administration

Ninety percent of all filum terminale tumors are myxopapillary ependymomas. It is classified as a WHO Grade I tumor and has a male predilection. These tumors present with high-T2, isointense, or low-T1 signal intensity masses with strong but inhomogeneous enhancement (Fig. 4.3). Scalloping of the vertebral bodies, scoliosis, and enlargement of the neural foramina are additional findings suggestive of myxopapillary ependymoma [10]. Myxopapillary ependymomas are characterized as histologically benign slow-growing tumors, but some patients demonstrate local recurrence or even distant metastasis that more likely occurs in the pediatric population [11].

Tanycytic ependymoma is a rare subtype of the WHO Grade II ependymoma. The female-to-male ratio was calculated as about 1:1.5 with a mean age at diagnosis of approximately 36.1 ± 18 years [12].

Histologically, these tumors have spindle cells arranged in a fascicular pattern, an absence of ependymal rosettes, and inconspicuous perivascular pseudorosettes. A recently published meta-analysis of all described cases did not find any specific imaging finding. Solid mass with T1 hypointense, or isointense signal and T2 hyperintensity with or without a cystic component with an associated syringomyelic cavity has been reported [13].

Total resection gives the best outcomes for spinal ependymomas. Precisely, classic Grade II ependymomas may benefit mostly from aggressive resection, whereas myxopapillary Grade I ependymomas do not have clear benefits from total resection [14].

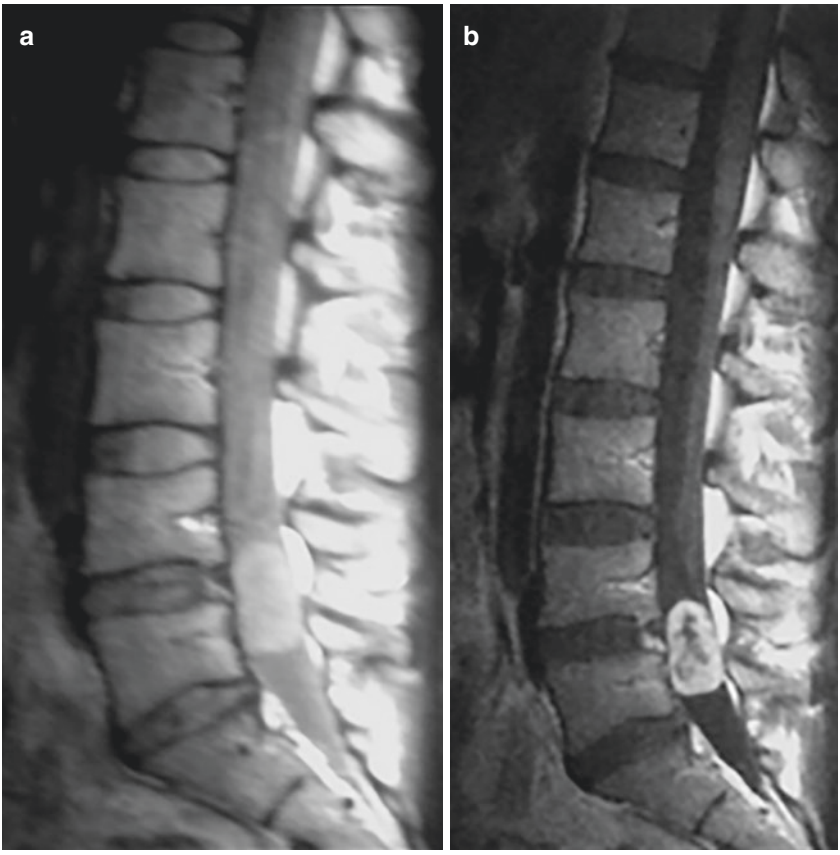

Fig. 4.3 Myxopapillary ependymoma in 29-year-old female with a history of mild lower-back pain. Sagittal proton-density (PD) weighted (**a**), and contrast-enhanced T1-weighted (**b**) image demonstrating well-define hyperintense cauda equina mass on proton-density (PD) weighted image, heterogeneously enhanced

There are only 14 reports of primary seeding of myxopapillary ependymomas in adults, which were treated as having "aggressive" behavior and as malignant tumors [15].

4.3 Astrocytoma

Astrocytoma is an intramedullary infiltrating mass present in 5–10% of all central nervous system (CNS) tumors. It is the most common spinal cord tumor in children and the second-most common tumor in adults with a slight male predilection. Astrocytomas are composed of neoplastically transformed astrocytes varying from well-differentiated to anaplastic. In almost 90% of cases, astrocytomas are low-grade neoplasms. An astrocytoma extending along four segments or fewer, and

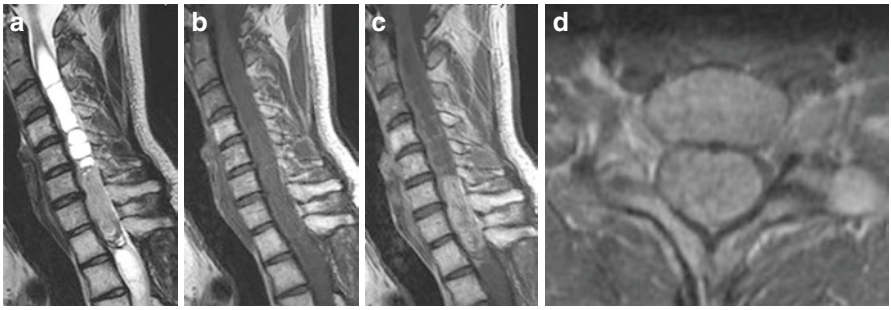

Fig. 4.4 Pilocytic astrocytoma after partial resection. Sagittal T2-weighted (**a**), T1-weighted (**b**), and contrast-enhanced T1-weighted (**c**, **d**) images demonstrating completely solid tumor with moderate contrast enhancement and an associated syrinx in the cervical cord

uncommonly, the entire length of the spinal cord predominantly seen in children, termed as "holocord" tumor [10].

Fibrillary astrocytoma (WHO II) is usually found in the cervical spine, whereas pilocytic astrocytoma (WHO I) is mostly found in the conus medullaris (Fig. 4.4). In 10% of cases high-grade astrocytoma can also occur, mostly as anaplastic astrocytoma [16]. Several cases in the spinal cord have been reported recently with diffuse meningeal dissemination [17]. Glioblastoma is uncommon in the spine. Astrocytomas are mostly a solid mass; they can show areas of necrotic-cystic degeneration, or they can be completely solid (in approximately 40% of the cases). For surgical planning is crucial to differentiate neoplastic cyst with enhancing wall from non-neoplastic cysts with non-enhancing wall after contrast administration. The solid portion of the tumor is isointense or mildly hypointense on T1-weighted images, hyperintense on T2-weighted images and T2-weighted gradient echo and may show mild-to-moderate contrast enhancement. On DTI, long-tract fibers may be interrupted.

Astrocytomas have an association with neurofibromatosis type 1 (NF1). Intramedullary spinal cord tumors associated with NF1 tend to occur predominantly in male patients and are histopathologically likely to be an astrocytoma [18, 19].

4.4 Ganglioglioma

Gangliogliomas (WHO Grade I) of the spinal cord are extremely rare and are mostly diagnosed in children and young adults. They are localized predominantly in the cervical and thoracic spine [20]. Anaplastic gangliogliomas that are WHO Grade III with anaplastic changes in the glial component have also been reported. Gangliogliomas are seen as circumscribed, solid, or mixed solid with cystic masses on MRI, spanning along cord segment of the spine (Fig. 4.5). Intensities of signals are similar to other intramedullary tumors—hypointense on T1-weighted images and hyperintense on T2-weighted images. Enhancement patterns have been

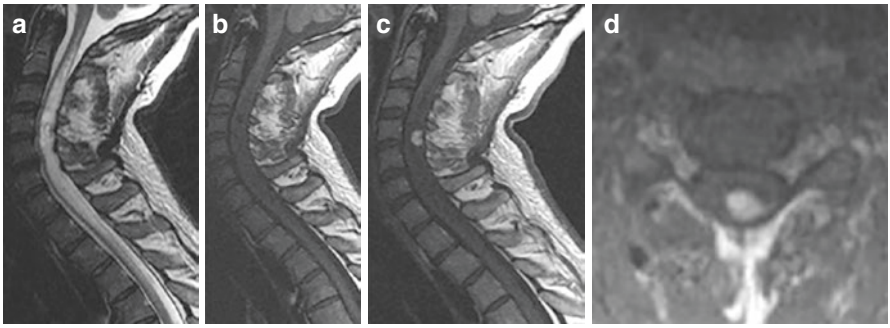

Fig. 4.5 Hemangioblastoma. Sagittal T2-weighted (**a**), T1-weighted (**b**), and contrast enhanced T1-weighted (**c**, **d**) images demonstrating well defined and strongly enhancing small mass in dorsal cervical spinal cord at the C4–C5 level, associated with edema and syrinx

described as highly variable, ranging from minimal to marked, and may be solid, rimmed, or nodular [21]. WHO Grade I gangliogliomas are usually cured with gross total resection.

4.5 Hemangioblastoma

Hemangioblastomas of the CNS are a benign neoplasm classified as a WHO Grade I tumor with mean age at presentation of 30 years. They usually occur in the cerebellum, brainstem, and spinal cord. Hemangioblastomas comprise about 3% of all primary spinal cord tumors [22, 23]. Hemangioblastoma may occur sporadically or in association with von Hippel-Lindau disease [24]. Hemangioblastomas are low-grade neoplasms and are composed of a dense network of vascular capillary channels containing endothelial cells, pericytes, and lipid-laden stromal cells. Spinal cord hemangioblastomas are located in the posterior aspect of the spinal cord. They are round, well defined, and usually small; still, they also can be several centimeters in size. "Flow voids" are always present. After contrast administration, small lesions enhance homogeneously, and large lesions enhance heterogeneously. Tumor nodules are usually associated with extensive hydrosyringomyelia (Fig. 4.6). Cysts are often presented with variable signal intensity, depending on their content. High signal intensity cysts have a high protein content due to previous hemorrhage or because of the transudation of tumor fluid itself. When no cystic component is present, extensive edema is usually found. Subarachnoid or even intramedullary hemorrhage caused by spinal cord hemangioblastomas is rare; however, they should be considered in the differential diagnosis [25].

Surgical resection follows rules that apply to the resection of arteriovascular malformations: coagulation of arterial feeders precedes the coagulation of the draining vein, which is preserved until the end of surgery [26, 27].

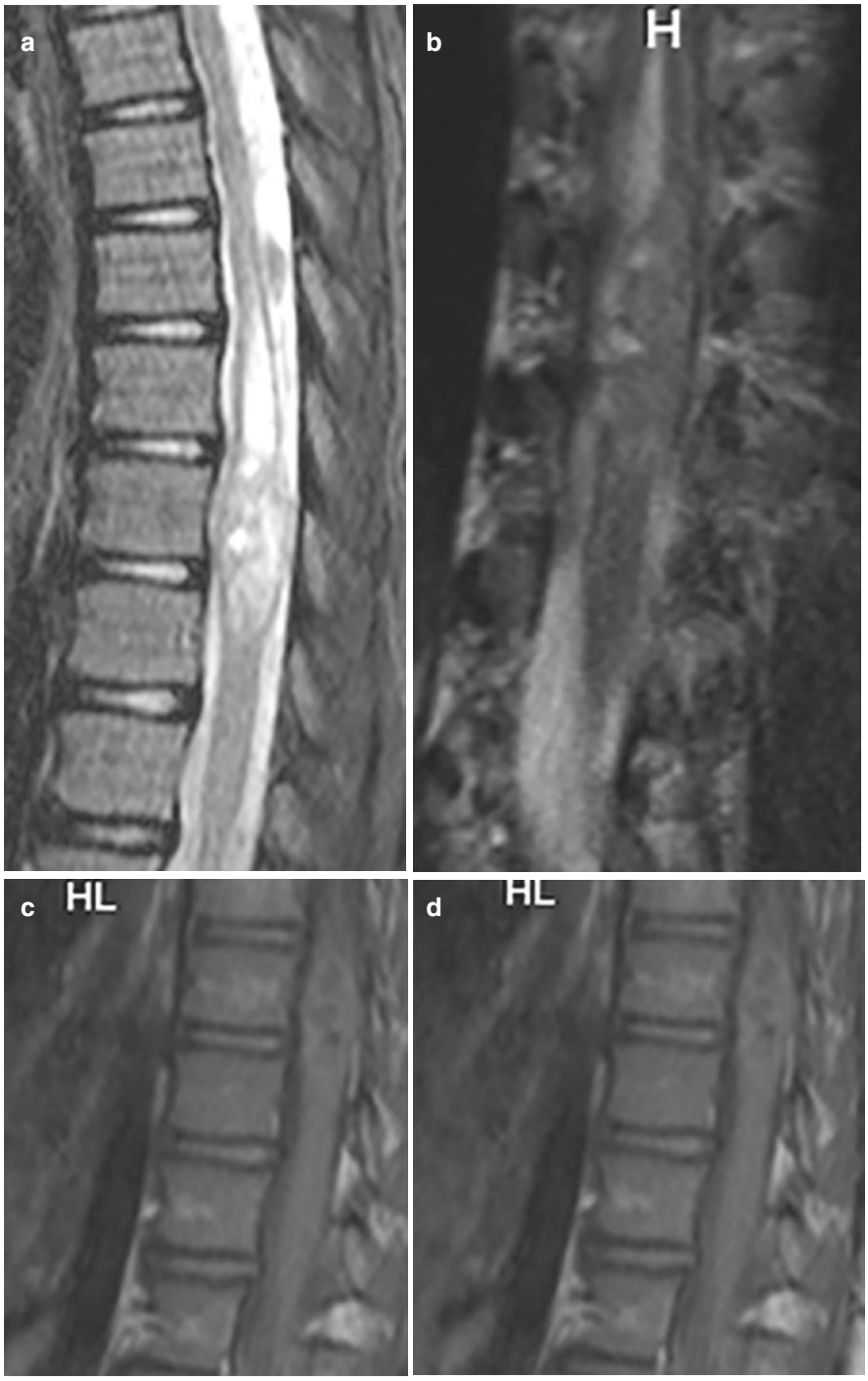

Fig. 4.6 Ganglioglioma. Sagittal and coronal STIR (**a**, **b**), T1-weighted (**c**), and contrast enhanced T1-weighted (**d**) images demonstrating well-defined poorly enhancing mass with areas of cyst degeneration

4.6 Nerve Sheath Tumors

4.6.1 Schwannomas

Spinal schwannomas (WHO Grade I) account for approximately 25% of all spinal tumors and are the most common nerve sheath tumors, originating in Schwann cells [28]. Their peak incidence is at 45-years of life.

Schwannomas are classified according to our novel classification system, which is based on consideration of tumor volume and localization relative to the dura and spinal canal. Seventy percent of all schwannomas are intradural; the other 30% can be extradural and dumbbell-shaped (intradural and extradural) [29].

Spinal schwannomas are typically solitary, well-circumscribed, encapsulated masses (Fig. 4.7). On MRI, schwannomas are isointense-to-hypointense on T1-weighted images, and isointense-to-hyperintense on T2-weighted images.

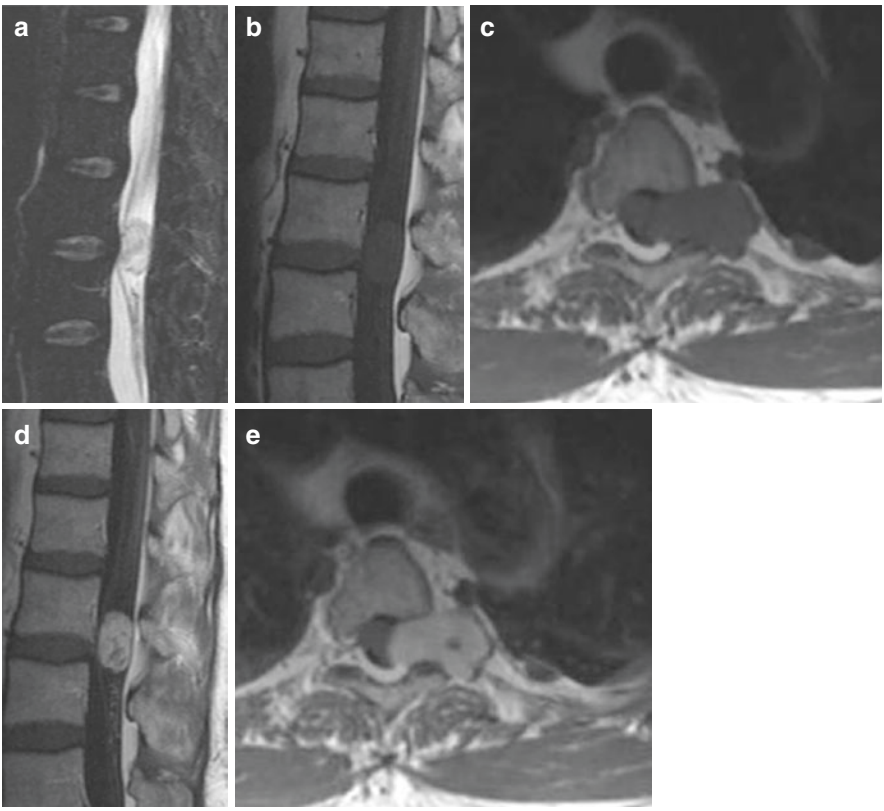

Fig. 4.7 Schwannoma. Sagittal STIR (**a**), T1-weighted (**b**), axial T1-weighted (**c**), sagittal and axial contrast enhanced T1-weighted (**d**, **e**) images showing well-defined mass in spinal canal compressing the spinal cord with "dumbbell" shape, extending through neural foramen left side. Intense homogeneous enhancement of the mass is seen

Contrast enhancement is moderate-to-marked and usually homogeneous. Cervical and lumbar schwannoma localization was more common than thoracic.

Schwannomas are more commonly seen in adults as a solitary mass, and less commonly are seen in children. Multiple schwannomas occur in children with neurofibromatosis type 2 (NF2). NF2 is an autosomal dominant genetic disorder caused by inactivation of the gene 22q, which acts as a tumor suppressor. Patients with NF2 develop multiple central and peripheral nervous system tumors, a hallmark bilateral vestibular schwannoma, and other cranial and spinal nerve schwannomas, as well as meningiomas and ependymomas [30].

Schwannomatosis or congenital neuri-lemmomatosis is a rare syndrome characterized by multiple schwannomas of the peripheral nervous system without involvement of the vestibular nerve. According to consensus criteria, patients with two or more non-intradermal schwannomas, and without eighth cranial nerve dysfunction symptoms after the age of 45 years could be diagnosed as having presumptive schwannomatosis [31].

Early surgical resection results in a promising outcome. Only 5% experience local recurrence several years after surgery [32]. According to a recently published study, heterogeneously enhancing schwannomas should be followed closely, as they grow more rapidly and may require surgery [33].

4.6.2 Neurofibromas

Neurofibromas are slow-growing benign tumors (WHO Grade I), composed of neoplastic Schwan cells and fibroblasts without a true capsule. Neurofibromas comprise 5% of all benign soft tissue tumors, and occur as sporadic solitary tumors in 90% [34]. Neurofibromas can develop from dorsal spinal nerve roots, as well as peripheral nerves and—in approximately 36–40% of patients—in the spinal canal.

Neurofibromas are typically recognized as round or fusiform tumors, isointense on T1-weighted images, and markedly hyperintense on T2-weighted MRI. On post-contrast images, intense and homogeneous enhancement is seen. However, some neurofibromas will show peripheral enhancement.

Neurofibromas are associated with NF1, which is a rare autosomal dominant genetic disorder and diagnosed based on the following clinical criteria: the presence of cutaneous spots (*café au lait*), freckling in the axillary or inguinal regions, neurofibromas (plexiform or otherwise), Lisch nodules, optic pilocytic astrocytoma, sphenoid wing hypoplasia or aplasia, long bone dysplasia and/or pseudoarthrosis, and a positive family history (NIH criteria). Spinal neoplasms in NF1 patients can be both extramedullary (neurofibromas and malignant peripheral nerve sheath tumors) and intramedullary (astrocytomas, ependymomas, and gangliogliomas) [35].

Patients with neurofibromatosis have an increased risk of developing malignant peripheral nerve sheath tumors, which tend to be more aggressive compared with patients without neurofibromatosis (Fig. 4.8). At present, the management of spinal neurofibromas consists of careful observation with resection reserved for the most severe cases. The anatomic location, degree of invasion, and risk of recurrence at the

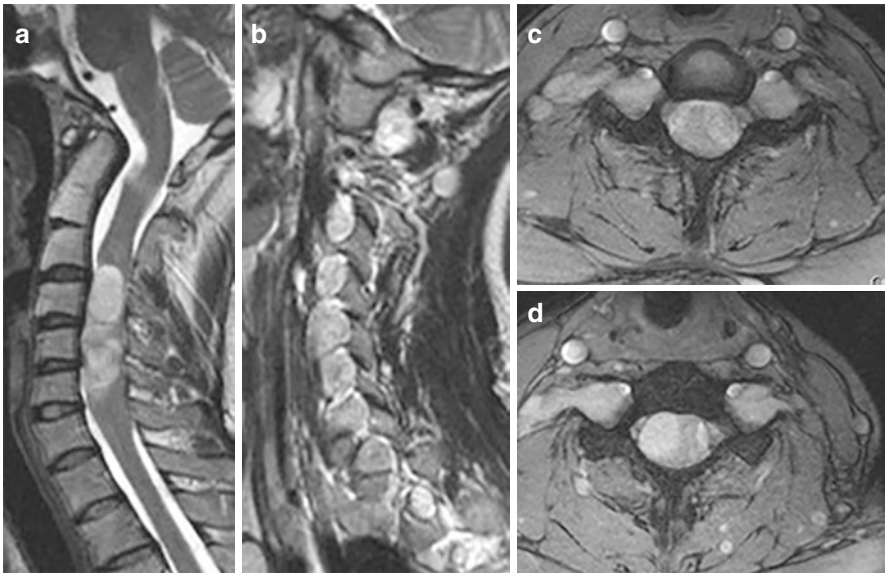

Fig. 4.8 Multiple neurofibromas in 30-year-old female patient with NF1. Sagittal T2-weighted (**a**, **b**) and axial T2-weighted gradient echo (**c**, **d**) images demonstrating multiple bilateral masses

surgical site affect decisions regarding surgery. No definitive chemotherapy has been reported to be successful for plexiform neurofibromas. Rapamycin, imatinib, sorafenib, and interferon have all been used with varying degrees of success [36].

4.7 Meningiomas

Meningiomas are the second-most common intraspinal tumor, with the highest incidence found in women between 45 and 74 years of age. Asian, Pacific Islander, and Caucasian individuals have the highest frequency of spinal meningiomas [37]. They can occur at any location throughout the spine but are predominant in the thoracic region (90% of the cases) and located posterolaterally (Fig. 4.9). Most meningiomas will be intradural and only 10% are extradural or dumbbell tumors. Meningiomas arise from the cells that make up the arachnoid membrane (arachnoid cap cells), and 95% are benign tumors (WHO Grade I).

The most common age interval is between 50 and 70 years, although any age group may be involved. They are more common in women. Multiple tumors (2%) are associated with NF2 [38].

On imaging, meningiomas are typically round, broad-base masses with a "tail" into the adjacent dura. In 5%, calcifications are present within the tumor, and easily diagnosed on CT. On T1-weighted and T2-weighted images, they are isointense to the spinal cord, but can be also hypointense on T1 weighted images and slightly hyperintense or hypointense on T2 weighted MRI. Upon contrast application, they

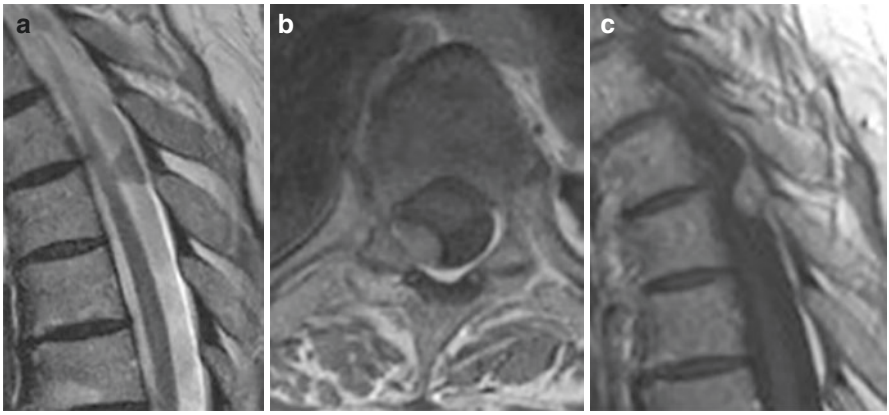

Fig. 4.9 Meningioma. sagittal T2-weighted (**a**) and sagittal (**b**) and axial contrast enhanced T1-weighted (**c**) images demonstrate well-circumscribed mass in the posterior right aspect of the spinal cord with a "tail" into the adjacent dura

enhance vividly (except for a calcified part), frequently display a "dural tail" sign, and exhibit marked homogeneous enhancement on postcontrast T1-weighted images. Of the various CNS tumors, meningiomas are the most common recipients of metastases from other primary cancers due in part to their increased vascularity [39].

Meningiomas have an excellent prognosis with complete surgical resection in more than 90% of cases.

4.8 Spinal Cord Metastases

More than 95% of spinal metastases occur in the extradural space, whereas intradural-extramedullary and intramedullary metastases are relatively rare [40].

Five routes for metastatic intradural spinal tumor spread have been hypothesized: the rich venous plexus (Batson plexus), perineural lymphatics, seeding from involved osseous structures to the CSF through the dura, spreading via the subarachnoid space, and hematogenous spreading via the arterial system [41]. Drop metastasis is considered to occur as a tertiary metastasis of brain metastasis, induced by the circulation of CSF and gravity in the subarachnoid space [42].

Leptomeningeal and spinal cord dissemination from CNS neoplasms occurs in younger patients, whereas metastases from lung or breast carcinomas occur in older patients. In children, spread from medulloblastoma and ependyma is common [43].

Imaging findings of seeding metastasis include multiple enhanced nodular lesions in the spinal canal and/or a diffuse sheet-like coating of the spinal cord or roots ("carcinomatous meningitis") and thickening of the cauda equina. Unenhanced T1-weighted and T2-weighted images will be less helpful as abnormalities are

isointense to the spinal cord. Contrast-enhanced T1-weighted images are mandatory to demonstrate enhancement.

A combination of routine MRI and autopsy observation has revealed that spinal cord metastatic tumors may be more common than initially reported.

Spinal cord metastases are well-encapsulated masses in the cord, usually eccentrically located with cord expansion. Rarely, they present with cystic changes or intralesional hemorrhage. The most common presentation is a single lesion in the thoracic cord. MRI is the tool of choice for diagnosing spinal cord metastatic disease [10]. Intramedullary metastases have a nonspecific MRI appearance with cord swelling, edema, and an enhancing lesion. In these cases, when there is no known history of primary cancer, the diagnosis of metastasis becomes difficult, and often the correct diagnosis is determined after pathology confirms the type of tumor [44] (Fig. 4.10). Recently described "rim" and "flame" signs are useful in differentiation of intramedullary metastases and primary spinal cord tumors. The rim sign is defined as a complete or partial rim of gadolinium enhancement, and the flame sign is defined as an ill-defined, flame-shaped, gadolinium-enhancing region at the superior or inferior margin of an otherwise well-defined lesion [45].

Treatment options for leptomeningeal metastasis are limited. Surgery may be attempted if there is a symptomatic large metastatic deposit causing cord compression metastasis; either a wait-and-scan policy or adjuvant radiation therapy is generally recommended [46]. After the excision of a solitary metastasis, it is believed that seeding from cord metastases are rare.

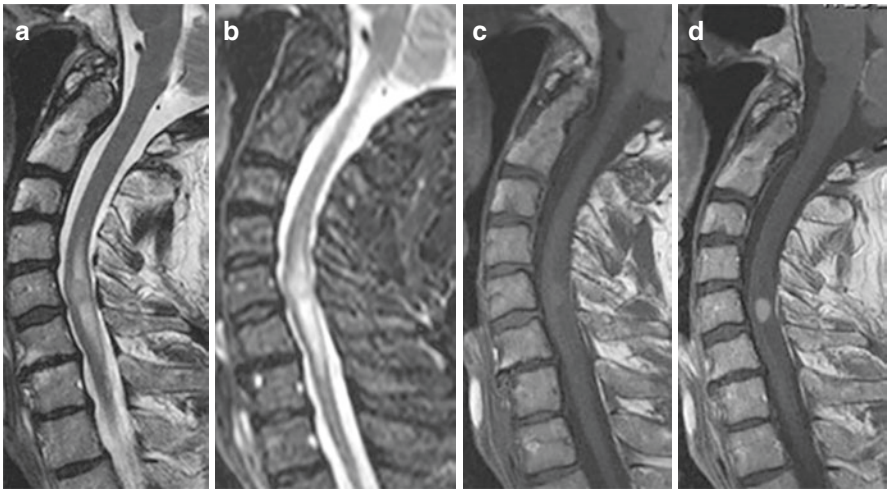

Fig. 4.10 Spinal cord metastases. Sagittal T2-weighted (**a**), STIR (**b**), T1-weighted (**c**), and contrast-enhanced T1-weighted (**d**) images. Well-defined oval mass in the cervical spinal cord, hyperintense in T2 and STIR, isointense to spinal cord on T1-weighted image; homogeneously enhancing after contrast administration

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Neuropathology of Spinal Cord Tumors

5

Stephanie Livingston and Blazej Zbytek

5.1 Introduction

Tumors of the spinal cord are relatively uncommon, accounting for approximately 1700–2700 of the more than 17,000 new primary central nervous system (CNS) lesions each year in the United States [1]. Spinal cord tumors can be classified according to their anatomic location—intramedullary, intradural-extramedullary, or extradurally.

5.1.1 Intramedullary Spinal Cord Tumors

Intramedullary spinal cord tumors (ISCTs) are neoplasms arising from cells within the spinal cord itself. ISCTs account for 20% of intraspinal tumors in adults and 30–35% of intraspinal tumors in children [2]. Most primary intramedullary tumors are either ependymomas (60%) or astrocytomas (30%) [2]. Spinal hemangioblastomas are the third most common intramedullary spinal neoplasm, representing 2–6% of all intramedullary tumors [3].

5.1.2 Intradural–Extramedullary Spinal Cord Tumors

Tumors arising within the dura but outside the actual spinal cord are termed intradural-extramedullary spinal cord tumors (IESCTs). The most common tumors in this group are myxopapillary ependymomas, meningiomas, and nerve sheath tumors (NSTs). NSTs are derived from the Schwann cells and perineurial cells of

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the peripheral nervous system and include schwannomas, neurofibromas, and malignant peripheral nerve sheath tumors (MPNSTs).

5.1.3 Extradural Spinal Cord Tumors

Extradural tumors are usually metastatic and most often arise in the vertebral bodies. Metastatic lesions can cause spinal cord compression, either by epidural growth resulting in extrinsic spinal cord or cauda equina compression, or less frequently by intradural invasion.

5.2 Intramedullary Spinal Cord Tumors

5.2.1 Ependymoma

Ependymomas represent a rare primary neoplasm of the CNS that account for 3–6% of all adult CNS tumors [4]. Spinal ependymomas of the classical type are intramedullary tumors, and can occur anywhere in the cervical or thoracic spinal cord.

Subtypes. In the World Health Organization (WHO) classification of brain tumors, ependymal tumors are divided into five major groups: classic ependymoma, subependymoma, myxopapillary ependymoma, RELA-fusion positive ependymoma, and anaplastic ependymoma. Myxopapillary ependymomas occur almost exclusively in the filum terminale and are intradural-extramedullary tumors. Classic ependymomas are mainly intracranial tumors, but do occur in the spine as intramedullary tumors of the spinal cord. The other three subtypes are predominantly intracranial tumors.

Ependymoma variants include three distinct histopathological phenotypes (papillary, clear cell, or tanycytic) that can be a prominent component of classic or anaplastic ependymoma. The tanycytic variant—composed of elongated cells spindle cells arranged in fascicles (Fig. 5.1)—is most commonly found in the spinal cord.

Grading. Ependymomas are characterized as grade I (myxopapillary ependymoma or subependymoma), grade II (ependymoma), and grade III (anaplastic ependymoma). While classic ependymoma and anaplastic ependymoma traditionally correspond to WHO Grades II and III respectively, no association between grade and biological behavior or survival has been definitively established [5].

Morphology. Classic ependymomas have a discrete interface with the surrounding parenchyma, are variably cellular, and are composed of monomorphic cells with round to oval nuclei and speckled nuclear chromatin. The mitotic count is usually low. Key histological features are perivascular anucleate zones (pseudorosettes) and (true) ependymal rosettes (Fig. 5.2). Pseudorosettes, found in most ependymomas, are composed of tumor cells radially arranged around blood vessels to create perivascular anucleate zones of fine fibrillary processes. True rosettes are present in about a quarter of ependymomas and composed of bland cuboidal or columnar

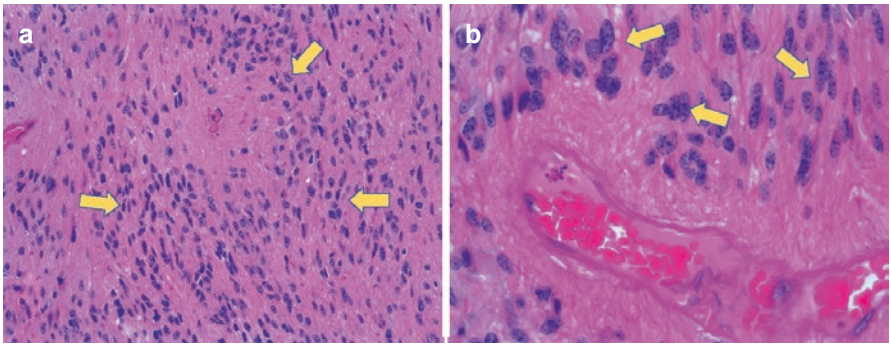

Fig. 5.1 Tancytic ependymoma. (**a**) Bipolar spindle cells with elongated processes around the central vessel (H&E, OM 20×). (**b**) Spindled nuclei with salt-and-pepper chromatin typical of ependymoma (H&E, OM 40×)

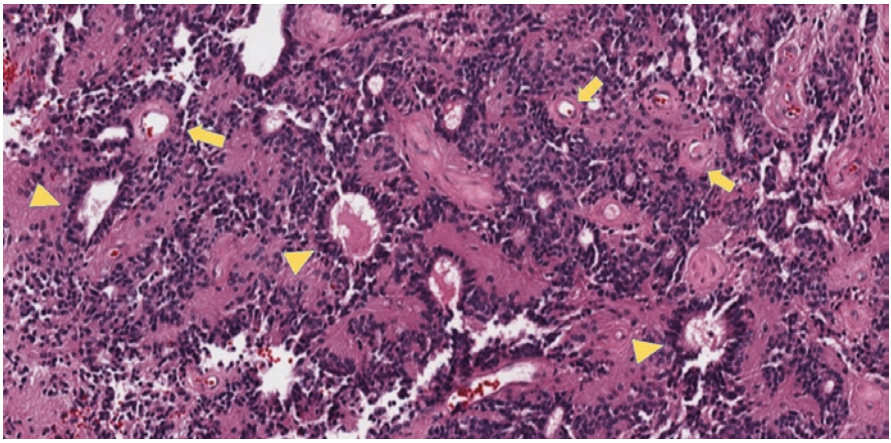

Fig. 5.2 Ependymoma. Perivascular anucleate zones (pseudorosettes) (**arrows**) and true ependymal rosettes (**arrowheads**) (hematoxylin and eosin staining [H&E], original magnification [OM] 20×)

tumor cells arranged around a central lumen. Prominent hyalinization of tumor vessels is often seen with spinal ependymomas.

Immunophenotype. Ependymomas characteristically express epithelial membrane antigen (EMA) along the luminal surface of ependymal rosettes, or as dot-like perinuclear or ring-like cytoplasmic reactivity [6]. Glial fibrillary acidic protein (GFAP) immunoreactivity is usually observed in pseudorosettes, but shows variable expression in other tumor elements, such as papillae and true rosettes S100 and vimentin are typically positive [7]. Oligodendrocyte transcription factor (OLIG2) expression is sparse compared with other gliomas [8]. Neuronal markers are rarely expressed [9].

5.2.2 Astrocytoma

The second most common type of ISCT is the astrocytoma, which most commonly localizes to the cervical spine [2].

Subtypes. The 2016 CNS WHO classification groups all diffuse gliomas (astrocytic or oligodendroglial) together, based on an integrated phenotypic and genotypic classification. Infiltrative astrocytic tumors, including diffuse astrocytoma, anaplastic astrocytoma, and glioblastoma, are classified according to their isocitrate dehydrogenase (IDH) mutational status. This approach sharply divides localized astrocytic neoplasms with a more circumscribed growth pattern, such as pilocytic astrocytoma, which lack IDH gene alterations but can harbor BRAF mutation from the group of diffuse gliomas.

About half of spinal astrocytomas are the low-grade pilocytic type, while the other half are infiltrative astrocytomas and include diffuse astrocytoma, anaplastic astrocytoma, and glioblastoma [10]. Diffuse astrocytic spinal tumors carrying the H3 K27M mutation are now classified along with the brainstem counterpart as H3 K27-mutant diffuse midline gliomas. This aggressive subtype predominantly affects children—although it can also affect adults—and carries a poor prognosis with a two-year survival rate of less than 10% [11].

Frequency. Intramedullary spinal cord astrocytomas are rare, representing only 6–8% of all spinal cord tumors [10], and are the second-most common intramedullary tumor in adults. They account for 60% of pediatric intramedullary tumors [12], representative of the fact that pilocytic astrocytoma is the most common glioma in children [11].

Grading. Pilocytic astrocytomas (WHO Grade I) are low-grade, well-circumscribed, and benign lesions that are clinically not aggressive. Diffuse astrocytomas correspond histologically to WHO Grade II, and anaplastic astrocytomas to WHO Grade III. Both glioblastoma and the H3 K27M-mutant diffuse midline glioma are designated WHO Grade IV.

Morphology. Pilocytic astrocytomas are classically characterized by a biphasic pattern, with a variable pattern and variable proportions of compacted bipolar cells with Rosenthal fibers, and loose textured multipolar cells with microcysts and occasional granular bodies.

Diffuse astrocytomas are composed of well-differentiated fibrillary astrocytes in a background of a loosely structured—often microcystic—tumor matrix. The cellularity of diffuse astrocytomas is moderately increased, with nuclear atypia and variability of cytoplasmic glial filaments and cell processes. Mitotic activity is generally absent.

Anaplastic astrocytoma is histologically similar to diffuse astrocytoma but with increased mitotic activity, distinctive nuclear atypia, and higher cellularity than its lower-grade counterpart (Fig. 5.3).

Necrosis or microvascular proliferation negates diagnosis of diffuse or anaplastic astrocytoma, but are key features of glioblastoma (Fig. 5.4) and H3 K27M-mutant diffuse midline gliomas. These higher-grade neoplasms are highly cellular and contain pleomorphic-to-anaplastic cells with brisk mitotic activity. Diagnostic

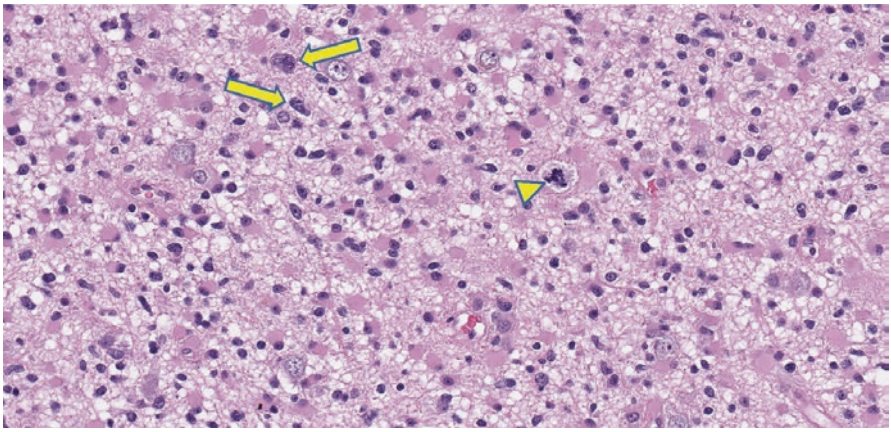

Fig. 5.3 Anaplastic astrocytoma showing increased cellularity, pleomorphism, and nuclear atypia (**arrows**), and frequent mitoses (**arrowhead**) (H&E, OM 40×)

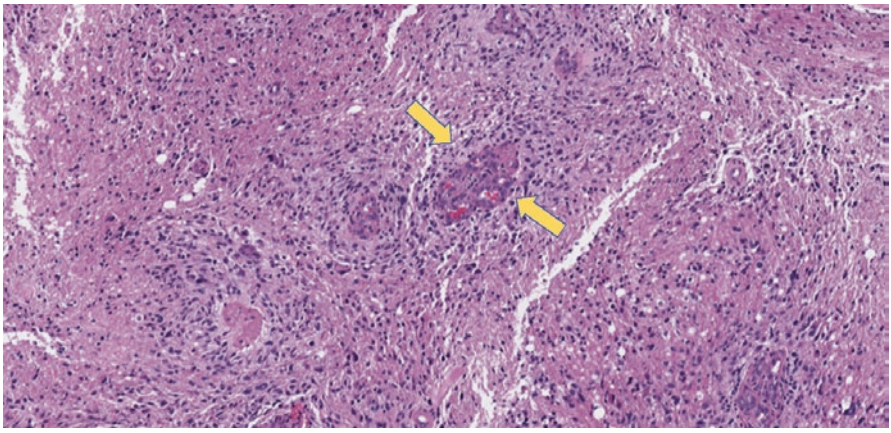

Fig. 5.4 Glioblastoma showing glomeruloid-like vascular proliferation (**arrows**) (H&E, OM 20×)

hallmarks are palisading necrosis (ie, irregular areas of ischemic necrosis surrounded by a dense accumulation of palisading tumor cells) and microvascular proliferation.

Immunophenotype. Astrocytomas express GFAP in various degrees and in a variable proportion of tumor cells. Strong nuclear expression of p53 is also characteristic, although not entirely sensitive or specific. Immunostaining is otherwise utilized to determine mutant status of tumors (ie, IDH and ATRX mutational status).

Biological Behavior. Diffuse IDH-mutant astrocytomas have an intrinsic capacity for malignant progression to IDH-mutant anaplastic astrocytoma, and eventually to IDH-mutant glioblastoma. IDH-wildtype glioblastoma, by contrast, is a primary glial neoplasm and arises de novo with no precursor lesion [11].

5.2.3 Hemangioblastoma

Hemangioblastomas are uncommon slow-growing tumors of the CNS, which most commonly occur in the cerebellum, brainstem, or spinal cord. They account for approximately 4% of all spinal cord tumors.

Subtypes. Hemangioblastomas may occur either sporadically or as a manifestation of von Hippel-Lindau (VHL) disease. Although approximately 75% of all hemangioblastomas appear to be sporadic, some of these may represent occult cases of VHL that can be detected if patients are appropriately screened for germline VHL mutations [13]. In patients with VHL disease, approximately one-half of tumors are found in the spinal cord, 40% in the cerebellum, and 10% in the brainstem [14].

Hemangioblastoma variants include the reticular variant, which is composed predominantly of small nests and individual cells, and the cellular variant in which larger lobules of cells predominate.

Frequency. Hemangioblastomas have no sex predilection and usually occur in adults. VHL-associated tumors have an average age at presentation approximately 20 years younger than sporadic tumors [15].

Morphology. Hemangioblastomas are capillary-rich neoplasms with lipidized stromal cells that vary in cell density, with highly cellular areas alternating with paucicellular regions composed of dilated vessels and cyst-like spaces (Fig. 5.5). Stromal cells constitute the neoplastic component of the tumor and are characteristically large and vacuolated. Their numerous lipid-containing vacuoles create the typical clear-cell morphology of hemangioblastomas, which can resemble metastatic renal cell carcinoma (RCC). This differential diagnosis is further complicated given that patients with VHL are also prone to RCC.

Immunophenotype. While capillary endothelial cells stain for endothelial cell markers, such as CD34 and von Willebrand factor, the stromal cells of hemangioblastomas variably stain express neuron-specific enolase (NSE), NCAM1, and S100. Oil-red O can highlight the lipid content of stromal cells in frozen sections (Fig. 5.6). Inhibin alpha also highlights stromal cells, and is useful in distinguishing hemangioblastoma from renal cell carcinoma.

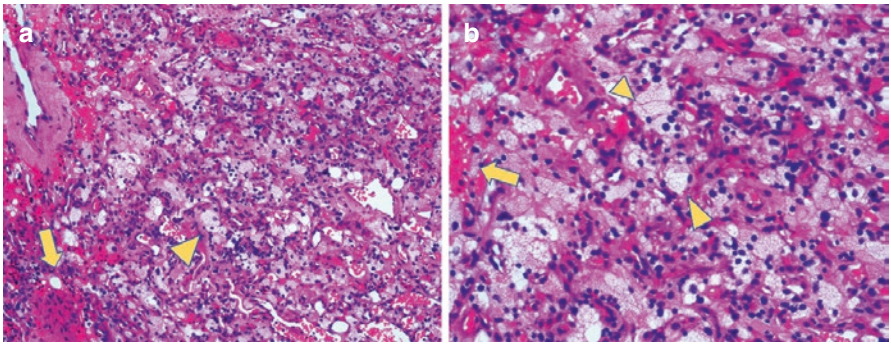

Fig. 5.5 Hemangioblastoma demonstrating rich vascularity (**arrows**) with interspersed vacuolated stromal cells (**arrowheads**) (H&E, OM [A] 10×, [B] 20×)

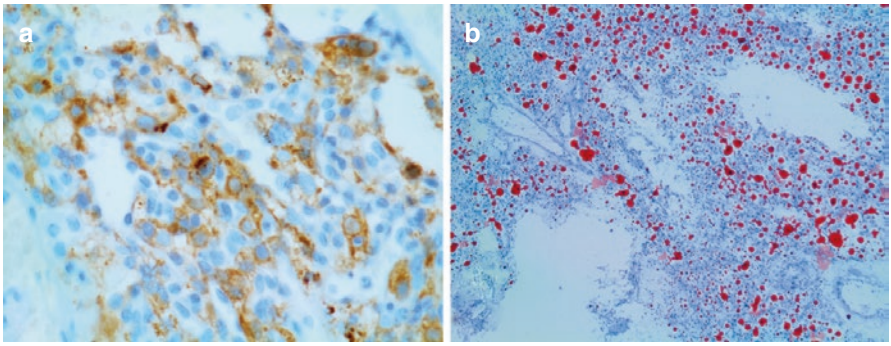

Fig. 5.6 Hemangioblastoma. (**a**) Inhibin immunostaining of the neoplastic stromal cells (inhibin, OM 40×). (**b**) Oil Red O staining of the lipid content of stromal cells (Oil Red O, OM 4×)

Grading. Hemangioblastoma corresponds histologically to WHO Grade I.

Biological Behavior. Complete surgical resection is possible in most cases of hemangioblastoma. The prognosis of patients with sporadic lesions is more favorable than those associated with VHL, as patients with VHL tend to develop multiple lesions [16].

5.3 Intradural–Extramedullary Spinal Cord Tumors

5.3.1 Myxopapillary Ependymoma

Myxopapillary ependymomas are considered a biologically and morphologically distinct variant of ependymoma, and behave in a more benign fashion than classic ependymomas.

Frequency. Myxopapillary ependymomas are an intradural-extramedullary neoplasm with annual incidence rates of about 0.08 cases per 100,000 males and 0.05 cases per 100,000 females. The age at presentation ranges from 6 to 82 years with an average of 36 years [17].

Morphology. Myxopapillary ependymomas occur almost exclusively in the region of the conus medullaris, cauda equina, and filum terminale. Grossly, they are grey or tan, soft, and lobulated. On microscopy, the tumor cells are cuboidal to elongated and arranged in papillary structures with accumulations of Alcian blue-positive myxoid material in microcysts and between tumor cells and blood vessels (Fig. 5.7). Additional cytomorphologic features include pseudorosettes composed of myxohyaline material rimmed by neoplastic cells. The ependymal cells appear singly and in multiple layers, surrounding the myxoid material, with prominent cytoplasmic processes. Tumor cells can appear in a monolayer or sheet-like fashion, with intracytoplasmic vacuoles, sparse mitotic figures, and intranuclear inclusions.

Immunophenotype. The diffuse reactivity of myxopapillary ependymomas for GFAP is useful in distinguishing these tumors from differentials, such as

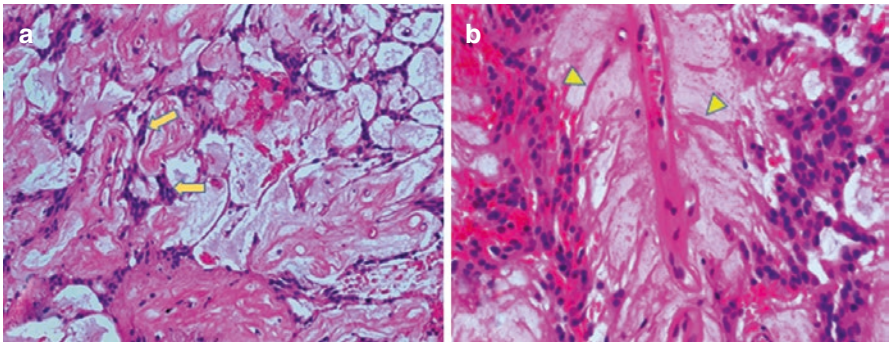

Fig. 5.7 Myxopapillary ependymoma. (**a**) Well-differentiated cuboidal-to-elongated tumor cells (**arrows**) radially oriented around myxoid cores with a myxopapillary appearance (H&E, OM 10×). (**b**) Elongated fibrillary processes (**arrowheads**) extended through myxoid regions to reach blood vessel (H&E, OM 20×)

metastatic carcinomas, chordomas, myxoid chondrosarcomas, paragangliomas, and schwannomas.

Grading. Myxopapillary ependymomas correspond to WHO Grade I histologically. In pediatric cases, however, they may exhibit a more aggressive biological behavior with poorer outcome after incomplete resection [4].

Biological Behavior. The prognosis of myxopapillary ependymomas is favorable with a 5-year survival rate of 98.4% following complete resection [13]. Distant metastases and late recurrence can occur after incomplete resections in both children and adults.

5.3.2 Meningioma

Meningiomas are slow-growing—and usually benign—neoplasms arising from the meningothelial cells of the arachnoid plexus.

Subtypes. The 2016 WHO classification of meningiomas described numerous morphological subtypes. The most common subtypes of meningioma are meningothelial, fibrous, and transitional (mixed) meningiomas. Other subtypes include psammomatous, angiomatous, microcystic, secretory, lymphoplasmacyte-rich, metaplastic, choroid, clear cell, atypical, papillary, rhabdoid, and anaplastic.

Frequency. Overall, meningiomas are the most common primary tumor of the CNS, accounting for about one-third of all primary brain and spinal tumors with a female to male ratio of 2:1 or 3:1 [17]. In spinal meningiomas, which comprise about 10% of all meningiomas, female predominance is considerably higher with a female-to-male ratio of 9:1.

Morphology. Meningiomas exhibit a wide range of histologic appearance, corresponding with the variety of subtypes (Figs. 5.8, 5.9, 5.10, 5.11, 5.12 and 5.13). They characteristically show a lobulated architecture containing "meningothelial" whorls of syncytial cells with indistinct cell membranes, eosinophilic cytoplasm,

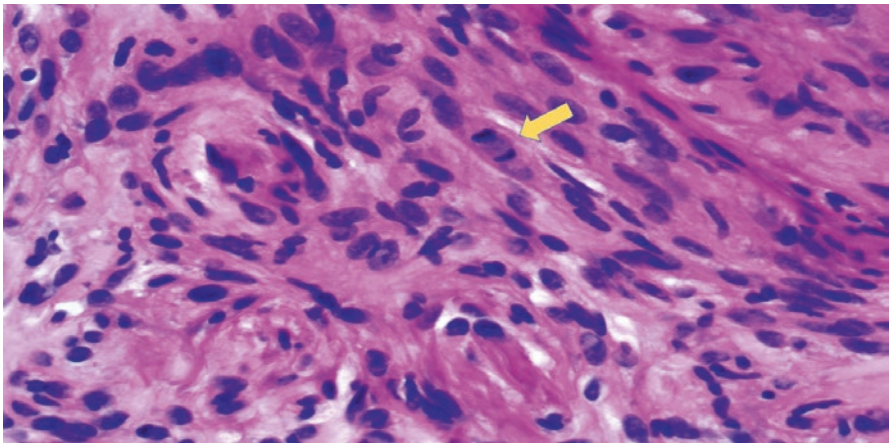

Fig. 5.8 Atypical meningioma with prominent mitoses (**arrow**) (H&E, OM 40×)

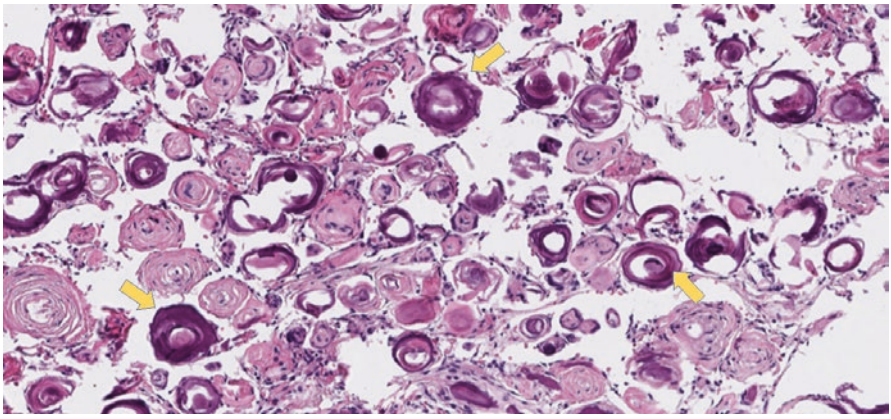

Fig. 5.9 Meningioma, psammomatous variant showing numerous psammoma bodies with concentric calcifications (**arrows**) (H&E, OM 20×)

and round uniform nuclei (Fig. 5.14). Intranuclear pseudoinclusions and psammoma bodies are common. Xanthomatous degeneration, moderate nuclear pleomorphism, and metaplasia may also be present. Necrosis or extensive hemorrhage is rare.

Immunophenotype Meningiomas are characterized by EMA and progesterone receptor (PR) positivity. Decreased PR positivity and increased Ki-67 labeling index correlated with increased recurrence rates and prognosis. Recently, meningioma methylation profile has been found to be correlated with recurrence rates better than traditional grading Scheme [18].

Grading. The three most common meningioma variants (meningothelial, fibrous, and transitional), as well as psammomatous, angiomatous, microcytic,

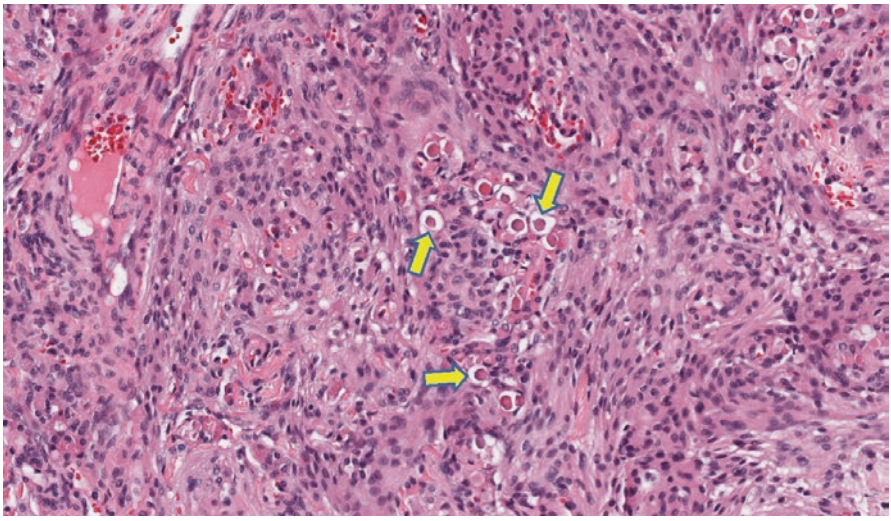

Fig. 5.10 Secretory meningioma characterized by intracellular lumina containing eosinophilic secretions called pseudopsammoma bodies (**arrowheads**) (H&E, OM 20×)

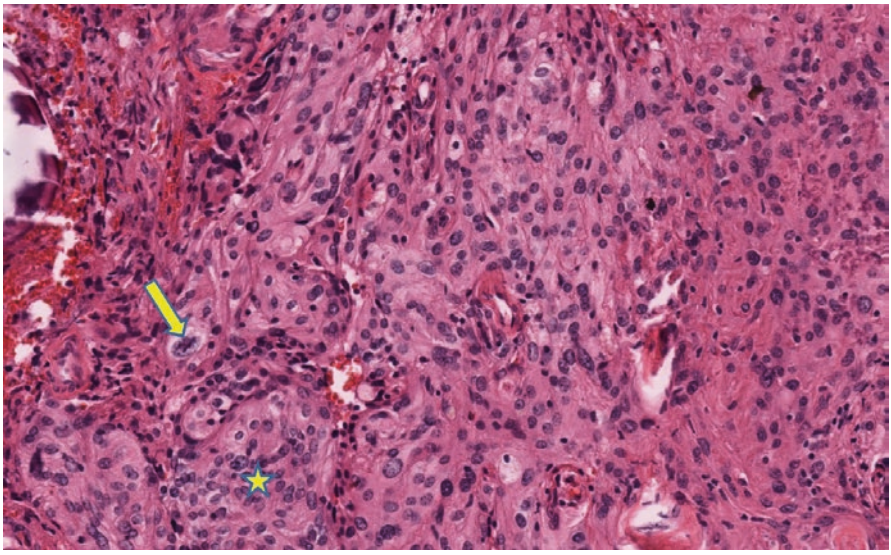

Fig. 5.11 Anaplastic meningioma showing increased cellularity and areas of small cell collections (**star**) and increased mitoses (**arrow**) (H&E, OM 20×)

secretory, lymphoplasmacyte-rich, and metaplastic meningiomas are benign and correspond to WHO Grade I. Grade II subtypes have an increased likelihood of recurrence and include choroid, clear cell, and atypical meningiomas. Papillary, rhabdoid, and anaplastic meningiomas are malignant variants with metastatic potential, corresponding to WHO Grade III.

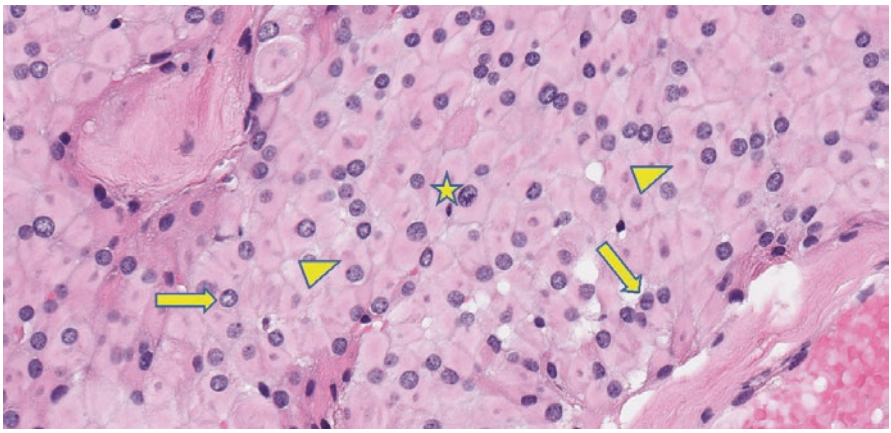

Fig. 5.12 Rhabdoid meningioma showing eccentrically placed vesicular nuclei (**arrows**), eosinophil cytoplasmic inclusions (**arrowheads**), and increased mitotic activity (H&E, OM 20×)

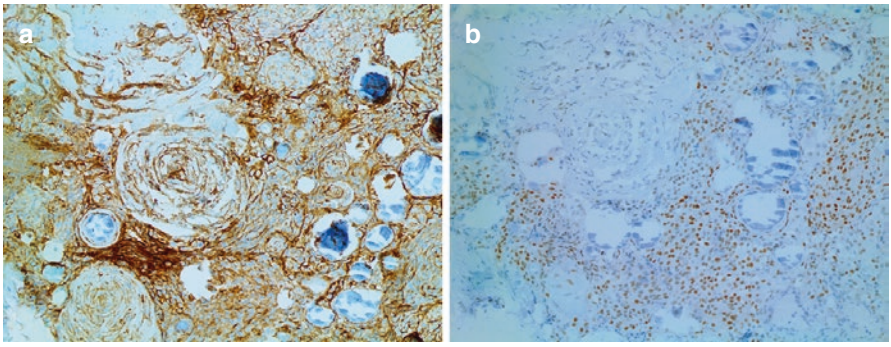

Fig. 5.13 Meningioma. (**a**) Surface staining of Epithelial Membrane Antigen staining, typical of all meningioma subtypes (10×). (**b**) Progesterone receptor positivity (10×)

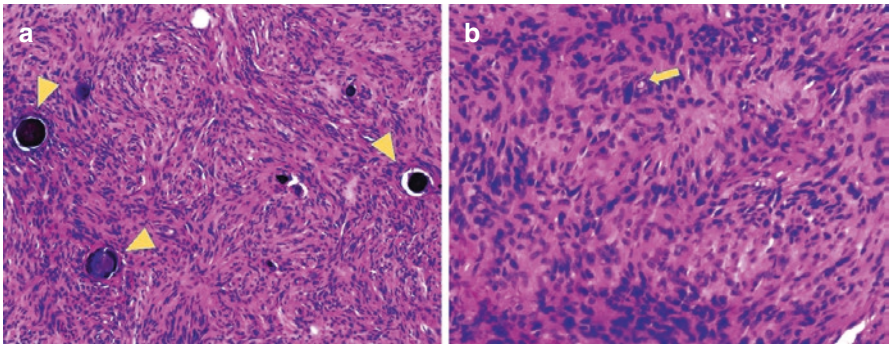

Fig. 5.14 Meningioma. (**a**) Features include syncytial cells with eosinophilic cytoplasm and indistinct cell membranes arranged in meningopithelial whorls, intranuclear pseudoinclusions, and psammoma bodies (**arrowheads**) (H&E, OM 10×). (**b**) Higher magnification showing uniform oval nuclei with delicate chromatin and occasional nuclear pseudoinclusion (**arrows**) (H&E, OM 20×)

Biological Behavior. While the rate and extent of local spread are greatest in the higher-grade subtypes, even benign meningiomas commonly invade adjacent anatomical structures. Spinal meningiomas most commonly occur within the thoracic spine, and are frequently adhere to the spinal dura, requiring dural resection for complete removal. They can also grow along intradural and extradural components of the nerve roots.

5.3.3 Nerve Sheath Tumors (Schwannoma & Neurofibroma)

Nerve sheath tumors constitute about 25% of tumors arising in the intradural-extramedullary space [19]. While the majority of intradural-extramedullary spinal cord tumors are confined to the intradural-extramedullary space, nerve sheath tumors sometimes extend to either the spinal cord or extramedullary compartment. Approximately 65% of intradural nerve sheath tumors are schwannomas, and most of the remainder are neurofibromas. Malignant NSTs are rare, constituting about 5% of such tumors.

Frequency. Both schwannoma and neurofibromas occur most commonly as solitary nodules, and are sporadic cases with no underlying hereditary syndrome. A minority of solitary lesions—and almost all cases of multiple lesions—are associated with one of three genetic syndromes: neurofibromatosis type I (NF1), neurofibromatosis type II (NF2), or schwannomatosis.

Neither schwannomas nor neurofibromas show a sex predilection. Neurofibromas can occur at any age, while schwannomas rarely affect children and show a peak incidence in the fourth-to-sixth decade.

5.3.4 Schwannoma

Conventional schwannoma are benign nerve sheath tumors composed entirely of well-differentiate Schwann cells.

Subtypes. Conventional schwannomas that show benign degenerative/"ancient" characteristics—including nuclear pleomorphism, occasional bizarre forms, cytoplasmic-nuclear inclusions, and mitoses—are referred to as ancient schwannomas. Cellular schwannoma is a hypercellular variant composed predominantly or exclusively of Antoni A tissue, and lacks well-formed Verocay bodies. Plexiform schwannoma is a multinodular variant occurring usually in skin or subcutaneous tissues of the extremities. Melanotic schwannoma is a rare schwannoma subtype that is grossly pigmented, unencapsulated, and contains Schwann cells with melanosomes and positivity for melanocytic markers.

Morphology. Most schwannomas are encapsulated globoid masses that do not invade but can displace the spinal cord, and may contain cystic, xanthomatous, or hemorrhagic changes. Though usually small, schwannomas in the lower lumbar and sacral regions may enlarge significantly and further extend into the paravertebral space, showing infarct-like necrosis related to degenerative vascular changes.

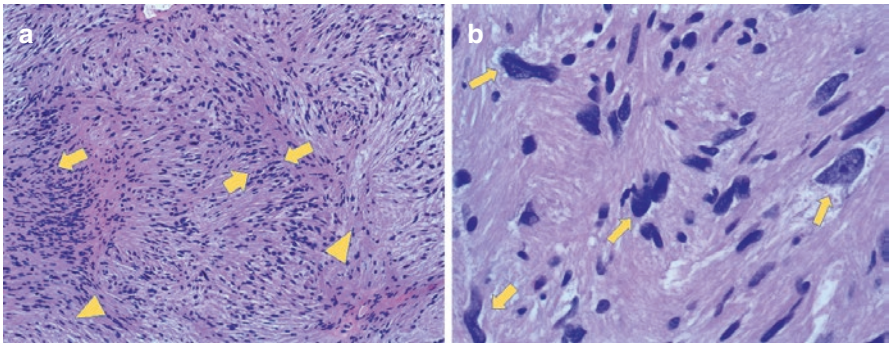

Fig. 5.15 Schwannoma. (**a**) Schwannoma showing Antoni A areas with nuclear palisades of Verocay bodies (**arrows**) surrounded by myxoid Antoni B areas (**arrowheads**) (H&E, OM 10×). (**b**) Schwannoma showing ancient change with marked degenerative nuclear atypia (H&E, OM 40×)

Histologically, conventional schwannomas are composed of neoplastic Schwann cells in a biphasic arrangement of two architectural patterns (Fig. 5.15). The Antoni A pattern contains compact uniformly spindled Schwann cells arranged in fascicles running in different directions. The nuclei, which are about the same size as those of smooth muscle cells but tapered rather than blunt-ended, tend to align in alternating parallels to form nuclear palisades called Verocay bodies. The Antoni B pattern is a less cellular myxoid or vacuolated area containing loosely textured cells with smaller round-to-ovoid nuclei. The vasculature of schwannomas is typically thick-walled and hyalinized, often with perivascular hemosiderin.

Immunophenotype. Immunohistochemically, schwannomas express S100 diffusely and are often positive for LEU7, SOX10, and calretinin, with extensive pericellular collagen type IV membranous staining of basal lamina.

Grading. Conventional, non-melanotic schwannomas and their variants correspond histologically to WHO Grade I.

Biologic Behavior. Spinal schwannomas show a strong predilection for sensory nerve roots, and affect motor or autonomic nerves far less commonly. Spinal meningiomas, therefore, rarely present with motor symptoms, rather with radicular pain or signs of nerve root compression. Most schwannomas are benign slow-growing tumors that do not recur and only very rarely undergo malignant change. Recurrences are more common with plexiform schwannomas and with cellular spinal schwannomas, occurring in 32–40% of cases.

5.3.5 Neurofibroma

Most sporadic neurofibromas occur as cutaneous nodules and rarely involve the spinal roots. In patients with NF1; however, spinal involvement is common, and multiple bilateral tumors can be associated with scoliosis and risk of malignant transformation [4].

Subtypes. Neurofibroma variants include atypical and plexiform neurofibromas. Atypical neurofibroma is a variant characterized by high cellularity, cytological atypia, scattered mitotic figures, monomorphic cytology, and/or fascicular growth, and can be difficult to distinguish from low-grade peripheral nerve sheath tumors. Plexiform neurofibroma is a variant defined by involvement of multiple fascicles, which are expanded by tumor cells and collagen, commonly demonstrating residual bundled nerve fibers at their centers. Analogous to ancient schwannomas, ancient neurofibromas are characterized by degenerative nuclear atypia without any other features of malignancy.

Morphology. Neurofibromas are nerve sheath tumors composed of neoplastic well-differentiated Schwann cells intermixed with non-neoplastic elements, including perineurial-like cells, fibroblasts, mast cells, a variably myxoid to collagenous matrix, and residual axons or ganglion cells.

Grossly, neurofibromas are unencapsulated and comparatively softer and more gelatinous than schwannomas, and create fusiform enlargement of the nerve from which they arise.

Histologically, neurofibromas are hypocellular proliferations of neoplastic spindled Schwann cells with bland wavy nuclei and scant cytoplasm, as well as fibroblasts and mast cells in a matrix of myxoid material with wire-like collagen fibers imparting a "shredded carrot" appearance (Fig. 5.16). While neurofibromas may resemble the Antoni B areas of schwannomas, they lack Antoni A areas, nuclear palisading, and Verocay bodies. The vessels are thin-walled without perivascular hemosiderin deposition. Organoid structures resembling Meissner corpuscles (pseudo-Meissnerian structures), melanotic cells, and epithelioid areas may be present.

Immunophenotype. Immunohistochemistry shows reactivity for S100 protein and nuclear positivity for SOX10, though the proportion of reactive cells is smaller than with schwannomas.

Grading. Neurofibromas are benign and correspond histologically to WHO Grade I.

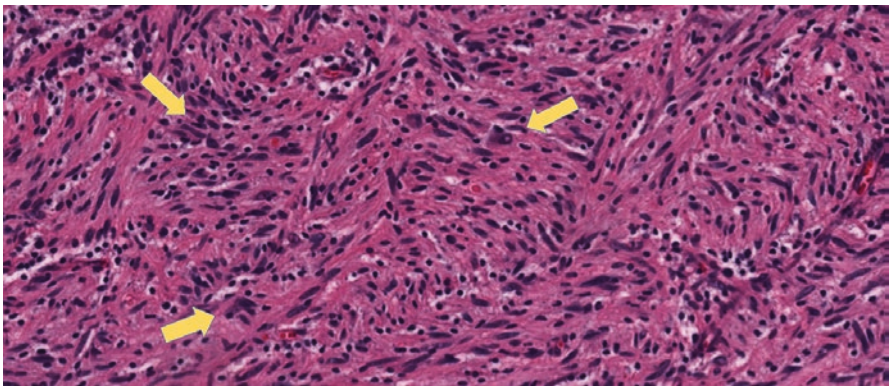

Fig. 5.16 Neurofibroma with degenerative atypia showing degenerative atypia (**arrows**) without any other features of malignancy (H&E, OM 20×)

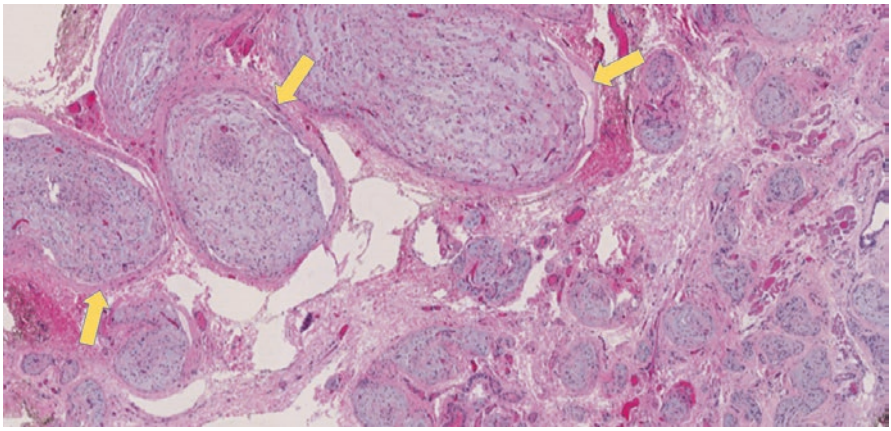

Fig. 5.17 Plexiform neurofibroma showing multiple fascicles (**arrows**) expanded by tumor cells and collagen (**arrows**) (OM 10×)

Biologic Behavior. Paraspinal neurofibromas present with motor and sensory deficits attributable to the nerve of origin. Neurofibromas of major nerves and plexiform neurofibromas are considered potential precursors of MPNST, with malignant transformation occurring in 5–10% of large plexiform tumors (Fig. 5.17). Malignant transformation in sporadic neurofibromas is rare.

5.3.6 Malignant Peripheral Nerve Sheath Tumor

MPNSTs can occur in the paraspinal region and often present with radicular pain.

Frequency. Sporadic MPNSTs affect adults in their third-to-sixth decade with no precursor lesion. About 50% of all MPNSTs are associated with neurofibromatosis, arising from deep-seated plexiform neurofibromas or large intraneural neurofibromas and in these patients occur about a decade earlier [20]. There is no sex predilection.

Subtypes. MPNSTs can contain angiosarcomatous areas or contain mesenchymal tissue, such as cartilage, bone, skeletal muscle, or smooth muscle. Those with rhabdomyosarcomatous differentiation are referred to as malignant triton tumors. Glandular MPNSTs are variants containing intestinal-type glandular epithelium. Epithelioid MPNSTs are partially or completely epithelioid, have no association with NF1, may arise from malignant transformation of a schwannoma, and are associated with a SMARCB1 (INI1) mutation in about 50% of cases. MPNSTs with perineural differentiation, termed malignant perineuriomas, rarely occur and are S100 negative and EMA positive.

Morphology. MPNSTs are composed of spindle cells (Fig. 5.18) with wavy nuclei that have tapered ends and can be arranged in a herringbone (ie, fibrosarcomatous), fasciculated, cell growth, or (rarely) hemangiopericytoma-like pattern. They can have loose areas alternating with densely cellular areas or grow diffusely.

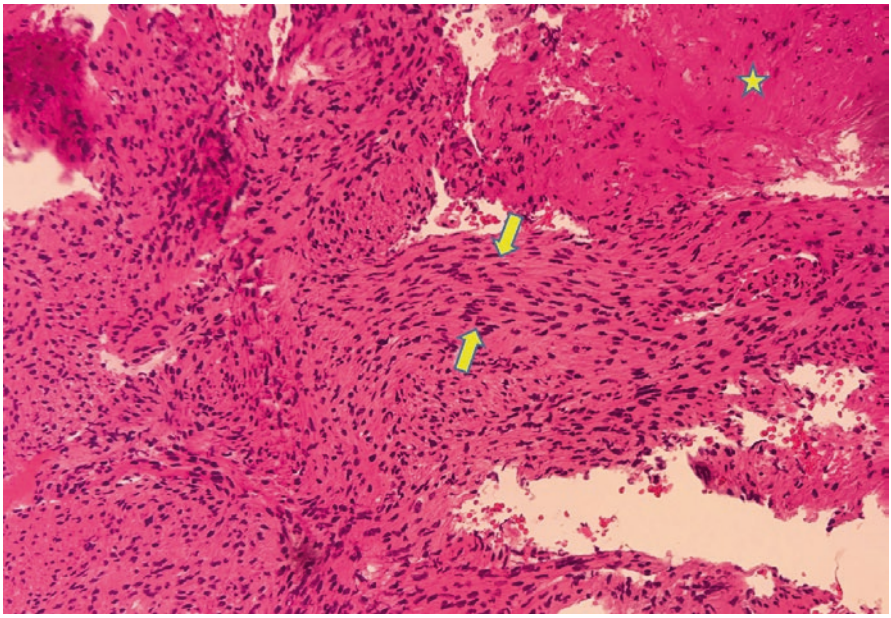

Fig. 5.18 Malignant peripheral nerve sheath tumor showing an interwoven fasciculated pattern with tightly packed spindle cells (**arrows**) and areas of necrosis (**star**) (H&E, OM 20×)

Perivascular hypercellularity and appearance of tumor aggregates within vascular lumina are common. Seventy-five percent of MPNSTs show brisk mitotic activity (>4/high-power field) and/or areas of geographic necrosis [11]. Immunohistochemistry shows S100 protein staining in only about 50–70% of cases.

Grading. Reproducible clinically validated grading systems for MPNSTs are lacking [4], but these tumors can be classified as low-grade if well differentiated. Pleomorphic MPNSTs or variants with divergent differentiation (eg, malignant triton tumors, glandular MPNSTs, chondrosarcomatous, osteosarcomatous, or angiosarcomatous differentiation) are considered high-grade [11].

Biological Behavior. MPNSTs are highly aggressive tumors with a poor prognosis. They may spread intraneurally or hematogenously and often infiltrate adjacent soft tissues. Twenty to twenty-five of patients develop metastases, most commonly to the lungs [11]. Decreased survival in cases associated with NF1 compared with sporadic cases has been reported.

5.4 Extradural Spinal Cord Tumors

5.4.1 Metastasis

While intramedullary spinal cord metastases are rare, extradural metastasis are common and can occur with any primary malignancies (Fig. 5.19). The spine is the

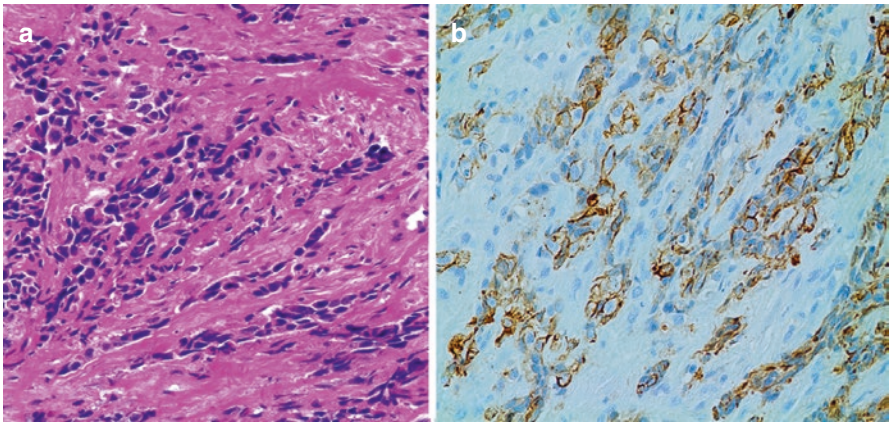

Fig. 5.19 Spinal metastasis. (**a**) Poorly differentiated metastatic breast cancer (H&E, OM 20×). (**b**) Immunostain for Cytokeratin 7 to support diagnosis in a patient with a known breast primary (Cytokeratin 7, OM 20×)

third-most common site of metastasis (after the lungs and liver), and the rate of spinal metastasis in cases of the patients having a history of malignant tumor has been reported up to 30–90%, based on autopsy [21]. The incidence of skeletal metastasis from autopsy studies is of 73% (range, 47–85%) in breast cancer, 68% (range, 33–85%) in prostate cancer, 42% (range, 28–60%) in thyroid cancer, 36% (range, 30–55%) in lung cancer, 35% (range, 33–40%) in kidney cancer, 6% (range, 5–7%) in esophageal cancer, 5% (range, 3–11%) in gastrointestinal tract cancers, and 11% (range, 8–13%) in rectal cancer [22]. Collectively, these tumors are particularly important because of the risk of epidural spinal cord compression.

5.4.2 Primary Extradural Tumors

A number of uncommon primary tumors can arise in the extradural space. Most of these are mesenchymal tumors arising from the bony spine and associated soft tissues, and include osteosarcoma, chondrosarcoma, leiomyosarcoma, Ewing's sarcoma, osteoid osteoma, osteoblastoma, osteochondroma, chondroblastoma, vertebral hemangioma, aneurysmal bone cyst, giant cell tumor, and chordoma. The spine may also be the initial site of involvement for hematopoietic malignancies, including plasmacytoma, multiple myeloma, lymphoma, and Langerhans cell histiocytosis.

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Neurological Aspects of Spinal Cord Tumors

6

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6.1 Overview

Spinal cord tumors are rare tumors that are either primary or metastatic. Without a timely intervention, they can lead to significant morbidity and—in some cases—mortality. The clinical presentation of these tumors is non-specific in most cases and is often mistaken for the more common degenerative spine disease, thus leading to a delay in diagnosis. Functional status at presentation is important in determining long-term prognosis, hence an early diagnosis is imperative in preserving quality of life and limiting morbidity [1–5]. The damage caused by acute cord compression can be irreversible, making early diagnosis particularly important. Many primary spinal cord tumors are benign and thus amenable to surgical resection [1]. Per clinical reports, average time to diagnosis of spinal cord tumors ranges from 8.1 to 17 months following symptom onset [2, 5–7]. Herein we will discuss neurological aspects of spinal cord tumors, emphasizing the clinical syndromes and examination techniques that can help in a timely diagnosis.

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6.2 Clinical Presentation

The presentation of spinal cord tumors tends to be of a slow and progressive nature. It is initially unilateral and later involves both sides of the spinal cord, causing bilateral symptoms. The most common presenting complaint is localized, radicular, or medullary pain [8]. The pain is described as gnawing and/or unremitting and may be more pronounced at night and with recumbency. This aggravation of pain may be due to distension of the epidural venous plexus upon lying down or diurnal variation of endogenous corticosteroids [9–11]. Lower back pain that worsens in the recumbent position should raise a red flag as it suggests a spinal cord tumor rather than a degenerative disc disease [3].

Pain is most commonly followed by motor weakness and sensory dysesthesias. Lhermitte's sign, described as an unpleasant electric shock-like sensation radiating down the spine and into the extremities, with flexion or extension of the neck is commonly associated with demyelinating lesions but can be elicited in cervical and thoracic spinal cord tumors. Other oncological causes are cisplatin neuropathy and radiation myelopathy [12–14]. Sphincter dysfunction may also occur in some cases. In children, gait disturbance and alteration of spinal curvature, such as scoliosis, are sensitive findings indicating space-occupying lesions of the spinal cord [9].

The distribution of the symptoms can suggest the location of the tumor. Cervical cord tumors present with neck pain and upper extremity numbness [2]. These tumors, due to the mild and persistent nature of symptoms, have the longest delay in diagnosis—as long as 24 months from symptom onset in one study—as compared with thoracic and lumbar cord tumors [1]. This delay may in part be due to the fact that patients with cervical cord tumors might be less likely to seek medical attention in the early stage of disease [2]. For thoracic cord tumors, low back pain is the most common complaint, along with numbness and/or weakness in the lower extremities [2]. Sensory abnormalities of the trunk region are far less common [2]. A diagnostic pitfall in the case of thoracic spinal cord tumors is that the clinical presentation is similar to that of a lumbar degenerative disease, which can delay diagnosis by an average of 21.3 months from symptom onset in the same study [2].

A significant contributing factor to the delay in diagnosis is imaging at the improper spinal level [2]. Patients with lumbar spinal cord or cauda equina tumors will have low back pain with distal radiation, weakness, and sensory dysesthesias, in addition to sphincter involvement, depending on the level involved [2]. Spinal cord tumors should always be considered as part of the differential diagnosis for patients with persistent neck and back pain, especially when symptoms are unresponsive to initial treatment.

Based on the anatomic location of the spinal cord tumor, the tumor can be:

1. Intramedullary
2. Intradural-extramedullary
3. Extradural-extramedullary

The resulting clinical sequelae constitute distinct neurological syndromes that are due to the disruption of the ascending and descending spinal cord tracts. Mild trauma can provoke acute cord compression in the setting of a long-standing tumor, which is a neurological emergency that must be promptly recognized and managed. The collection of symptoms and signs depends on the specific level and location within the spinal cord.

6.2.1 Segmental Syndrome

Segmental syndrome, also known as complete cord transection or complete transverse myelopathy, is the most severe pattern of spinal injury that may be experienced. The lesion, as the name suggests, affects both the anterior and posterior aspects of the spinal cord bilaterally and causes loss of all function below the level of the lesion. Symptoms include paralysis below the affected spinal cord level, a circumferential boundary below which there is loss of sensation known as a "sensory level," sphincter dysfunction with urinary or bowel urgency, retention, or incontinence, loss of reflexes at the affected level, hyperreflexia below the affected level, and Babinski's sign. In acute cases, the patient may present with spinal shock that is characterized by flaccid paralysis, areflexia, loss of sphincter function, and dysautonomia, which commonly constitutes bradycardia and systemic hypotension [15]. Though seen more commonly in traumatic conditions, metastatic epidural disease and intramedullary metastases can present with this syndrome [12].

6.2.2 Brown–Séquard (Hemicord) Syndrome

Brown-Séquard syndrome is caused by unilateral injury to both the anterior and posterior spinal cord. It is characterized by weakness, ipsilateral loss of position and vibration sense below the affected cord level due to injury to the posterior columns, and contralateral loss of pain and temperature sensation due to injury to the lateral spinothalamic tract [15, 16]. Spinal cord tumors that commonly cause Brown-Séquard syndrome are intradural-extramedullary tumors, such as meningioma and nerve sheath tumors. Sometimes intramedullary tumors, such as astrocytoma, ganglioglioma, hemangioblastoma, intramedullary metastases, and radiation myelopathy, can present with a similar clinical picture [12, 17, 18].

6.2.3 Ventral Cord Syndrome

Ventral cord syndrome, also known as anterior cord syndrome, causes damage to the anterior cord, which conveys the anterolateral pathways. There is loss of pain and temperature below the level of the lesion due to the disruption of spinothalamic

tract. Damage to anterior horn cells causes a lower motor neuron pattern of weakness at the level of the lesion. Disruption of the corticospinal tract can cause upper motor neuron signs below the level of the lesion. Bowel and bladder symptoms are common as the pathway for sphincter function is located in the anterior cord [16]. However, as the dorsal column is undisturbed, proprioception and vibratory sense remain intact [12, 16]. Although ischemic injury to the anterior spinal artery most often causes ventral cord syndrome, the leading neoplastic cause is anterior epidural metastatic disease [12]. Rarely, radiation myelopathy and intramedullary tumors, such as astrocytoma can cause this syndrome as well [12, 19].

6.2.4 Central Cord Syndrome

Central cord syndrome occurs when a centrally located tumor compresses the central grey matter and the crossing spinothalamic tract fibers. Cervical cord lesions result in a unique pattern of injury with more pronounced distal upper extremity (hands) than lower extremity weakness, and loss of pain and temperature sensation in a "shawl-like" or "cape" distribution over the upper neck, shoulders, and upper trunk [16]. Vibratory sense, proprioception, and bowel and bladder function are rarely affected [12]. This syndrome is noted more commonly in syringomyelia and intramedullary tumors, such as ependymoma, astrocytoma, hemangioblastoma, lipoma, or metastasis [12].

6.2.5 Dorsal Cord Syndrome

Dorsal cord syndrome, also known as posterior cord syndrome, is caused by injury to the dorsal column, causing loss of vibration and position sense below the level of the lesion [16]. Larger tumors can encroach more anteriorly and involve the corticospinal tracts and descending autonomic tracts [12, 16]. The most common neoplastic causes of dorsal cord syndrome include compression from extradural tumors (such as epidural metastasis), intradural intramedullary tumors (such as astrocytoma and hemangioblastoma), and sometimes radiation myelopathy [12, 19].

6.2.6 Conus Medullaris Syndrome

The classical presentation of conus medullaris syndrome is with lower extremity weakness that may be mild, variable lower extremity reflexes, early sphincter dysfunction, impotence, sensory level at or below the waist—including loss of sensation at the lower lumbar (perineal) and sacral dermatomes which, is called saddle anesthesia [15]. Ataxia can sometimes be seen. Tumors that can cause conus medullaris syndrome are myxopapillary ependymoma, lymphoma, astrocytoma, and metastasis [12].

6.2.7 Cauda Equina Syndrome

Cauda equina syndrome is caused by root compression between the L2–S1 vertebral bodies and causes loss of function in two or more of the 18 nerve roots that comprise the cauda equina [12, 20]. The classical symptoms consist of radicular lower back pain, weakness, and areflexia at the affected level, with sciatic or other lower extremity radiculopathy, and loss of sensation in a dermatomal distribution. Sphincter dysfunction occurs later in the course [15]. The oncologic causes for cauda equina syndrome are epidural metastasis, myxopapillary ependymoma, meningioma, nerve sheath tumor, leptomeningeal disease, or paragangliomas [12].

6.3 Physical Examination

A thorough neurological examination is crucial for identifying signs of a space-occupying spinal cord lesion and can help in localization prior to imaging. It is imperative to assess the functional status at presentation, especially the ambulatory status of the patient as it has a significant prognostic implication. Misinterpreting exam findings has been cited as a major factor in delaying diagnosis of spinal cord tumors [1–5].

Symptoms tend to be mild earlier in the course and in those who complain of mild sensory anomalies, Valsalva maneuver can increase the intensity of the radicular symptoms [14, 21]. Radiculopathy can also be intensified by spinal motion that narrows space at the level of the lesion [8]. Unilateral weakness or sensory deficit (to either light touch or pinprick) and asymmetric reflexes should always be noted as they may represent unilateral cord or nerve root compression by a tumor. Horner's syndrome occurs more commonly in paravertebral tumors, but also seen in cord compression at C7– T1 level [14]. Myelopathic signs—such as spasticity, hyperreflexia with or without clonus, Hoffman's sign, and/or Babinski sign–characteristic of cord compression demand an expedited work-up. Autonomic dysfunction is seen as well in these patients. They should undergo further examination to check for sphincter dysfunction. Abdomen may be percussed to rule out bladder distension and in obese patients, bladder ultrasound may be ordered to measure residual urine. Rectal examination should be performed to assess the sphincter tone [14].

6.4 Diagnostic Techniques

6.4.1 Labs

Blood and chemistry panels rarely play a role in diagnosing spinal cord tumors other than being a part of the pre-operative evaluation.

6.4.2 Lumbar Puncture

Although lumbar punctures are not generally used for diagnosing spinal cord tumors, concentration of neoplastic cells in the cerebrospinal fluid (CSF) can identify the extent of disease and neoplastic seeding [22, 23]. In addition to CSF cytology, limited studies have utilized immunocytochemistry, flow cytometry, fluorescence *in situ* hybridization (FISH), polymerase chain reaction (PCR), and non-cellular biomarkers for attempted diagnosis of central nervous system (CNS) malignancy [22]. More recent studies have focused on finding tumor cell-free deoxyribonucleic acid (cfDNA) mutations in the CSF of patients with primary CNS tumors yielding mixed results, being most promising for tumors directly adjacent to the ventricular space [24, 25].

6.4.3 Imaging

Gadolinium-enhanced magnetic resonance imaging (Gd-MRI) provides the best view of the spinal cord and the surrounding structures as compared with other modes of imaging, thus making it the diagnostic test of choice in the evaluation of spinal cord tumors. Almost all spinal cord tumors tend to enhance with gadolinium and should be differentiated from the degenerative disc disease [26]. Imaging area should be concentrated on the affected level as identified by the history and physical examination. However, as discussed earlier, low back pain should not be used as criteria to exclude a thoracic tumor. Delay in obtaining the appropriate imaging studies is cited as one of the top reasons for delay in diagnosis of spinal tumors [1].

6.4.4 Biopsy

It is difficult to distinguish between the spinal cord tumors solely based on clinical and radiological characteristics. Biopsy of the lesion is warranted to determine pathology type of the tumor and remains the gold standard for diagnosis. This helps guide treatment strategies for the patient, including radiation, chemotherapy, and/or surgical resection.

6.5 Familial Tumor Syndromes

Neurofibromatosis type 2 (NF2), schwannomatosis, and Von Hippel-Lindau disease (VHL) are familial tumor syndromes that are associated with spinal cord tumors. NF2 is an autosomal dominant disorder caused by mutation of the NF2 gene (merlin or schwannomin) on chromosome 22 and is associated with multiple intracranial and spinal tumors, most common of which are vestibular schwannomas [27].

The prominent spinal tumors seen here are extramedullary tumors such as meningioma and schwannoma and intramedullary tumors such as ependymoma [28].

Schwannomatosis is a clinically and molecularly distinct form of neurofibromatosis that is separate from neurofibromatosis type 1 and type 2. It is mostly a sporadic disorder but can be familial in some cases, and is caused by the mutations in SMARCB1 or LZTR1 on chromosome 22 [29–31]. It is characterized by multiple schwannomas and meningiomas in the absence of vestibular schwannomas [32].

VHL is an autosomal dominant disorder caused by mutation of the VHL gene on chromosome 3 [33]. It is known for its association with hemangioblastomas of the CNS and retina. Approximately 20–30% of spinal cord hemangioblastomas occur in patients with VHL. Other sites of involvement in VHL are kidney (clear cell renal cell carcinoma), adrenal gland (pheochromocytoma), pancreas (neuroendocrine islet cell tumors), inner ear (endolymphatic sac tumor), and epididymis and broad ligament (papillary cystadenoma) [34–37].

Diagnostic criteria for NF2, VHL, and schwannomatosis can be found in Table 6.1 [8, 31, 38].

Table 6.1 Diagnostic criteria for NF2, VHL, and Schwannomatosis

NF2	VHL	Schwannomatosis
Definitive criteria (any one of the below):	*Suggested criteria (any one of the below):*	*Definitive criteria (all of the following):*
1. Bilateral vestibular schwannoma 2. First degree relative with NF2 **plus** (a) Unilateral vestibular schwannoma **OR** (b) any two of the following: Meningioma, schwannoma, glioma, or posterior subcapsular lens opacity 3. Unilateral vestibular schwannoma **plus** meningioma, schwannoma, glioma, neurofibroma, or posterior subcapsular lens opacity 4. Multiple meningiomas **plus** (a) Unilateral vestibular schwannoma **OR** (b) Schwannoma, glioma, neurofibroma, or posterior subcapsular lens opacity	1. Multi-generational family history **plus** one CNS or visceral hemangioblastoma 2. Two hemangioblastomas, one of which must be CNS or retinal 3. Positive genetic testing	1. At least two non-intradermal schwannomas (one with histologic confirmation) 2. Diagnostic criteria for NF2 not fulfilled 3. No evidence of vestibular tumor on MRI 4. No first-degree relative with NF2 5. No known constitutional NF2 mutation 6. One pathologically confirmed non-vestibular schwannoma plus a first-degree relative who meets the above criteria

Physicians should be aware of these syndromes, especially in young patients with multiple spinal cord tumors and a positive family history, and refer them accordingly to specialized centers for genetic testing and counseling.

6.6 Illustrative Cases

6.6.1 T2 Plasmacytoma

58-year-old woman with no significant past medical history who presented with 3-month history of upper back and shoulder pain. She was neurologically intact except long tract signs on physical exam. MRI revealed a pathological T2 fracture with severe loss of height and enhancement spanning from T1 to T2, with significant extension into the upper right thoracic cavity. Patient underwent T1–4 laminectomies and C4 to T5 posterior fixation / fusion, as intraoperative biopsy confirmed plasmacytoma sensitive systemic therapy (Fig. 6.1).

6.6.2 T3–T6 Posterior Arachnoid Cyst

70-year-old right-handed female presented with chronic back with radiation to bilateral lower extremities and minor problems with bladder control. MRI revealed a large intradural, extramedullary cyst posterior to the spinal cord causing significant compression. The patient underwent T2-6 laminectomy with resection of the cyst. Histopathology revealed arachnoid cyst (Fig. 6.2).

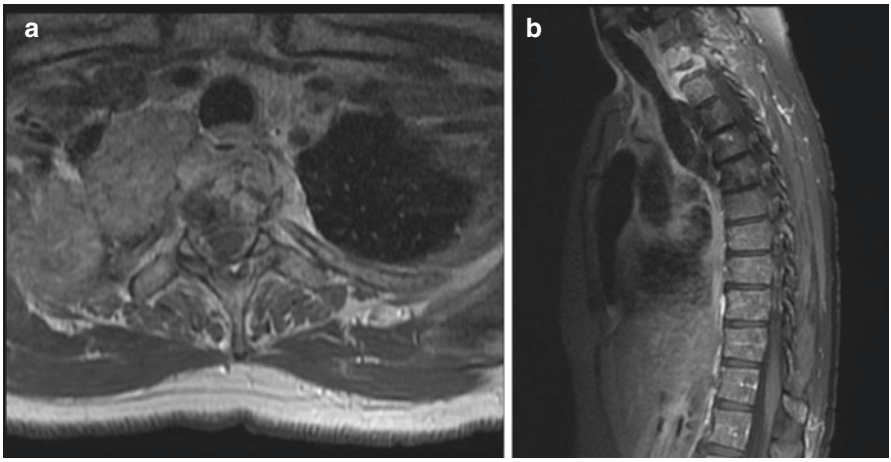

Fig. 6.1 (**a**) T1-weighted axial MRI with contrast showing tumor-invaded T2 with significant extension to the right intrathoracic cavity and compression of the anterior spinal cord. (**b**) T1-weighted sagittal MRI with contrast showing a tumor invaded collapsed T2 and anterior epidural as well as anterior spinal extension

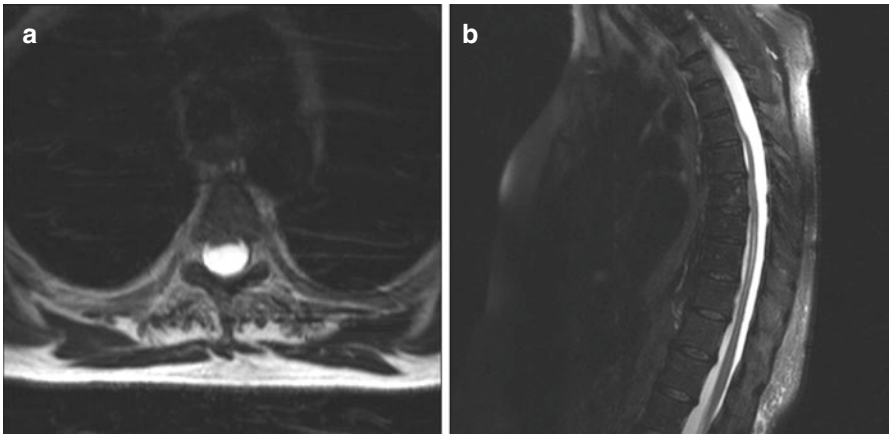

Fig. 6.2 T2-weighted axial and sagittal MRI showing large cystic lesion compressing the spinal cord at its posterior aspect. Please note the content of the cyst is equal to CSF

6.6.3 T4 Lymphoma

An 81-year-old right-handed Caucasian female presented with a few weeks of thoracic back pain and an acute history of bowel dysfunction. A pathological T4 compression fracture was seen on computed tomography (CT.) MRI thoracic spine with contrast revealed T4 pathological fracture with 70% height loss and an enhancing lesion compressing the anterior spinal cord. Subsequent oncological workup showed hilar and mediastinal lymphadenopathy. The patient underwent T3–4 laminectomy to decompress the spinal cord, open surgical biopsy that showed diffuse large B-cell lymphoma, and posterior T2–6 internal fixation and fusion followed by chemotherapy and radiation (Fig. 6.3).

6.6.4 T5 Hemangioma/Highly Vascular Schwannoma

69-year-old male with history of prostate cancer and previously radiated T5 bony metastasis who presented with increasing PSA levels. MRI of the thoracic spine revealed a large T5 right intradural / extramedullary mass. Surgical resection revealed hemangioma versus highly vascular schwannoma (Fig. 6.4).

6.6.5 Right T6 Malignant Nerve Sheath Tumor with Rapid Intracanalicular Recurrence

37-year-old right handed female with suspected Li-Fraumeni Syndrome, given history of breast cancer, hip fibrosarcoma, and pelvic osteosarcoma. She had a known right intra-thoracic paraspinal mass that was biopsied 7 years prior, demonstrating schwannoma. The patient at that time did not want to have surgery.

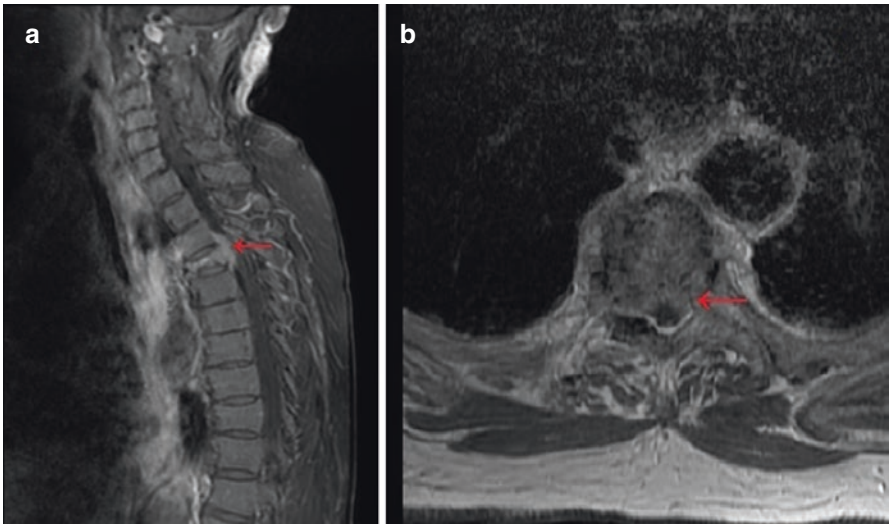

Fig. 6.3 Thoracic spine T1-wighted MRI with contrast showing T4 pathological fracture with significant height loss, and an enhancing lesion with extension into epidural and bilateral foraminal spaces. (**a**) Midline sagittal view. (**b**) Axial view at T4 vertebral body level

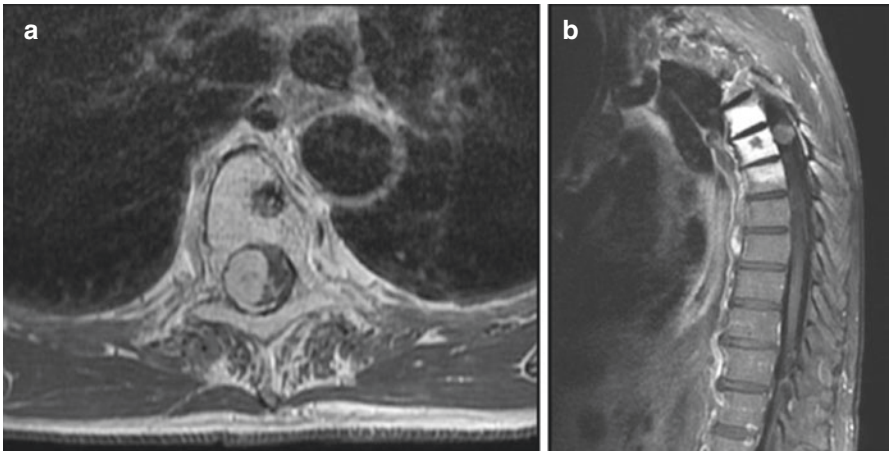

Fig. 6.4 (**a**, **b**) T1-weighted axial and sagittal MRI with contrast showing a large enhancing intradural extramedullary mass compressing the spinal cord at its right aspect. Please note the tumor's lateral borders closely following the dura being suspicious of being intradural. Also note hyperintense bodies secondary to previously radiated spine for known metastatic prostate cancer

She presented with recurrent pneumonia and significant weight loss. Imaging revealed a very large right paraspinal mass extending from approximately T2 down to the diaphragm, compressing the aorta and pulmonary veins. The mass appeared contiguous with an intrathecal nodule along the right T6 nerve root with epidural

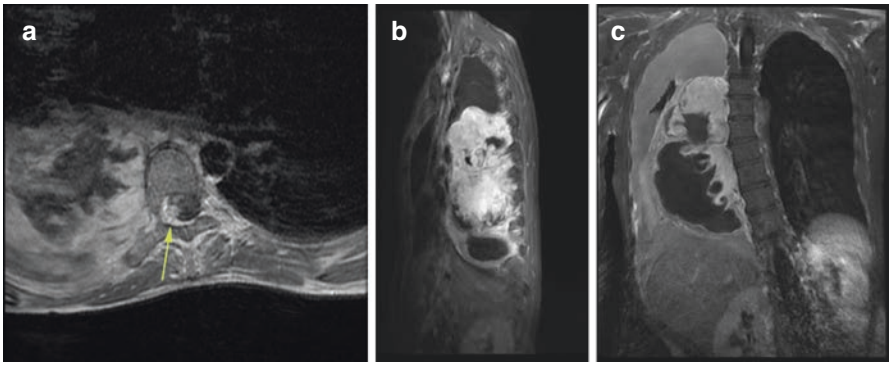

Fig. 6.5 T1-weighted MRI with contrast. (**a**) Axial series showing an extradural enhancing mass along the right T6 root. (**b**, **c**) Sagittal and coronal series showing the giant extraforaminal, intrathoracic malignant nerve sheath tumor

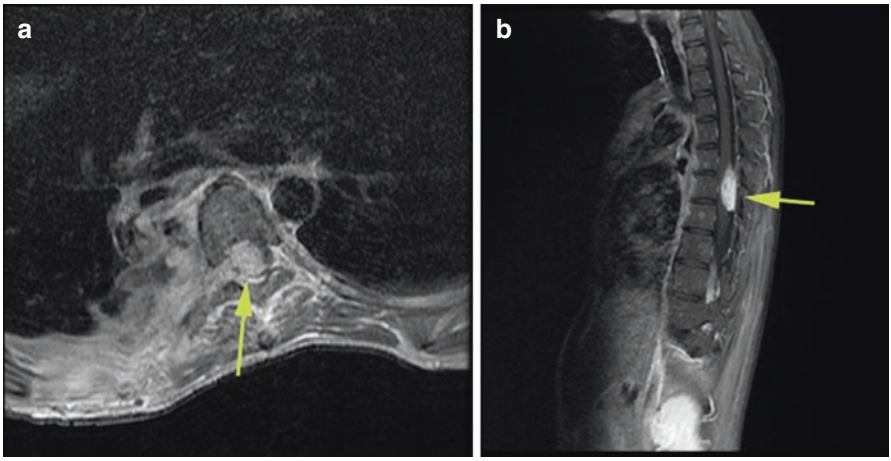

Fig. 6.6 (**a**, **b**) T1-weighted axial and sagittal series showing resection of the giant right intrathoracic malignant nerve sheet tumor with both extraforaminal as well as intraspinal extradural recurrence compressing the spinal cord

thickening and enhancement along the right epidural space from T5 to T8 (see Figs. 6.5 and 6.6). She underwent a right thoracotomy for resection of the mass. Histopathology confirmed malignant peripheral nerve sheath tumor. The intrathecal nodule was left to be resected at a later time once patient recovered from the thoracotomy. Two weeks later, she developed quick increasing right lower extremity weakness and bowel dysfunction. Imaging revealed significant growth of the prior intrathecal nodule. Consequently, she underwent T4-T7 laminectomies for resection of the mass (Figs. 6.5 and 6.6).

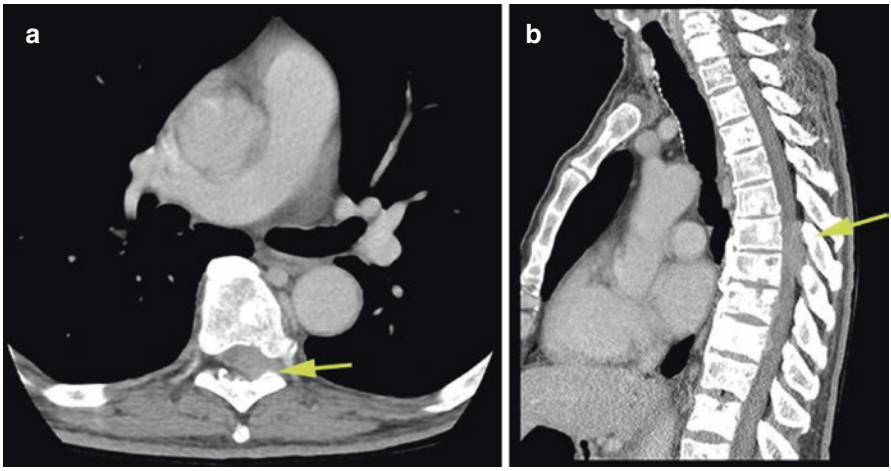

Fig. 6.7 (**a**, **b**) Axial and sagittal non-contrast CT showing extradural masses compressing T6–T9. Areas of previously metastatic spine tumor from prostate cancer are visible throughout the spine. Due to quick neurological decline, and salvageable neurological function, patient went to surgery directly after non-contrast CT

6.6.6 Prostate Cancer Metastasis with Spinal Cord Compression at T6 to T9

71-year-old right-handed male presented with four-day history of progressive paraparesis and bladder dysfunction, along with several weeks of mid-thoracic back pain. Neurological exam revealed lower extremities with strength graded 2-3/5 and sensory level at T7. A CT scan revealed a T7/T8 extradural mass dorsal to the dural sac. Due to accelerated progressive paraparesis, and to avoid delay, surgery was performed based on CT. Patient underwent T6–T9 laminectomies and gross total resection of the mass. Histopathology confirmed metastatic prostate carcinoma (Fig. 6.7).

6.6.7 T12–L1 Schwannoma

A 68-year-old right-handed Caucasian female presented with a several month history of increasing lumbar back pain with radicular left leg pain with acute exacerbation and extension into right leg, numbness, ataxia, and bladder dysfunction initially suspected of being secondary to normal pressure hydrocephalus. MRI of the lumbar spine with contrast showed midline enhancing intradural extramedullary mass at T12–L1. She underwent T12–L1 laminectomy and gross total resection of the schwannoma that appeared to originate from left T12 nerve root compressing the

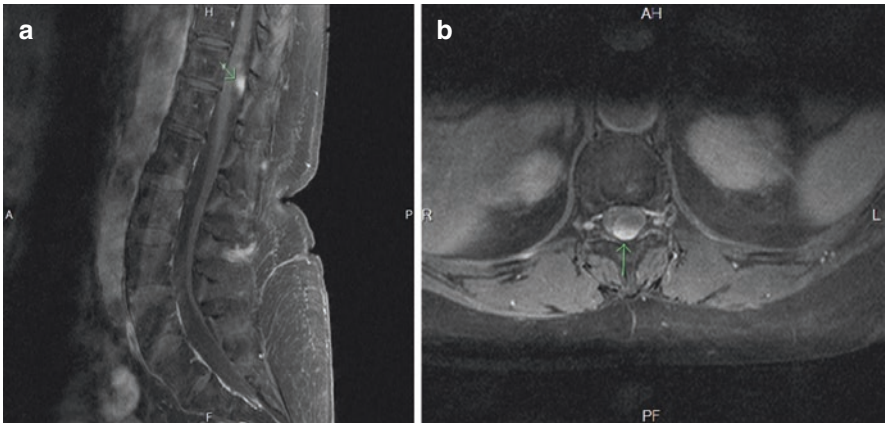

Fig. 6.8 Lumbar spine T1-weighted MRI with contrast showing posterior midline intradural-extramedullary tumor compressing the conus medullaris. (**a**) Midline sagittal view. (**b**) Axial view at T12–L1 intervertebral disc level

conus medullaris and severely attached to cauda equina. Histopathology confirmed schwannoma (Fig. 6.8).

6.6.8 T12–L1 Lipoma

A 65-year-old right-handed African-American female with history of scoliosis and spina bifida presented with chronic back pain associated with right leg radicular pain for past 2 years, and bladder and bowel dysfunction in past 7 months. MRI lumbar spine with contrast showed tethered cord with lipoma at L1 compressing the conus medullaris at its posterior aspect. She underwent laminectomy, untethering of spinal cord, and subtotal resection of lipoma with a 2-mm-thick anterior lipoma layer left attached to posterior spinal cord to avoid compromise of spinal cord circulation (Fig. 6.9).

6.6.9 L1–L2 Cauda Equina Prostate Cancer Metastasis

57-year-old man with a history of metastatic prostate carcinoma and a previously radiated L2 spinal metastasis who presented with 5 weeks of progressive right lower extremity pain, saddle paresthesia, and mild distal lower extremity weakness. MRI revealed an enhancing, intradural mass spanning the entire canal at the L1–L2 level, with significant compression of the cauda equina. Patient underwent L1–L2 laminectomies for gross total resection of the mass. Histopathology confirmed metastatic prostate carcinoma (Fig. 6.10).

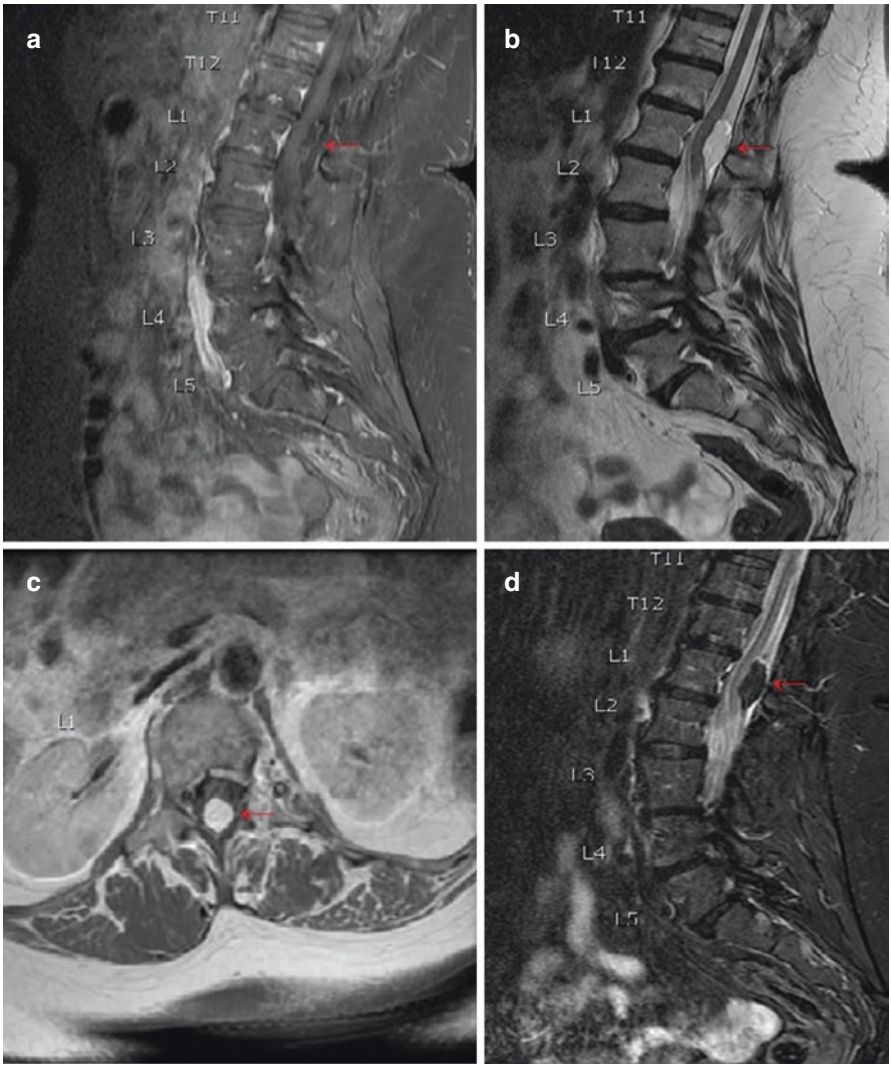

Fig. 6.9 Lumbar spine MRI showing tethered spinal cord with conus medullaris at the L2 level. Imaging also shows a 28 mm × 11 mm × 10 mm fat signal mass at T12–L1 level compressing the posterior aspect of distal spinal cord. (**a**) Midline sagittal view of T1-weighted with contrast. (**b**) Midline sagittal view of T2-weighted. (**c**) Axial view of T1-weighted with contrast at L1 vertebral body level. (**d**) Midline sagittal view of STIR series

6.6.10 L2 Schwannoma

A 68-year-old right-handed Caucasian female presented with a chronic history of back pain and altered sensation in right thigh. MRI lumbar spine with contrast revealed an enhancing epidural mass at L2 vertebral level, compressing the cauda equina. She underwent gross total resection of tumor and histopathology confirmed schwannoma (Fig. 6.11).

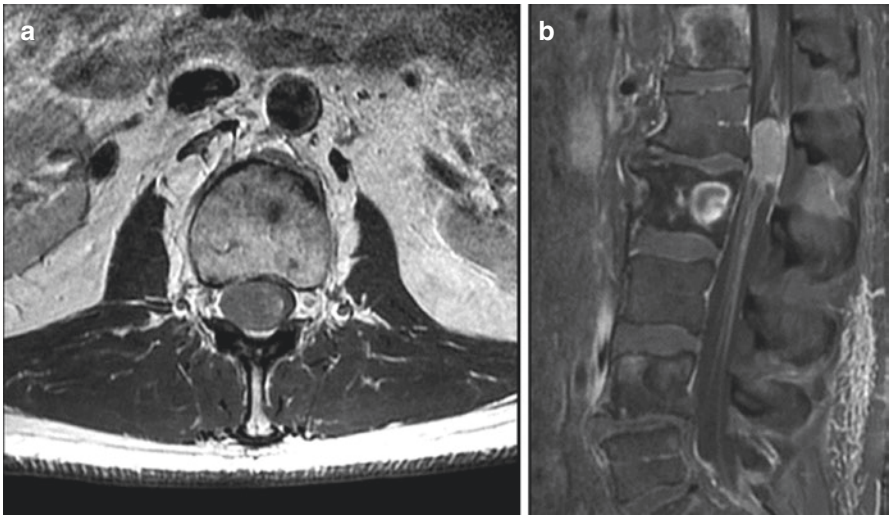

Fig. 6.10 (**a**) T2-weighted axial MRI showing a large round tumor compressing the cauda equina. (**b**) T1-weighted sagittal MRI with contrast showing enhancing mass occupying the entire canal at L1–L2

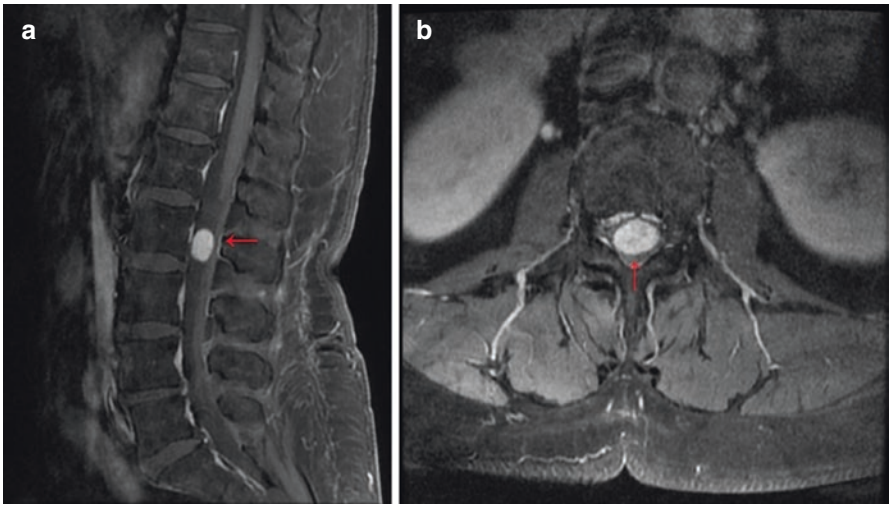

Fig. 6.11 Lumbar spine MRI with contrast showing enhancing intradural extramedullary lesion 11 mm × 17 mm × 15 mm at L2 vertebral body level consistent with Schwannoma. (**a**) Midline sagittal view of T1-weighted with contrast. (**b**) Axial view of T1-weighted with contrast at L2 vertebral body level

6.6.11 L2–L3 Schwannoma

37-year-old right-handed male presented with chronic back pain for several months, with radiation to the thighs greater on the left side. He also noted worsening bowel and bladder dysfunction. An MRI of the lumbar spine revealed an

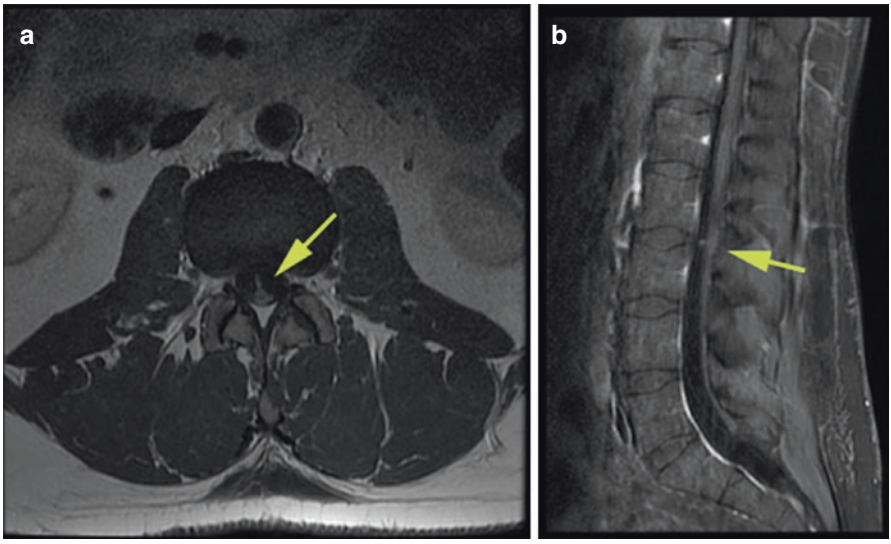

Fig. 6.12 (**a**, **b**) Axial and sagittal T1-weighted MRI with contrast depicting intradural extramedullary cauda equina schwannoma

intradural enhancing mass posterior to the cauda equina at L2–L3. He underwent L2–L3 laminectomies with gross total resection. Histopathology confirmed schwannoma (Fig. 6.12).

6.7 Summary

Spinal cord tumors are known for delayed diagnosis relative to other CNS diseases. Proposed reasons include non-specific symptoms, slow clinical progression, delay in seeking medical care, improper and incomplete physical examination, and late or improper imaging. Physicians should consider spinal cord tumors in all patients with neck or back pain—with or without neuropathic findings—especially when patients are unresponsive to initial treatment. In children, alterations in gait and spinal curvature should raise suspicion for a spinal cord tumor. The advent of gadolinium-enhanced MRI and its wider availability has helped in the earlier diagnosis and early referral of spinal cord tumors, which in turn improves disease prognosis.

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Intraoperative Neurophysiology during Surgery for Spinal Cord Tumors

7

Vedran Deletis and Kathleen Seidel

7.1 What Neurosurgeons Expect and What Neurophysiologists Can Provide

7.1.1 Surgical Perspective on Intraoperative Neurophysiological Monitoring

Intraoperative neurophysiological monitoring (IOM) is becoming increasingly important with technical advances in neurosurgery [1–3]. Functional neurophysiological guidance may preserve neurological function with increased patient safety, but also might allow more radical tumor resection [4–11]. However, there is no doubt that IOM methods should be adapted to the specific pathology and surgical strategy.

7.1.2 Intramedullary Tumors

Despite important technical advances, surgery for intramedullary spinal cord tumors (IMSCTs) is still very challenging and may carry significant risk of patient morbidity. Tumor proximity to crucial neural tracts, nuclei, and partially infiltrated borders—as well as distorted spinal cord anatomy—necessitate real-time functional feedback [2, 4, 10].

Intraoperative neurophysiological monitoring of the functional integrity of spinal cord pathways is crucial to prevent, limit or document the moment of surgically

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induced injury [3, 4, 10, 12, 13]. The available methods can be divided into monitoring and mapping techniques.

Monitoring Methods. Monitoring methods are used to continuously assess the functional integrity of the tracts in the white matter and/or synaptic circuits in the grey matter (Fig. 7.1). Monitoring modalities are firmly established as an integral

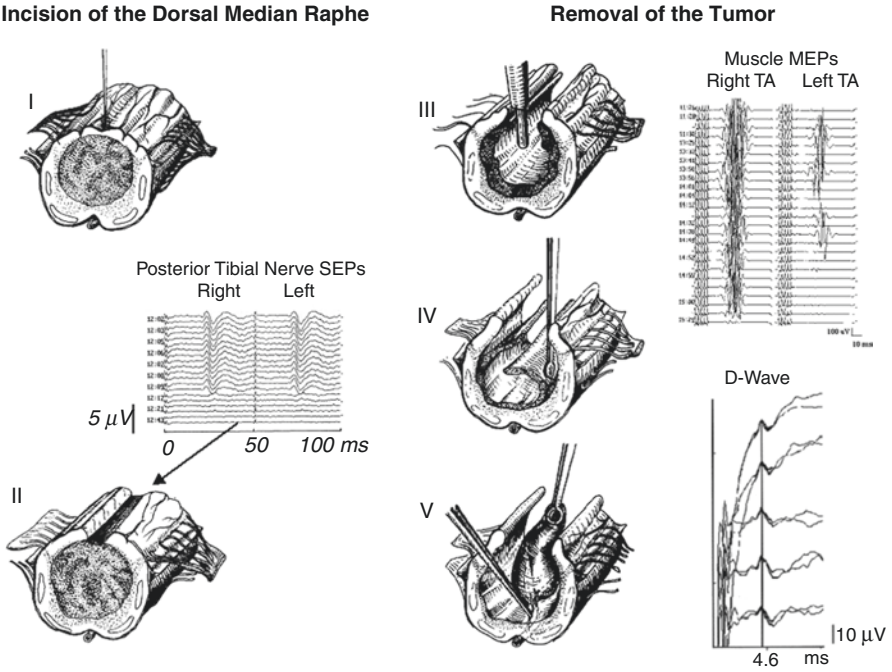

Fig. 7.1 Neurophysiological monitoring during surgery for intramedullary spinal cord tumors. Incision of the dorsal median raphe (left): myelotomy is carried out by using a fine blade or laser. In spite of any attempts to stay within the median raphe (Panel I) to avoid damage to the dorsal column, SEPs are frequently compromised or lost during this surgical step (Panel II). Although the drop in amplitude is usually reversible, SEPs may remain unmonitorable for several hours. Removal of the tumor (right): there is direct access to the tumor after dorsal columns are separated. If there is no adequate lateral visualization to safely remove the tumor without excessive retraction to normal neural tissues, ultrasonic aspiration can be used to debulk the central part of the tumor (Panel III). At this point it is possible to gently dissect the tumor from the neural tissue. In doing so, traction on the corticospinal and other descending motor tracts can occur (Panel IV). Accordingly, muscle MEPs, as well as epidural MEPs (D-wave), should be strictly monitored during this surgical step. The upper right panel shows the disappearance of the left tibialis anterior MEP during tumor removal. The lower right panel illustrates a stable D-wave, which warrants good long-term motor outcome (see text for more details). Finally, the ventral part of the tumor is detached from the anterior spinal cord where perforating vessels from the anterior spinal artery are located (Panel V). It is critical to monitor motor pathways since a vascular injury to the cord may result in an irreversible and severe motor deficit. (Illustration reproduced from: Sala F, Lanteri P, Bricolo A. Intraoperative neurophysiological monitoring of motor evoked potentials during brain stem and spinal cord surgery. In: J.D. Pickard (Editor in Chief), V.V. Dolenc, J. Lobo Antunes, H.J. Reulen, M. Sindou, A.J. Strong, N. de Tribolet, C.A. F. Tulleken, M. Vapalahti (eds.) Advanced and Technical Standards in Neurosurgery. Vol. 29, pp. 133–169, 2004)

part of surgical strategy for spine, and particularly for spinal cord surgery [4, 10]. Motor evoked potentials (MEPs) and sensory evoked potentials (SEPs) with established interpretation and warning criteria are used for this purpose [14]. In selected patients with conus pathology, intraoperative monitoring of the bulbocavernosus reflex might be of additional value [15]. However, monitoring can only identify loss of integrity but not location and somatotopy.

Mapping Methods. Mapping methods identify structures within the exposed part of the spinal cord [2, 13]. Mapping methods for the spinal cord long tracts are less well developed. Three methods have been reported for mapping the dorsal column: (1) by measuring the amplitude gradient of the SEP, recorded using a miniature multicontact electrode over the surgically exposed spinal cord after stimulation of the peripheral nerves [13, 16, 17]; (2) by recording phase-reversal SEPs over the scalp after direct stimulation of exposed dorsal column [18]; and (3) by recording antidromic responses over peripheral nerves after stimulation of the dorsal column [19].

Two mapping methods have been described for identifying the corticospinal tract (CST): (1) the D-wave collision technique [16, 20] and (2) direct stimulation of the spinal cord to elicit responses from limb muscles [21–24].

Recently, we were able to present neurophysiological background and clinical experience of identification of dorsal column and CST by direct electrical stimulation of the spinal cord during intramedullary spinal cord tumor surgery. First, we showed that responses recorded from limb muscles after stimulation of the exposed spinal cord can also be obtained by stimulation of the dorsal column and not exclusively by stimulation of the CST [25, 26]. Second, we demonstrated that muscle responses after CST or dorsal column stimulation have distinguishable features, if double train stimulation is used [26].

7.1.3 Cervical Myelopathy and Intradural–Extramedullary Tumors

In high cervical myelopathy patients prepped in the prone position, recording of SEP and MEP during positioning might be beneficial because changes in neurophysiologic parameters could indicate that positioning adjustments are necessary and, therefore, help prevent position-related injury to the spinal cord [27–29]. This approach might be especially helpful in high cervical intraspinal-intradural or sometimes even large extradural tumors. Rotation and manipulation of the spinal cord can be controlled by monitoring MEP and SEP when approaching anterior or anterolateral tumors via dorsal hemilaminectomy [30, 31].

7.1.4 Tumors Involving the Conus Medullaris

Neurosurgical procedures involving the conus medullaris or cauda equine might be also considered high risk surgeries [5, 8, 9, 32, 33]. During many surgeries, resection planes may be difficult to identify [8, 9]. Pathologies like ependymomas, astrocytomas, and

lipomas are rather benign pathologies, so preservation of neurological function and quality of life plays an important role [2, 8, 9, 34]. During those surgeries, mapping techniques are available that help to identify neural tissue and to define resection borders [2, 5, 35, 36]. In surgeries of large tumors in which the single nerve roots are not visible, a modality to monitor the integrity of sacral structures—such as the bulbocavernosus reflex (BCR)—might be important, too [5, 8, 32].

7.2 Intraoperative Neurophysiologic Methodologies for Monitoring Functional Integrity of the Spinal Cord

7.2.1 Monitoring Techniques of the Motor System

Muscle MEP and D-wave. Motor potentials can be elicited by transcranial electrical stimulation via cork screw electrodes. The electrodes are placed at C3, C4, C1, C2, Cz- and a point 6 cm in front of Cz accordingly to the international 10/20 EEG electrode system (Fig. 7.2). Different montages can be applied: bilateral hemispheric stimulation (C3/C4; C1/2) or uni-hemispheric stimulation (C3/Cz-; C4/Cz-). For eliciting leg MEPs, Cz- against 6 cm in front of Cz- might be an alternative with less movement artifact. Electrical stimulation is performed using rectangular constant-current stimuli of 500 μs duration and intensities between 50 mA and 250 mA [10, 37].

Muscle MEPs are elicited with a train-stimulation technique consisting of a short train of 5–7 stimuli with 4 ms interstimulus intervals [39] (Fig. 7.3). MEPs are recorded using needle electrodes from target muscles in all four extremities: usually

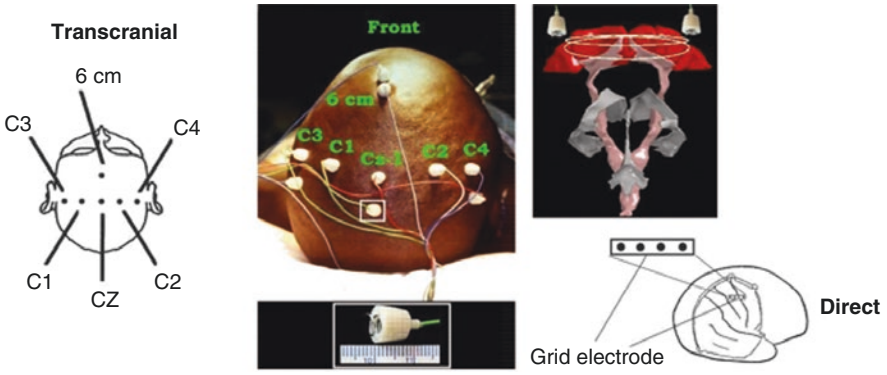

Fig. 7.2 Schematic (left) and actual illustration (middle) of electrode placement for transcranial electrical stimulation and direct stimulation of the motor cortex (right). C1,C3,Cz,C2,C4 are the positions of the stimulating electrodes aligned over the projection of the motor strip to the head. Upper right is the schematics of the coronal posterior view to the motor cortex (in red) and corticospinal tracts (in pink) with an electrical field between the stimulating electrodes. Schematics of the grid electrode (bottom right) overlying the exposed motor and sensory cortexes. (Modified from: Deletis V. Intraoperative neurophysiology and methodology used to monitor the functional integrity of the motor system. In: Neurophysiology in Neurosurgery. A Modern Intraoperative Approach. V. Deletis and J. Shils (Eds.). Academic Press. pp. 25–51, 2002)

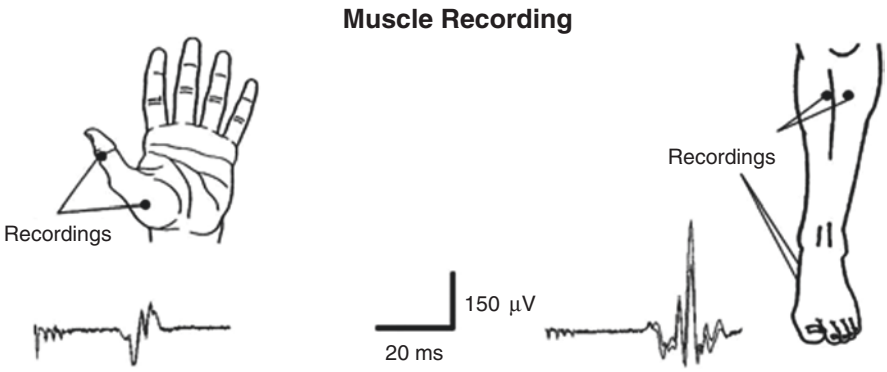

Fig. 7.3 Recordings of MEPs from the thenar, tibial anterior and abductor hallucis muscles after eliciting them with multipulse stimuli applied either transcranially or over the exposed motor cortex. (Modified from: Deletis V. Intraoperative neurophysiology and methodology used to monitor the functional integrity of the motor system. In: Neurophysiology in Neurosurgery. A Modern Intraoperative Approach. V. Deletis and J. Shils (Eds.). Academic Press. pp. 25–51, 2002)

small hand muscles and abductor hallucis/anterior tibialis muscle. Proximal muscle of upper and lower extremities might be added for monitoring as well. The signals are amplified 10,000 times and recorded on epochs of 100 ms with a filter bandpass from 1.5 to 853 Hz. The signals also do not require averaging and can be repeated at a rate of 0.5–2 Hz [10, 12, 37].

Epidural MEP (D-wave) is elicited with a single stimulus (single stimulus technique) and it is recorded with an electrode inserted into the spinal epidural or subdural space by the surgeon after (hemi)laminectomy (Fig. 7.4) [37, 38]. The electrode is placed caudally and, if tumor location allows, a second electrode is placed cranially to the tumor of the spinal cord for control recordings. The D-wave is filtered between 1.5 Hz and 1700 Hz and it is recorded at the epochs of 20 ms. Usually, no averaging of single sweeps is necessary to successfully record D-waves. However, averaging after alternating anodal and cathodal stimulation might sometimes reduce the stimulus artifact.

In intramedullary spinal cord surgery, the best correlation between muscle MEP recordings and postoperative neurologic deficits lies in the assessment of disappearance of a previously present MEP, regardless of thresholds or amplitudes. Increase in stimulus thresholds for muscle MEPs or, to a lesser degree, decrement of signal amplitudes may be considered as subclinical injury indicators without correlation to neurological dysfunction, and thus is considered a minor warning criterion [40].

D-wave preservation has been shown to be the strongest predictor of maintained corticospinal tract integrity and therefore of long term motor outcome [13]. Combining the use of muscle MEPs with D-wave recordings provides the most comprehensive approach for assessing the functional integrity of the spinal cord motor tracts during surgery for intramedullary spinal cord tumors (Table 7.1) [10, 12, 13]. A historical control study could demonstrate that long term outcome improves applying intraoperative monitoring of muscle MEP and D-Wave in IMSCT surgery [4].

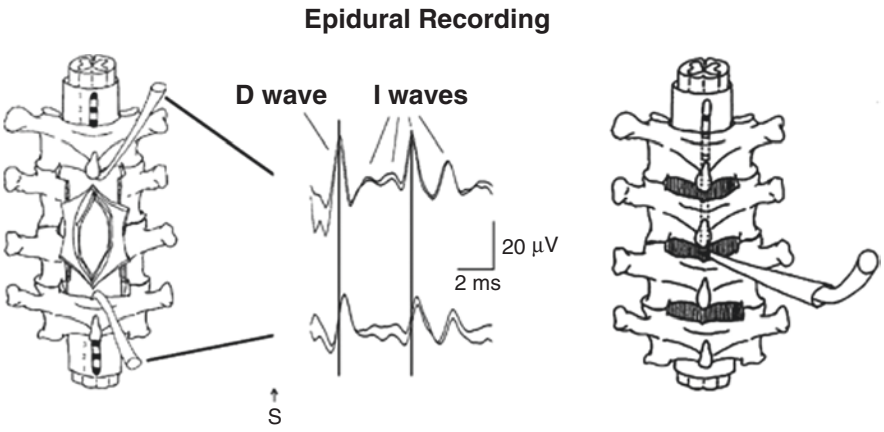

Fig. 7.4 Schematic diagram of the positions of the catheter electrodes (each with three recording cylinders) placed cranially to the tumor (control electrode) and caudally to the tumor to monitor the descending signals after passing through the surgery site (left). In the middle are D- and I-waves recorded rostrally and caudally to the tumor site. On the right, the placement of an epidural electrode is depicted percutaneously, through a flavectomy/flavotomy, or when the spinal cord is not exposed. (Modified from: Deletis V. Intraoperative neurophysiology and methodology used to monitor the functional integrity of the motor system. In: Neurophysiology in Neurosurgery. A Modern Intraoperative Approach. V. Deletis and J. Shils (Eds.). Academic Press. pp. 25–51, 2002)

Table 7.1 Principles of MEP Interpretation (Spinal Cord Surgery

D-Wave	Muscle MEP	Motor status
Unchanged or 30–50% decrease	Preserved	Unchanged
	Lost unilaterally or bilaterally	Temporary motor deficit
>50% decrease	Lost bilaterally	Long term motor deficit

Principles of D Wave and muscle MEPs interpretation during surgery for intramedullary spinal cord tumors. (Reproduced from Deletis V. Intraoperative neurophysiological monitoring. In: McLone DG and Marlin AE (Eds.). *Pediatric Neurosurgery: Surgery of the Developing Nervous System* fourth Ed. Philadelphia: W.B.Saunders, 2001, pp. 1204–1213 [41]).

7.2.2 Somatosensory Evoked Potentials (SEPs)

Upper limb SEP stimulation is performed over the median or ulnar nerves at the wrist; for lower extremities the tibial nerve at the ankle is generally selected. Stimulation can be performed either by surface or needle electrodes, with a stimulation frequency ranging from 0.7 to 5.7 Hz [8]. Recording is performed via scalp electrodes according to the 10–20 EEG system. Lateral derivations (C3' or C4' vs Cz') are chosen for upper extremity SEPs and, in most patients, medial derivations (Fz/Cz') for lower extremity SEPs. However, sometimes other derivations might improve quality of signal recording [42]. The classical warning criterion is a 50% drop in signal amplitude [8, 42].

SEPs should not be used exclusively without MEP monitoring. However, SEPs continue to retain value as they provide specificity for assessing the integrity of the dorsal column [13].

7.3 Intraoperative Neurophysiologic Methodologies for Mapping Functional Integrity of the Spinal Cord

7.3.1 Dorsal Column Mapping

To define the midline for the myelotomy, several neurophysiological methods are available.

The first method measures the amplitude gradient of the SEP recorded by using a miniature multi-contact electrode over the surgically exposed spinal cord after stimulation of the peripheral nerves. Therefore, a miniature multi-electrode grid, consisting of eight parallel stainless-steel wires (numbered 1–8), with diameters of 76 μm, and spaced 1 mm apart can be placed on the supposed dorsal column [13, 16]. The recording wires are placed parallel to the long axis of the spinal cord, with a reference needle electrode placed in a nearby muscle. Stimulation of the right and left tibial or median nerve is applied with up 40 mA intensity with 0.2 ms pulse duration and a 13.3 Hz repetition rate. Recording is performed via the multi-electrode grid by 2 sets of 100–200 sweeps averaged from each of the 8 parallel recording surfaces [17]. The midline is determined as the point lying between two maximum amplitudes of the tibial SEP travelling waves or median nerve SEP stationary waves (Fig. 7.5) [13, 16].

The second method uses recording phase-reversal SEPs over the scalp after direct stimulation of exposed dorsal column [18]. The third possibility is recording antidromic responses over peripheral nerves, after stimulation of the dorsal column [19].

7.3.2 Corticospinal Tract Mapping

D-wave collision technique. The D-wave collision technique is applied to identify the CST. D-wave collision can be achieved by stimulating the exposed spinal cord (with a hand-held probe delivering a single stimulus of 1–2 mA intensity) simultaneously with transcranial electrical stimulation to elicit a D-wave. Since the resulting signals are transmitted along the same axons, the descending D-wave collides with the ascending signal carried antidromically along the CST (Fig. 7.6) [16]. This result in a (maximal 50%) decrease in the D-wave amplitude recorded caudal to the collision site. This phenomena indicates that the mapping probe is in close proximity to the CST [16].

7.3.3 Mapping the Dorsal Column and CST with a Double Stimulation Paradigm

Mapping of the exposed spinal cord can also be performed with a double train paradigm. The inter-train interval (ITI) is set at 60 ms [26]. This time is chosen because a partial recovery time of approximately 70 ms and a complete recovery of 150–300 ms was reported in a study of recovery time after stimulation of the dorsal

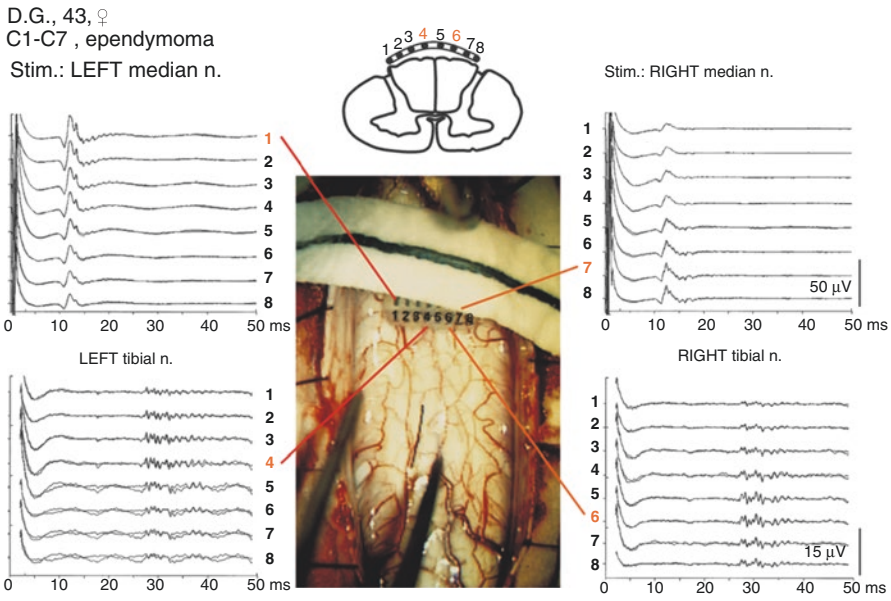

Fig. 7.5 Dorsal column mapping in a 43-year-old patient with an ependymoma between the C1 and C7 segments of the spinal cord. Spinal SEP responses were obtained from the eight recording sites after left and right tibial (bottom two sets of traces) and median nerve stimulations (top two sets of traces). Two sets of 100 sweeps were averaged. Note the amplitude gradient of conducted potentials across the recording surfaces with maximum amplitude after left tibial stimulation at recording site 4 and recording site 6 after right tibial stimulation. There is also an amplitude gradient of segmental potentials across the recording sites after median nerves stimulation. The maximum amplitude after left median nerve stimulation was at recording site 1, while after right median nerve stimulation, it was at site 7. Between the traces is an intraoperative picture of the exposed spinal cord taken during the measurement. (Reproduced from: Kržan M.J.: Intraoperative Neurophysiological mapping of the spinal cord's dorsal column. In: Neurophysiology in Neurosurgery. A Modern Intraoperative Approach. V. Deletis and J. Shils (Eds.). Academic Press. 2002. pp. 153–164)

column [43]. In other words, the spinal interneurons targeted by CST-fibres have a much shorter recovery time than 60 ms, whereas the spinal interneurons targeted by branches of dorsal column fibers ending up to the alpha motoneurons as a part of reflex arc have a recovery time significantly longer than 60 ms [43].

Therefore, it is expected that CST stimulation with this ITI would also generate a response after the second train, whereas stimulation of the dorsal column would not do so. The different patterns of muscle response after CST and dorsal column stimulation will be different in patients with and without spasticity [26]. In patients without spasticity, stimulation of the CST elicits 2 responses with identical features (Fig. 7.7a). Stimulation of the dorsal column generates only 1 response (Fig. 7.7b). In patients with severe clinical spasticity, the second response recorded after dorsal column stimulation is different from the first: either with higher or lower

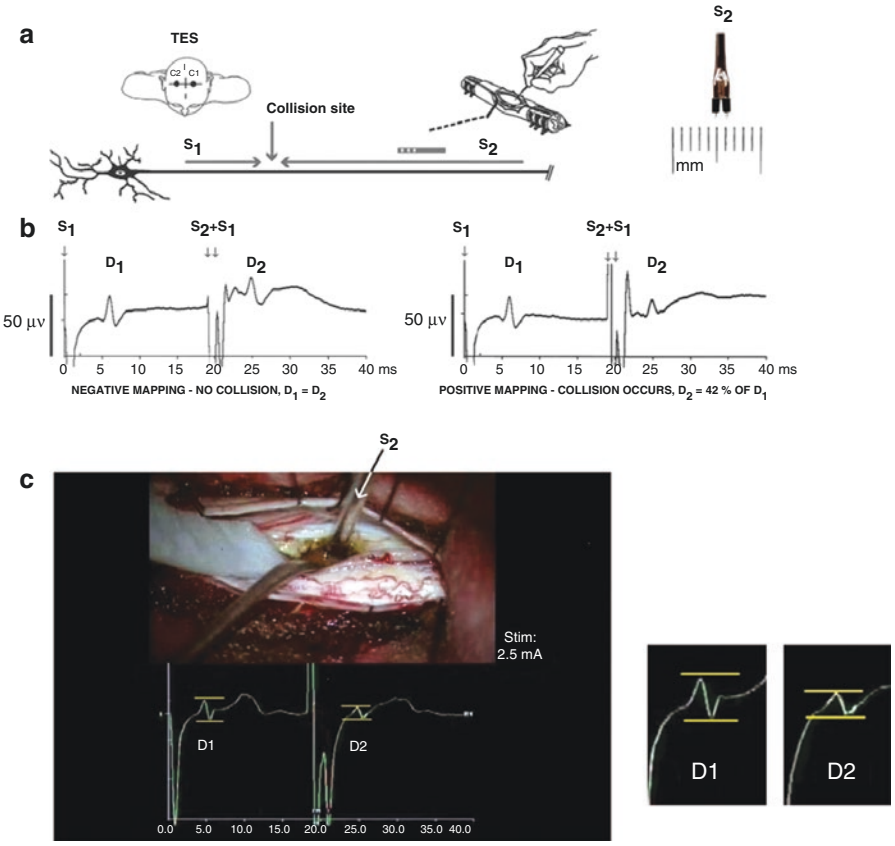

Fig. 7.6 Mapping of the CST using the D-wave collision technique (see text for explanation): (**a**) *S1* transcranial electrical stimulation (TES), *S2* spinal cord electrical stimulation, *D1* control D-wave (TES only), *D2* D-wave after combined stimulation of the brain and spinal cord, *R* the cranial electrode for recording the D-wave in the spinal epidural space. Right: the tip of the hand held stimulating probe with a scale in millimeters. (**b**) Left: negative mapping results (D1 = D2); Right: positive mapping results (D2 wave amplitude significantly diminished after collision). (**c**) Intraoperative mapping of the CST within spinal cord in 44-year-old patient with intramedullary arterio-venous malformation at T3-T5 level; stimulating probe delivering 2.5 mA current pulse in the close proximity with CST, revealed by a decrement of the D2 wave amplitude of proximately 50% compared with D1 wave amplitude (control). (Modified from: Deletis V, de Camargo AB. Interventional neurophysiological mapping during spinal cord procedures. Stereotactic and Functional Neurosurgery 2001, 77, 25–28)

amplitudes, usually variable response, but never equal to the first one (Fig. 7.8a. Stimulation of the CST generates two responses of equal amplitude, identical to those of the non-spastic patients (Fig. 7.8b) [26].

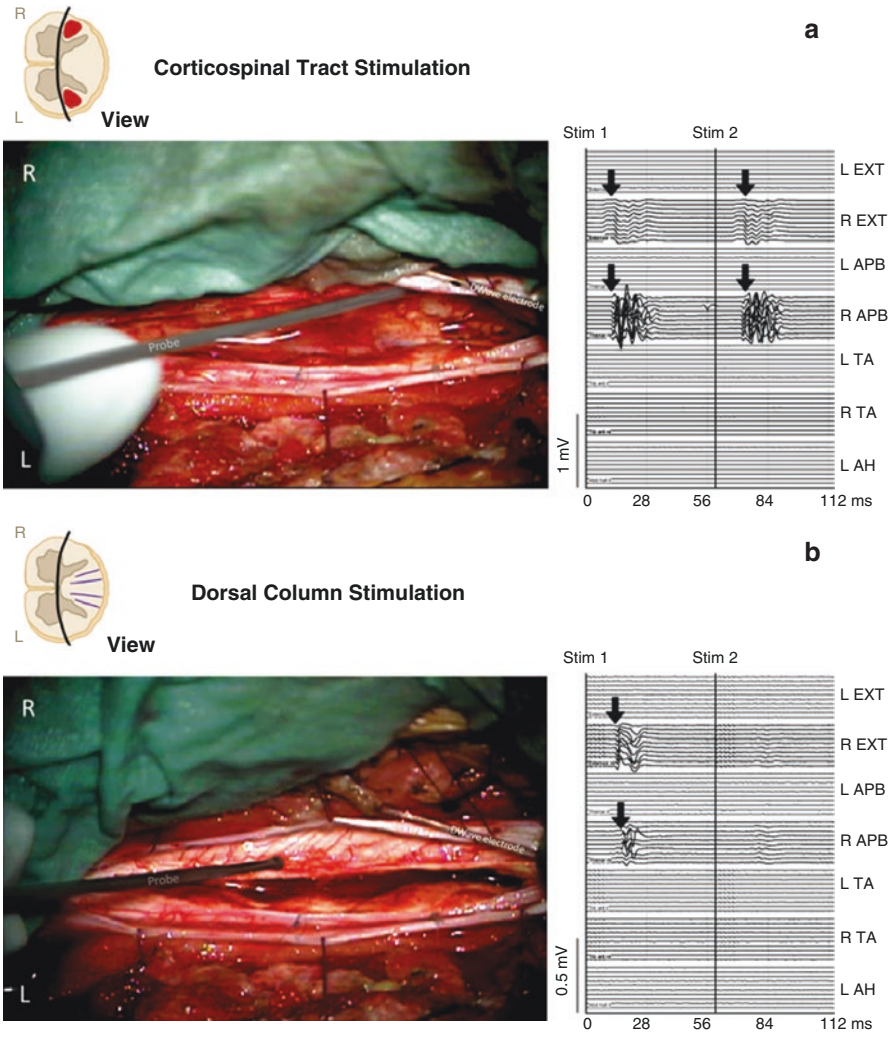

Fig. 7.7 Seven groups of muscle recordings of 10 consecutive trials of double train stimulation (stim 1 and 2 with an ITI of 60 ms) of the CST and dorsal column in a patient **without spasticity**. Intramedullary pilocytic astrocytoma at level C2–T1 approached via laminectomy. Stimulation of the CST with double trains of stimuli elicited identical double responses (**a**). Stimulation of the dorsal column elicited only one response after the first train, but no response after the second train (**b**). The vertical arrows depict beginning of the responses. *AH* abductor hallucis, *APB* abductor pollicis brevis, *EXT* extensor digitorum, *L* left, *Probe* stimulating hand held probe, *R* right, *TA* tibialis anterior. The vertical arrows depict beginning of the responses. (Reproduced from: Deletis V, Seidel K, Sala F, Raabe A, Chudy D, Beck J, Kothbauer KF. Intraoperative identification of the corticospinal tract and dorsal column of the spinal cord by electrical stimulation. *J Neurol Neurosurg Psychiatry*. 2018 Feb 7. pii: jnnp-2017-317,172. https://doi.org/10.1136/jnnp-2017-317,172. [Epub ahead of print])

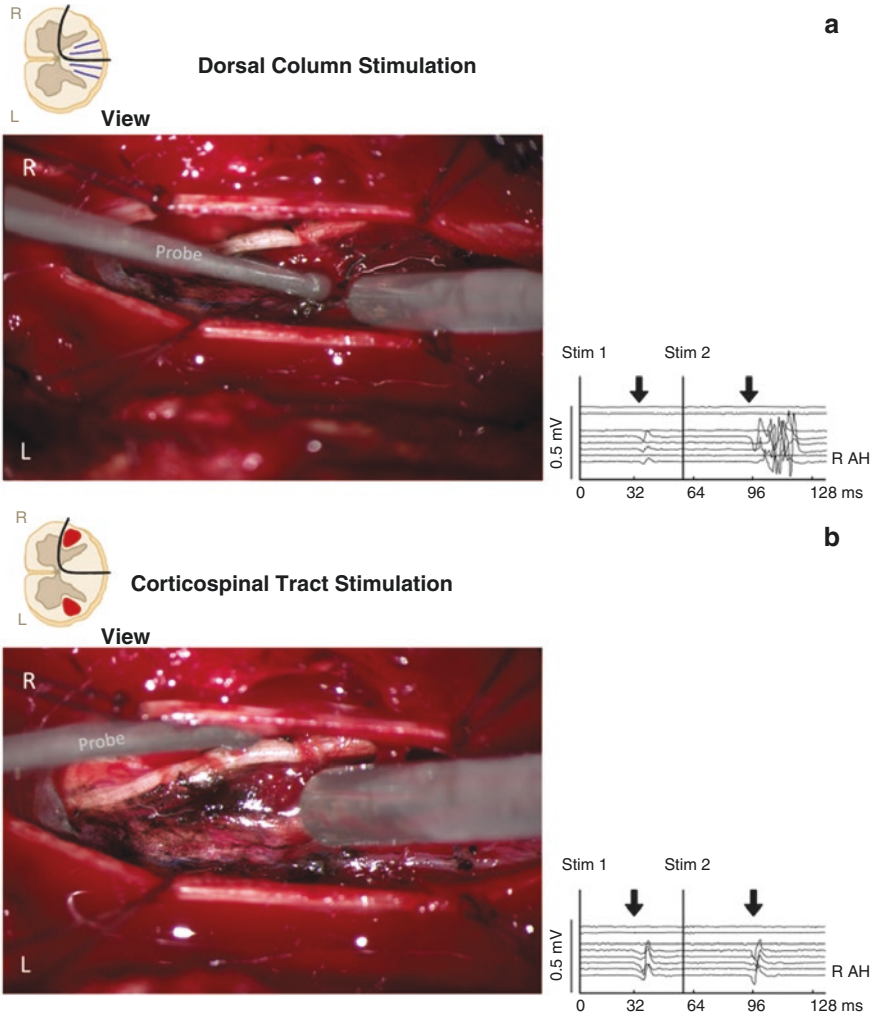

Fig. 7.8 Six consecutive trials of muscle recordings of double train stimulation (stim 1 and 2 with an ITI of 60 ms) of the CST and dorsal column dorsal column in a patient **with severe spasticity.** Melanocytic schwannoma at level T1/2 approached by hemi-laminectomy. Responses recorded in the right abductor halluces muscle (R AH) after stimulation of the CST and dorsal column. Note that after a double train stimulation of the dorsal column the second response has significantly higher amplitude than the first response and is polyphasic. This is in contrast to the example from a patient without spasticity shown in Fig. 7.7. The vertical arrows depict beginning of the responses. *L* left, *Probe* stimulating hand held probe, *R* right. (Reproduced from: Deletis V, Seidel K, Sala F, Raabe A, Chudy D, Beck J, Kothbauer KF. Intraoperative identification of the corticospinal tract and dorsal column of the spinal cord by electrical stimulation. J Neurol Neurosurg Psychiatry. 2018 Feb 7. pii: jnnp-2017-317,172. https://doi.org/10.1136/jnnp-2017-317,172. [Epub ahead of print])

7.4 Intraoperative Clinical Neurophysiology of the Sacral Nervous System

A couple of neurophysiological methods are available to monitor efficiently the lumbosacral nervous system. In anesthetized subjects, it is technically feasible to record the following neurophysiological signals (Fig. 7.9):

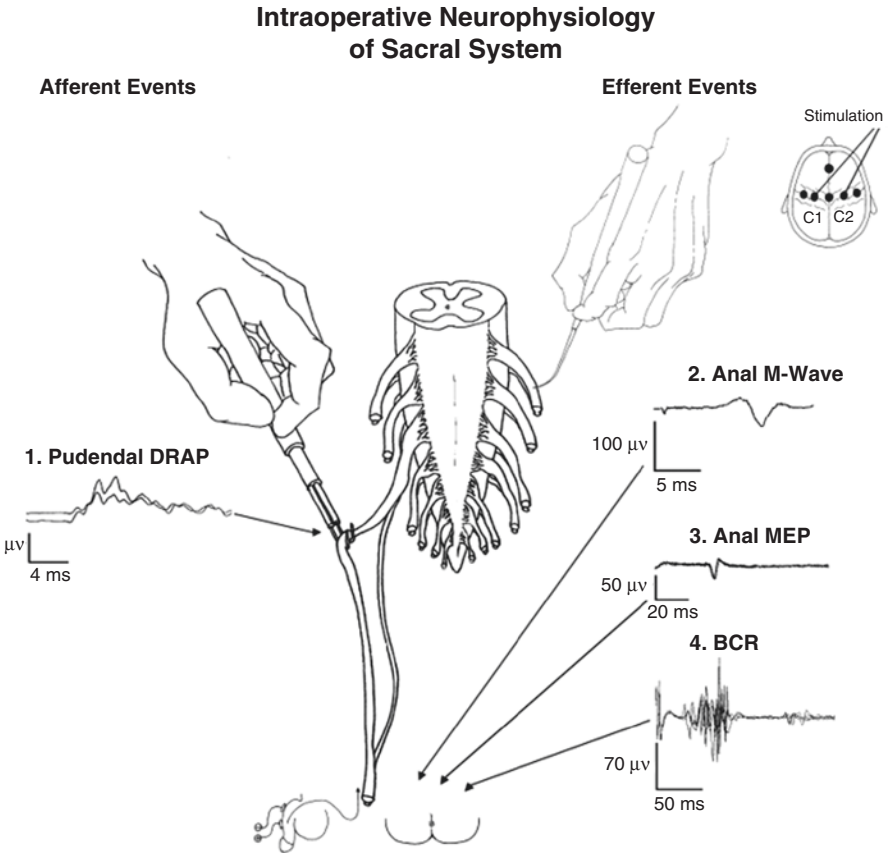

Fig. 7.9 Neurophysiological methods used to intraoperatively monitor the sacral nervous system. To the left are "afferent" events after stimulation of the dorsal penile/clitoral nerves and recording: (1) pudendal DRAP. To the right are "efferent" events: (2) anal M-wave recorded from the anal sphincter after stimulation of the S1–S3 ventral roots; (3) anal MEPs recorded from the anal sphincter after transcranial electrical stimulation of the motor cortex; and (4) bulbocavernosus reflex obtained from the anal sphincter muscle after electrical stimulation of the dorsal penile/clitoral nerves. (Modified from Deletis, V. (2001). Neuromonitoring. In "Pediatric Neurosurgery" (D. MacLeone, Ed.) Fourth Edition, pgs 1204–1213. W.B. Saunders Co., Philadelphia)

1. Afferent events
   (a) Dorsal root action potentials (DRAP) after pudendal nerve stimulation
2. Efferent events
   (a) Sphincter compound muscle action potential (CMAP) responses after sacral ventral root stimulation
   (b) Sphincter MEP after motor cortex stimulation
   (c) Bulbocavernosus reflex

7.4.1 Basic Technical Aspects of stimulation for Intraoperative Sacral Monitoring

For recording DRAP and BCR, the appropriate peripheral sensory structure (ie, the sensory part of pudendal, dorsal, penile, or clitoral nerves) has to be stimulated by silver/silver chloride cup EEG-type electrodes or other types of adhesive surface electrodes. These are placed on the dorsal surface of the penis or clitoris (this electrode represents the cathode). The other electrode (ie, anode) is placed either distally on the penis (1–2 cm apart from the proximal electrode) or on the adjacent labia [15, 44].

To record DRAP from sacral roots, which carry afferents from pudendal nerves, a hand held bipolar hook electrode is used. Stimuli of 20 mA intensity at 0.2 ms duration have been applied, involving stimulation of the penis or clitoris (at various frequencies up to 13.3 Hz). For BCR stimulation, low frequency around 2.3 Hz should be used [15]. Stimulation can also be performed at the level of the spinal roots where a hand-held sterile monopolar or bipolar electrode can be placed on the appropriate roots or rootlets. Square wave pulses of up to 2 mA intensity and 0.2 ms duration are then delivered (Fig. 7.9).

In order to record MEP from the external anal sphincter muscle, the identical methodology should be applied as stimulating and recording other muscle MEPs.

7.4.2 Bulbocavernosus Reflex

For male patients, the cathode is placed on the base of the glans penis and the anode is placed 5 to 10 mm distally [15]. For female patients the cathode is placed over the clitoris and the anode is placed on one of the labia major [15, 45]. Recording is done by 2 pairs of hook wire electrodes placed on the left and right side of the external anal sphincter muscle [15]. Even though this muscle is concentric, lateral recordings is used to have a more complete coverage of the left and right side of the anal sphincter [46]. The selection of the stimulation paradigm is done as described by Deletis et al. [15] We recommend using a short train of 5 stimuli, increasing to 7 stimuli when the response is small in amplitude or unelicitable. Pulse duration of

the stimuli should be kept to 0.5 ms with an inter-stimulus interval of 4 ms [5, 15, 47]. Applied stimulation intensity ranges from 10–40 mA; the lowest current needed to elicit a stable response is used. The repetition rate of the individual trials of stimulation will be set between 0.4 and 2.3 Hz for up to maximal four trials and then paused to avoid reflex habituation [46].

The BCR is used to assess the functional integrity of motor and sensory sacral nerve roots, as well as grey matter of S2 to S4 spinal cord segments [15]. The correlation between sphincter control and BCR is even more complex since the BCR cannot detect injury to the suprasegmental pathways controlling sphincter activity. However, BCR monitoring improves the reliability of intraoperative neurophysiology, although it may require a higher degree of neuromonitoring expertise [48].

7.4.3 Intraoperative Neurophysiologic Methodologies for Mapping Other Roots of Cauda Equine

Mapping of the cauda equine can be performed either with monopolar, bipolar, or coaxial bipolar stimulation probes. Stimulation intensity ranges from 0.1 to 2 mA, depending on the direct visibility of neural tissue or mapping on the surface of a tumor. Stimulation can be either performed with a single pulse at low frequency (2.0–3.0 Hz) or with a short train. Recording is done in the muscles of interest, including the external anal sphincter. It is important to keep the surgical field as dry as possible to avoid current spreading. Stimulation of dorsal and ventral roots will both elicit a muscle response; however, for dorsal roots, the threshold might be higher [48].

7.5 Conclusion

Applying advanced intraoperative neurophysiological monitoring and mapping techniques may significantly decrease surgical induced injury to the spinal cord without limiting the extent of tumor resection. We describe methods for monitoring and mapping the white matter long tracts, as well as grey matter structures of the spinal cord. A team approach between neurosurgeon, neurophysiologist and neuroanesthesiologist may change surgery of tumors of the spinal cord.

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Neuro-Anesthesiology Considerations in Spinal Cord Tumors

8

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8.1 Introduction

Surgery for spinal cord tumors provides unique challenges in anesthetic management. Patients often present with significant comorbid conditions, including serious cardiovascular, respiratory, renal, and neurologic impairments. Airway management may be complicated by cervical spine involvement or the need for single lung ventilation. Positioning for spine surgery, in particular prone positioning, introduces physiologic strains and increases the risk of iatrogenic injury. Anesthetic management may need to be altered to facilitate neurophysiological monitoring. Given the risk of major blood loss, steps can—and should—be taken to minimize blood loss and the need for allogeneic blood transfusion. In addition, patients undergoing spinal surgery often have significant postoperative pain, and this must be addressed both intraoperatively and postoperatively.

The anesthesiologist has a duty to confront these challenges and minimize risk to the patient while facilitating optimal surgical conditions. This will ensure that every patient undergoing spine surgery for a spinal tumor has the opportunity to achieve the best possible outcome.

8.2 Preoperative Assessment

For every patient coming to the operating room, a detailed preoperative assessment should be performed with a focus on history, physical exam, and assessment of the airway, respiratory, cardiovascular, musculoskeletal, and neurological systems.

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Cardiovascular evaluation should include preoperative cardiac risk assessment and risk stratification based on American College of Cardiology/American Heart Association guidelines. If they are unable to exercise due to their underlying neurologic status or chronic pain, assessing functional status may be challenging. Spinal tumors in the cervical region may cause respiratory dysfunction and these patients may have restrictive lung disease. In addition to routine preoperative respiratory assessment, pulmonary function testing and arterial blood gas analysis may be indicated. Neurological evaluation should include documentation of any preexisting motor, sensory and autonomic neurologic dysfunction before the surgery. The knowledge about these preexisting deficits and/or dysfunctions will be very helpful in early recognition and diagnosis of new onset postoperative neurological deficits. These patients may also have musculoskeletal conditions which might make positioning them for surgery challenging.

Pain is a very common complaint in patients with spinal cord tumors and perioperative management of pain will be very important. Patients should be instructed to continue all of their pain medications, including opioids prior to surgery. Continuation of nonsteroidal anti-inflammatory drugs (NSAIDs) should be discussed with the surgical team in view of the risk of platelet dysfunction and potential for surgical bleeding. Since some patients might have been already treated for their primary tumor, careful attention should be paid to the adverse systemic effects of chemotherapy drugs. Patients with large or symptomatic tumors are often treated with steroids (e.g., dexamethasone) to decrease edema and cord compression, and are thus at risk for hyperglycemia that may require perioperative treatment.

Laboratory testing should be based on preexisting medical conditions and the extent of the surgical procedure. This will typically include a complete blood count and basic coagulation profile. Blood cross matching and an antibodies screen is required if significant blood loss is anticipated; otherwise blood typing and an antibodies screen is sufficient.

8.3 Airway Management

Patients presenting for surgical resection of a spinal cord tumor can pose significant challenges for airway management. The level of surgery, which can extend from the cervical to sacral areas, impacts the planning for airway management. It is important that the anesthesiologist communicates with the surgical team to understand the type of the tumor and surgical approach. A tumor of the cervical spine might require awake flexible fiber-optic intubation and a patient with a thoracic spine tumor might need placement of a double lumen endobronchial tube. In 2013, the American Society of Anesthesiologists (ASA) published an updated ASA Difficult Airway Algorithm [1], which is used as the general guideline for all aspects of clinical airway management and should be applied for airway management of patients undergoing resection of spinal cord tumors.

8.3.1 Evaluation of the Airway

The ASA practice guidelines for management of the difficult airway start with an evaluation of the airway. In many cases, a failure to recognize potential airway difficulties is a root cause of an airway disaster [2]. The failure to successfully manage the airway has been identified as a major factor leading to poor outcomes in many specialties, including anesthesiology, critical care, and emergency medicine [3, 4]. The ASA practice guidelines recommend that multiple airway features should be assessed during a physical examination of the airway. These features may suggest the presence of a difficult airway, and their assessment can help predict difficult ventilation and/or difficult intubation scenarios [1]. Although there is no standard definition of a "difficult airway," many national airway guidelines agree that a difficult airway can be defined in terms of difficulty with ventilation via a facemask, difficulties with supraglottic airway placement, difficult laryngoscopy, difficult tracheal intubation, or difficult surgical airway access [1, 5].

8.3.2 Airway Management Techniques

Most of the patients undergoing resection of spinal cord tumors have their airway managed via endotracheal intubation. The placement of the endotracheal tube can be accomplished by multiple different techniques, including direct laryngoscopy, video laryngoscopy, or flexible fiber-optic intubation. First, the decision has to be made if intubation should be accomplished with the patient awake or after induction of general anesthesia. In patients with a cervical spine tumor, many anesthesiologists prefer to place the endotracheal tube with the patient awake using a flexible fiber-optic bronchoscope. This technique is least likely to cause cervical spine movement in comparison with other methods and it is considered an ideal method when cervical spine movement is not feasible [6]. If the patient's airway evaluation did not reveal a difficult airway, placement of the endotracheal tube can be carried out after induction of general anesthesia. The direct laryngoscopy technique with Macintosh or Miller laryngoscopy blades is traditionally used. Recently, video laryngoscopy has found to be the technique of choice in patients with "anterior" view of the larynx for patients who require cervical spine immobilization [7].

The resection of the thoracic spinal cord tumor may require collapsing of one lung to facilitate surgical exposure and the procedure itself. The placement of a double lumen endobronchial tube (DLT) is needed to achieve lung separation and accommodate the surgical procedure. Again, in the patient with an anticipated difficult airway, an awake method of placement might be a more desirable technique. Although DLT can be inserted by flexible fiber-optic bronchoscope in an awake patient, some anesthesiologists prefer to begin with single-lumen tube insertion in an awake patient. After induction of general anesthesia, a single-lumen tube can be exchanged to DLT using an airway exchange catheter. After surgery is completed, a

DLT is typically exchanged to a single-lumen tube, again using the airway exchange catheter combined with video laryngoscopy. Lung isolation can be also achieved using a bronchial blocker, particularly when faced with a difficult tracheal intubation, thus avoiding an endotracheal tube exchange.

8.3.3 Complications during Extubation

It is highly recommended to document any difficulties encountered during insertion of the endotracheal tube since these will be taken into consideration when developing a plan for extubation. The Intubation Difficulty Scale introduced by Adnet et al. [8] can be useful. This scale incorporates seven variables: (1) the number of supplementary attempts needed; (2) the number of supplementary persons directly attempting intubation; (3) the number of alternative techniques used; (4) the need for applied external laryngeal pressure; (5) the lifting force applied during laryngoscopy; (6) the degree of glottic exposure obtained, and (7) the position of vocal cords noted at laryngoscopy.

The resection of spinal cord tumors can be associated with a long operative time, vigorous fluid administration, blood loss, or a need for blood transfusion. All these components can contribute to postoperative airway edema, which is one of the major factors of postoperative airway complications. When these risk factors are present, it may be preferable to postpone extubation or to extubate over an airway exchange catheter in order to avoid potentially catastrophic complications [9].

8.4 Positioning for Spine Surgery

Positioning should be used to facilitate exposure and minimize both bleeding and the likelihood of damage to vital structures. Surgery for spinal cord tumors is generally performed in the prone position, although many other approaches are possible. The ideal positioning will depend upon the location and extension of the tumor and institutional and surgeon preferences. An understanding of the effects of positioning is important to allow proper ventilation and perfusion of the anesthetized patient and avoid any postoperative morbidity secondary to the position during surgery.

8.4.1 Cardiovascular Effects of Prone Positioning

Decreased Cardiac Index. One of the most important cardiovascular complications during spine surgery in the prone position is a decrease in the cardiac index. Cardiac Index is a calculated parameter that normalizes cardiac output (itself a combination of heart rate and stroke volume) to body surface area. The decrease in cardiac index is due to a decrease in stroke volume in the setting of minimal change in heart rate [10]. This decrease in stroke volume occurs due to increased

intra-thoracic pressures that cause a decrease in venous return and a decrease in atrial filling [11]. Secondarily, reflex baroreceptor activation increases sympathetic activity, which increases systemic vascular resistance and pulmonary vascular resistance. This might mean that mean arterial pressures are maintained due to the increased systemic vascular resistance and there are no changes in mean right atrial or pulmonary artery pressures, but often a lower mean arterial pressure results [12].

Inferior Vena Cava Obstruction. Physical compression of the inferior vena cava and the resulting obstruction of blood flow in the prone position also lead to a decrease in venous return and cardiac output [13]. Additionally, inferior vena cava obstruction leads to distention of the vertebral column venous plexus, which contributes to increased blood loss during spine surgery. Inferior vena cava obstruction is exacerbated by any degree of abdominal compression [14]. Therefore, careful positioning and use of a support system that allows for a free abdomen is essential to minimize these risks.

8.4.2 Respiratory Effects of Prone Positioning

Respiratory changes in anesthetized and paralyzed patients in the prone position are influenced by the body habitus of the patient and the type of frame or support used. When a patient is moved from supine to the prone position there is increase in functional residual capacity and PaO_2. There is very minimal change in forced vital capacity and forced expiratory volume in one second (i.e., FEV_1) and no changes in $PaCO_2$ [15, 16]. It should be noted that when an upright and conscious patient is placed in the supine position while anaesthetized and paralyzed, their functional residual capacity will decrease by up to 44%, but when the patient moves from upright to the prone position, functional residual capacity is decreased by only 12% [17]. Delivered tidal volumes, inspiratory flow rates, and static compliances of the respiratory system (chest wall and lung) are unchanged. The resistance of the respiratory system increases by 20% but airway resistance is not altered [16]. Functional residual capacity increase is due to the reduction of cephalad pressure on the diaphragm and the reopening of atelectatic lung segments [18]. The changes in ventilation and perfusion from the supine to prone position results in better ventilation/perfusion matching and improved arterial oxygen tension [19].

8.4.3 Neurologic Complications of Prone Positioning

Injury to the Central Nervous System. Injury to the central nervous system during spine surgery in the prone position can result from arterial occlusion, venous occlusion, cervical spine injury, or the effect of undiagnosed space-occupying lesions [18]. Occlusion of the vertebral or carotid arteries from unrecognized extension or rotation of the neck during prone positioning can result in lateral medullary syndrome, quadriplegia, permanent hemiparesis, fatal stroke, vertebral artery dissection, or carotid artery dissection.

Cervical Spine Injury. Excessive flexion or extension of the neck in prone position under anesthesia with muscle relaxation can result in acute cervical spine disc herniation or injury in patients with preexisting cervical spine disease. Spinal cord infarction has been reported in patients with skeletal dysplasia and chest wall deformity [20]. Dislocation injuries without any preexisting cervical spine dislocations are extremely uncommon.

Peripheral Nerve Injury. Peripheral nerve injury during prone position results from nerve ischemia from undue stretching or direct pressure. The nerves at highest risk of injury during prone position are the brachial plexus, ulnar nerve, and lateral cutaneous nerve of the thigh [21]. Other nerve injuries less frequently reported are axillary nerve, musculocutaneous nerve, radial nerve, sciatic nerve, lingual, buccal, supra-orbital, phrenic, and recurrent laryngeal nerves. Somatosensory evoked potentials (SSEPs) can be used as an indirect monitor to detect impending peripheral injury during position. During SSEP monitoring of the upper limbs in the prone "Superman" position, reversible position-related SSEP changes occurred in 7.0% of patients. In contrast, use of the prone position with arms tucked by the patient's side caused changes in only 2.1% of patients [22].

Pressure Injuries in Prone Position. Pressure injuries in the prone position to dependent parts of the body can result from either direct pressure or indirect pressure or occlusion of the vascular supply.

Direct pressure injury with pressure necrosis of the skin is a common iatrogenic injury that can occur in the prone position. The common sites of direct pressure injuries are the malar regions, iliac crests, chin, eyelids, nose, and tongue. Tracheal compression is possible in the prone position in patients with connective tissue defects of the trachea like Marfan's syndrome or tracheomalacia. Acute bilateral painful swelling of the submandibular glands has been reported after surgery in the prone position with the head rotation. Submandibular swelling can also result from stretching of the salivary ducts, leading to stasis. Tongue and lip lacerations can occur as a result of intraoperative transcranial motor evoked potential stimulation; these can usually be prevented by routine use of a soft bite block. A more rigid oral airway may aggravate oropharyngeal swelling.

Macroglossia and oropharyngeal swelling are rare complications in prone position. It can result from extreme flexion of the head with an oral airway or endotracheal tube causing obstruction of the internal jugular vein, which further obstructs lingual and pharyngeal veins. Swelling of the tongue and oropharynx can lead to increased risk of postoperative upper airway edema, which may then require emergency airway management.

Mediastinal compression has been reported in patients with previous cardiothoracic surgery or congenital anatomical abnormalities, like scoliosis or pectus excavatum. Severe hypotension and decreased cardiac output can result from compression of the heart and great vessels during surgical manipulations of the spine in prone position.

Abdominal compression with visceral ischemia leading to hepatic ischemia and pancreatitis are reported in prolonged surgery in prone position.

Avascular necrosis of the femoral head has been reported in patients with osteoarthritis of the hip who underwent spinal surgery in the prone position using hypotensive anesthesia. Deliberate hypotension and increased venous pressure from the prone position resulted in intraosseous hypertension and ischemia leading to avascular necrosis of compromised femoral head.

Compression and occlusion of the axillary artery, femoral artery, and external iliac artery can occur during spine surgery in prone position. Axillary artery occlusion has been detected by pulse oximetry or radial artery monitoring on the affected arm. Femoral artery occlusion has been detected by sudden loss of SSEP from the posterior tibial nerve and absence of the dorsalis pedis pulse.

Compartment syndrome after spine surgery is rare, but several cases have been reported. Compartment syndrome occurred in patients in prone positioning that involved flexion of the hips and knees and surgery lasting more than 3 h. Fasciotomies may be required and can be complicated by rhabdomyolysis and acute renal failure.

8.4.4 Perioperative Visual Loss

Perioperative visual loss is a rare but devastating complication in patients undergoing spinal surgery, and is associated with significant physical disability and loss of quality of life. Visual loss after spine surgery is rare with ophthalmic complications occurring in less than 0.2% [23]. Perioperative visual loss can be classified into four different types: anterior ischemic optic neuropathy (AION), posterior ischemic optic neuropathy (PION), central retinal artery occlusion (CRAO), and cortical blindness [24].

AION can occur most commonly with cardiac bypass procedures, but can also occur during spine surgery in prone position. Predisposing risk factors for AION include hypotension, anemia, large fluid shifts, high crystalloid volume resuscitation, coexisting vascular disease, and a small cup-to-disc ratio.

PION can occur after spine surgery in prone position in the setting of elevated venous pressure in the head. Independent risk factors for ischemic optic neuropathy are male sex, obesity, use of a Wilson frame, longer anesthetic duration, greater estimated blood loss, and lower percent colloid administration. Older age, hypertension, atherosclerosis, smoking, or diabetes were not associated risk factors for ischemic optic neuropathy (ION), suggesting acute intraoperative physiological changes in development of ION. Recovery from ischemic optic neuropathy is very poor and no proven beneficial treatments are known.

CRAO occurs after spine surgery in the prone position due to globe compression. External eyeball compression increases intraocular pressure; this can lead to occlusion of retinal vessels. Patients usually complain of unilateral and complete visual loss shortly after awakening from anesthesia. Signs of periorbital trauma, such as swelling, erythema, bruising, proptosis, or ophthalmoplegia, may be present.

Cortical Blindness occurs most commonly in children undergoing complex spinal fusion surgery. Cortical blindness is caused by emboli to the parieto-occipital cortex or by profound hypoperfusion with bilateral posterior watershed infarctions. Cortical blindness has a good prognosis compared with other types of Perioperative visual loss with improvement in vision over weeks, but may have permanent defects in spatial orientation despite normal visual acuity and visual fields.

Guidelines and Recommendation in Management of Perioperative Visual Loss. The ASA's Task Force on Perioperative Blindness has published recommendations for prevention and management of Perioperative visual loss in patients undergoing major spinal surgery in the prone position. These recommendations include informing patients that there is a small unpredictable risk of Perioperative visual loss, monitoring blood pressure (and use of central venous pressure monitoring in high-risk patients), the use of colloids along with crystalloids in fluid resuscitation, positioning the head at or above the level of the heart, maintaining neutral head position (e.g., without significant neck flexion, extension, lateral flexion, or rotation), avoiding direct pressure on the globe, staging spine procedures in high-risk patients, visual assessment when a patient becomes alert, urgent ophthalmologic consultation, and optimization of hemoglobin/hematocrit values, hemodynamic status, and arterial oxygenation [25].

8.5 Anesthesia for Neurophysiological Monitoring

Almost all surgery for spinal tumors is performed under general anesthesia. The choice and dose of specific anesthetic agents will be guided by the patient's condition and comorbidities, but the type of neurophysiological monitoring being employed will have a bearing on the anesthetic technique. Maintaining a stable anesthetic depth with agents that are compatible with the neurophysiological monitoring modalities in use is important so that changes in neurologic function can be detected and interpreted.

Evoked potential monitoring is affected by multiple factors, such as temperature, mean arterial blood pressure, spinal cord perfusion, nerve compression, hypoxia, ventilation, anemia, anesthetic type and dose, and metabolic diseases. All anesthetic agents alter neural functions by producing dose dependent depression in synaptic activity. The greater the number of synapses involved in neural signal transmission, the greater the depressant effect of anesthetic agent. Although several types of anesthetic agents are used for anesthesia maintenance including inhalational and intravenous (IV) agents, total intravenous anesthesia (TIVA) is the standard technique when neurophysiological monitoring is employed during spine surgery. IV anesthetic agents, such as propofol, dexmedetomidine, barbiturates, benzodiazepines, opioids, etomidate, and ketamine, have significantly fewer effects on evoked potentials than inhalational agents (Table 8.1) [26–28]. Volatile halogenated inhalation anesthetic agents, including halothane, isoflurane, sevoflurane, and desflurane, cause a dose-dependent decrease in amplitude and an increase in latency of evoked responses [29–31]. These effects are greater on cortical evoked responses than on subcortical responses.

Table 8.1 Effects of anesthetic agents on Cortical SSEP and Myogenic MEP

	Cortical SSEP		Myogenic MEP	
Anesthetic Agent	Latency	Amplitude	Latency	Amplitude
Halothane	↑	↓	↑↑	↓↓
Isoflurane	↑	↓	↑↑	↓↓
Sevoflurane	↑	↓	↑↑	↓↓
Desflurane	↑	↓	↑↑	↓↓
Nitrous oxide	↑	↓↓	↑↑	↓↓↓
Propofol	Minimal effect ↑ at high doses	Minimal effect ↓ at high doses	Minimal ↑ at high doses	Minimal effect ↓ at high doses
Etomidate	No effect	↑at low doses ↓at high doses	No effect	↑at low doses ↓at high doses
Ketamine	No effect	↑at low doses	Minimal effect	↑at low doses ↓at high doses
Opioids	No effect	Minimal effect	Minimal effect	Minimal effect
Dexmedetomidine	No effect	No effect		Minimal effect at low doses ↓at high doses
Benzodiazepines	↑	↓	↑	↓
Barbiturates	↑	Minimal effect	↑	↓
Lidocaine	Minimal effect	Minimal effect		Minimal effect

8.5.1 Effects of Anesthetic Agents on SSEPs

SSEPs are used in evaluation of the sensory pathway: peripheral nerves, dorsal root ganglia, the dorsal column of the spinal cord, the sensory thalamus, and the sensory cortex. Using needle or surface electrodes, the median or ulnar nerve is stimulated at the wrist for upper extremity SSEPs and the posterior tibial nerve at the ankle for lower extremity SSEPs. The stimulation of these mixed nerves results in activation of the sensory pathway and the responses travel all along the sensory pathway and ascends to the brain. The evoked responses are recorded over Erb's point, popliteal fossa, cervical spine, and the sensory cortex. Stimulation of these mixed nerves also results in activation of the motor components, which is seen as muscle twitches in distal musculature.

When compared with intravenous anesthetic agents, volatile inhalational anesthetics agents cause greater depression of the cortical SSEPs. Adequate cortical SSEPs can be recorded at 0.5 minimal alveolar concentration (MAC) of volatile inhalational agents in patients without any preexisting neurological impairment. Volatile agents, such as halothane, isoflurane, sevoflurane and desflurane, cause dose-dependent increases in latency and decreases in amplitude

of cortical SSEP. As the concentration increases above 1 MAC, the recorded signal amplitude drops at a much faster rate [28, 30]. Nitrous oxide (N_2O) causes an increase in latency and decrease in amplitude of cortical SSEP, and also augments these effects on volatile agents [30, 32]. The effects on the spinal SSEP responses are significantly less, allowing recordings at higher anesthetic concentrations. Although propofol does cause a dose-dependent decrease in amplitude of cortical SSEPs, this effect is notably less than that from inhalational anesthetics. At very high doses, propofol can cause significant decremental effect on the SSEP [33]. Opioids [34, 35], lidocaine [36], and dexmedetomidine [26, 37] have little effect on latency and amplitude of SSEP. Ketamine and etomidate at low concentrations [38, 39] can actually cause augmentation of the cortical SSEP response. All other intravenous drugs cause dose dependent reduction in the amplitude, as well as ketamine and etomidate at higher concentrations [39, 40].

8.5.2 Effects of Anesthetic Agents on MEPs

MEPs are used in evaluation of the motor pathway involving motor cortex, corticospinal tract, alpha motor neuron connecting the primary and secondary motor neurons, peripheral nerve, and muscle. MEPs are elicited by magnetic stimulation or transcranial electrical stimulation either to the scalp utilizing two needles or by direct stimulation of the surface of the brain.

Volatile inhalational anesthetics agents have a profound negative effect on the myogenic MEP responses. In patients without any preexisting neurological pathology, muscle responses might be recorded with up to 0.5 MAC of a volatile agent [41], but often less is required. Nitrous oxide has synergistic action when combined with volatile inhalational agent [42] and is generally avoided. Intravenous anesthetic agents, such as propofol, also affect the amplitude and latency of the myogenic MEP, but these effects are only seen at higher doses. Propofol has a dose-related inhibitory effect on the MEPs, but at standard anesthetic dose, this effect is less than inhalational anesthetics; adequate MEPs can be easily monitored [27, 35]. Opioids have minimal effect on muscle MEPs [43]. Ketamine [44] and etomidate [27] at low doses enhance the MEP but are depressant at higher doses. Dexmedetomidine does not affect myogenic MEP when used as adjuvant to propofol-based TIVA at lower target plasma concentration less than 0.6 ng/ml but can significantly attenuate the amplitude at higher target plasma concentration of 0.6–0.8 ng/ml [45, 46]. Lidocaine can be used as a component of balanced anesthesia without adversely affecting the monitoring MEPs [36].

Neuromuscular blockade (NMB) with non-depolarizing muscle relaxants, such as vecuronium, rocuronium, atracurium and cisatracurium is generally avoided. If NMB agents are used, the degree of paralysis must be monitored with a "train-of-four" response with a goal of 2 out of 4 twitches or a single twitch of 10–20% of baseline.

8.5.3 Effects of Anesthetic Agents on EMG

Electromyography (EMG) during spine surgery can be either free run electromyography (fEMG) or triggered EMG (tEMG). fEMG records muscle activity resulting from potential irritation of a nerve innervating the muscle, and tEMG records muscle activity in response to stimulation of a nerve.

Anesthetic agents, including intravenous and volatile inhalational agents, have minimal effect on EMG recording. Neuromuscular blocking agents, on the other hand, have a profound effect and are avoided. The EMG requires the neural signal to pass through the neuromuscular junction, the site where nerve transmission is blocked by muscle relaxants. The degree of neuromuscular blockade (NMB) is most commonly assessed by the "train-of-four" response; 4 out of 4 twitches are required to monitor EMG response.

8.5.4 Anesthesia Recommendations for Neuromonitoring during Spine Surgery

Premedication. Routine premedication with benzodiazepines (e.g., midazolam) and/or opioids.

Induction of anesthesia. Induction is routine unless the patient has special considerations, like significant cardiopulmonary illness, airway concerns, aspiration risks, or other medical conditions. The use of a NMB agent to facilitate endotracheal intubation depends on the type of neuromonitoring used. The depolarizing muscle relaxant succinylcholine can be used, if rapid recovery of neuromuscular transmission is desired (i.e., if MEP and EMG are monitored). Non-depolarizing muscle relaxants, such as rocuronium or vecuronium, can be used if only SSEPs are monitored or there will be a significant length of time before evoked potential monitoring is initiated. If necessary, neuromuscular blockade can be reversed with sugammadex or neostigmine prior to MEP recording.

Maintenance of anesthesia. Maintaining a stable anesthetic depth is vital for adequate neurophysiological monitoring, irrespective of the particular anesthesia agent employed. In most cases, general anesthesia can be best maintained with a TIVA, consisting of a propofol infusion and an opioid infusion. Many institutions routinely use EEG-based hypnotic depth monitoring to titrate an adequate dose of intravenous anesthetic.

The dose of propofol used in the infusion typically ranges between 100 and 150 mcg/kg/min. An opioid infusion will provide analgesia and decrease the dose of hypnotic required. A variety of intravenous opioids infusions can be used, for example sufentanil (0.2–1 μg/kg/h), remifentanil (0.05–0.5 μg/kg/min), fentanyl (0.5–10 μg/kg/h), or alfentanil (0.5–1.5 μg/kg/min).

If volatile anesthetics are to be used, it is recommended to avoid nitrous oxide and restrict the use of volatile agents to 0.5 MAC or below for both SSEP and MEP

monitoring. A lower-dose propofol infusion (e.g., 50–100 mcg/kg/min) can be used to supplement additional anesthesia.

Adjuvant anesthetic agents, such as ketamine and etomidate in low dose infusion, can be added to improve quality of MEP and SSEP. Dexmedetomidine (≤0.6 μg/kg/h), lidocaine (1–1.5 mg/kg/h), and ketamine infusion (0.5–1 mg/kg/h) can be added to supplement TIVA or inhaled agents. These adjuvants allow lower doses of propofol and opioid infusions, and also decrease the MAC requirement of volatile agents. NMB agents are avoided for maintenance when MEP and EMG are monitored, but there is no restriction to use when only SSEP is monitored.

A soft bite block should be placed to prevent tongue, lips and oropharyngeal injuries which may result during MEP stimulation.

8.6 Blood Conservation

Blood loss during spinal surgery may be considerable due to disruption of rich venous networks and the increased abdominal pressure that results from prone positioning. Moreover, surgery for tumors is associated with increased blood loss due to the vascularity of the tumor. Patients who then require allogeneic blood transfusion are at risk for a large number of complications, including coagulation dysfunction, electrolyte abnormalities, transfusion reactions, transfusion-related acute lung injury, transfusion-associated circulatory overload, immune suppression, cancer recurrence, and serious viral or bacterial infections. Blood transfusion is also incredibly expensive [47]. Therefore, consideration of strategies to decrease blood loss and the need for allogeneic blood transfusion is critical to the perioperative management of these patients. Importantly, many of these strategies are compatible with patients, such a Jehovah's Witnesses, who have a religious objection to the use of blood products. A careful discussion regarding those patient's wishes should occur well prior to surgery.

8.6.1 Preoperative Optimization

Anemia is defined by the World Health Organization (WHO) definition as Hb < 12 g/dL for females and Hb < 13 g/dL for males. Preoperative anemia is common in surgical patients and is associated with increased rates of blood transfusion and increased perioperative morbidity after surgery. However, with advanced screening and diagnosis, effective treatment of preoperative anemia is available with oral or intravenous therapies. Most commonly, these treatments include iron, folic acid, and/or vitamin B12 supplementation and erythropoiesis stimulation agents like epoetin alfa. These preoperative interventions are very cost effective, and many institutions have created preoperative anemia clinics to facilitate the coordination of care for these patients [48].

8.6.2 Stored Autologous Transfusion

Autologous blood transfusion is defined as the collection and reinfusion of the patient's own red blood cells. Prior to surgery patients can donate their own whole blood that is then stored for reinfusion intra- or postoperatively. In some studies of spine surgery, the use of previously donated blood reduced allogeneic transfusion by 50–75% [49], but those benefits are not universally seen [50].

Using the patient's own blood avoids some (but not all) of the risks inherent in allogeneic blood transfusion. Unfortunately, this process is costly and requires multiple visits for preoperative phlebotomy. It may also not be feasible for patients with pre-existing anemia or cardiovascular disease. Since the blood is stored in discontinuity from the body, this type of transfusion is not usually compatible with the wishes of patients who have religious objections to the use of blood products. Unused blood is wasted.

8.6.3 Intraoperative Normovolemic Hemodilution

Acute normovolemic hemodilution is a procedure that entails removing whole blood immediately prior to incision while maintaining normovolemia via simultaneous infusion of crystalloid or colloid. The volume to be removed can be calculated from the formula for allowable blood loss: the patients estimated blood volume multiplied by the difference between initial hemoglobin and target hemoglobin, divided by the mean hemoglobin. Estimated blood volume depends on many factors, including sex, weight, and height. Starting hemoglobin will vary patient-to-patient. Even with a conservative target hemoglobin of 10 g/dL, up to a liter or more of whole blood can be removed and stored in anticoagulant-containing blood storage bags. This volume is replaced with crystalloid (3 ml for every 1 ml of blood removed) or colloid (1 ml for every 1 ml of blood removed). The result is normovolemia with a lower hemoglobin. This has the advantage of subsequent blood loss being that blood which is already diluted. At the same time, clotting factors and platelets are also proportionally reduced, which may impair hemostasis. The removed blood can be reinfused when the procedure is complete, or when a minimum hemoglobin value has been reached. If care is taken to maintain continuity of the circuits and storage bags at all times, this technique may be compatible with patient who have a religious objection to the use of blood products.

8.6.4 Positioning

There are several venous plexuses associated with the vertebrae that typically contain blood at low pressure. These veins are connected to veins in the chest,

abdomen, and pelvis. Good patient positioning can minimize the amount of blood lost during surgery by avoiding engorgement of these veins. Positioning devices, such as chest rolls, Relton-Hall frame, or Wilson frame, can help minimize intra-abdominal pressure and reduce compression of the inferior vena cava [14]. Reducing intraabdominal pressure is associated with significantly reduced blood loss during surgery [51].

8.6.5 Hypotensive Anesthesia

Allowing for a lower blood pressure, or actively lowering blood pressure with antihypertensive agents, has long been used to decrease blood loss during spinal surgery. However, care must be taken to avoid risks associated with low blood pressure. Large retrospective studies have suggested that intraoperative time spent with blood pressures below normal is associated with increased risk of acute kidney injury, myocardial injury, and stroke, but the definition of intraoperative hypotension and its effect on postoperative outcome remains controversial [52].

8.6.6 Antifibrinolytic Agents

Fibrin is a protein that forms the framework of blood clots. Fibrinolytics are naturally occurring proteolytic enzymes that break down cross-linked fibrin clots. Antifibrinolytics are medications that inhibit plasmin, trypsin, and related proteolytic enzymes or inhibit the formation of such enzymes (e.g., inhibit the activation of plasminogen to plasmin). The most studied of these medications are aprotinin, tranexamic acid, and aminocaproic acid.

Aprotinin is a polypeptide derived from bovine lung that acts as potent inhibitor of trypsin, plasmin, and kallikrein. Aprotinin has been proven to reduce intraoperative blood loss during a variety of major blood loss surgeries but fell out of favor following the publication of the Blood conservation using Antifibrinolytics Randomized Trial (BART) in 2008 [53]. In this study of cardiac surgery patients, aprotinin was associated with a strong and consistent negative mortality trend. In 2010, a panel of experts “unanimously recommended against its use in spine surgery on the basis of the reports of increased complications” [54].

Tranexamic acid (TXA) is a lysine analogue that competitively inhibits the activation of plasminogen to plasmin. It has been associated with a significant decrease in blood loss and transfusion when used during spine surgery [55]. Typical dosing involves a bolus (10 mg/kg or 1–10 g) followed by an infusion (0.1–2 g/h or 1–5 mg/kg/h). Renal insufficiency is a relative contraindication to the use of TXA; urinary excretion is the main route of elimination and there are case reports of ureteric clots and acute renal failure from cortical necrosis. In cardiac patients, TXA is also an independent risk factor for postoperative seizures [56], and so many anesthesiologists will avoid the use of TXA in any patient thought to be at increased risk of postoperative seizures.

Aminocaproic acid is another derivative and analogue of the amino acid lysine, and has also been associated with less blood loss and less transfusion during spine surgery [57]. For aminocaproic acid, typical dosing involves a loading dose of 50 mg/kg followed by an infusion of 25 mg/kg/h.

8.6.7 Intraoperative Cell Salvage

Blood that is lost during surgery can be recycled and given back to the patient. This requires commercially-available equipment that connects the suction in the surgical field to a collection device that contains anticoagulant and filters out blood clots, bone, and other debris. The collected blood is then centrifuged and resuspended into bags that are compatible with regular blood administration sets. There is no limit to the amount of blood that can be recycled in this manner, but it is important to note that many coagulation factors and platelets are consumed at the surgical site or during suctioning from the wound, and so these factors may need to still be replaced with allogeneic frozen plasma and platelets. Blood salvage is rarely used for tumor surgery out of concern that malignant cells could be collected and then disseminated throughout the body**.** However, arguments have been made that with appropriate treatment of the salvaged blood (e.g., leukoreduction), the benefits of cell salvage may outweigh the risks, especially since allogeneic blood transfusion is also associated with an increase in the rate of cancer recurrence after tumor surgery [58]**.**

8.7 Pain Management

Patients undergoing surgery for spinal cord tumors often struggle with severe postoperative pain. In a large retrospective study looking at 179 different types of surgery, three of the six most painful surgeries (as assessed on postoperative day 1) were major spinal procedures [59]. These patients typically have large incisions that may cross multiple dermatomes. Cancer patients in particular may also suffer from pre-existing chronic pain and often have developed a tolerance to opioids. Therefore, preemptive multimodal ("balanced") analgesia is critical to prevent the establishment of central sensitization and minimize difficult-to-treat postoperative pain. However, even with appropriate intraoperative management, severe postoperative pain remains a problem.

Multimodal analgesia begins preoperatively. Oral medications, such as acetaminophen, gabapentin, and pregabalin may reduce postoperative pain scores and opioid requirements [60–62]. These preoperative medications should be administered with only small sips of water to minimize gastric contents prior to induction.

Intraoperatively, parenteral opioids can be combined with a wide variety of adjuncts. The particular opioid selected (e.g., fentanyl, hydromorphone, morphine, alfentanil, or sufentanil) may not be critical as all work primarily at the same opioid receptors. One exception—methadone—is a combined opiate receptor agonist and NMDA antagonist, and that may make it superior to a pure opioid in spine surgery

[63]. Remifentanil is excellent at controlling intraoperative responses to pain, but higher doses may be associated with hyperalgesia postoperatively [64]. Ketamine is an NMDA antagonist, weak agonist of opioid receptors, and inhibits reuptake of neurotransmitters like serotonin, dopamine, and norepinephrine. When used in spine surgery, it reduces perioperative opioid consumption and may also reduce chronic pain weeks later [65]. Ketamine at analgesic doses also improves the quality of neuromonitoring by increasing the amplitude of evoked potentials. If not given preoperatively, acetaminophen can also be given intravenously. Local anesthetics can be administered epidurally or as an intravenous infusion. Dexmedetomidine, an alpha-2 adrenergic receptor agonist, will provide analgesia as well as sedation. Magnesium, while associated with more side effects, has shown promise in spine surgery [66, 67]. NSAID medications remain controversial in spine surgery due to concerns about bone healing.

Postoperatively, it is useful to resume all analgesics the patient was receiving preoperatively. Additional therapy will certainly be required. Typically, this is accomplished with intravenous opioid patient controlled analgesia, although as many adjuncts as possible should be continued.

8.8 Conclusion

Anesthetic management for patients undergoing surgery for spinal cord tumor is very complex and requires a multidisciplinary approach with involvement of anesthesiologists, neurosurgeons, and neurophysiological monitoring team. Complete understanding of tumor type, location, and its mass effects is required. Comprehensive preoperative assessment should be done since many patients with spinal tumors may be metastatic in nature. Complete evaluation and understanding of chronic pain will guide in optimal management of perioperative pain. The planned surgical procedure including extent of surgery, intraoperative neurophysiological monitoring, anticipated blood loss, intraoperative blood salvage, and perioperative pain management should be discussed in detail to achieve the best possible outcome.

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Spinal Meningiomas

9

Roberto Delfini, Benedetta Fazzolari, and Davide Colistra

9.1 Epidemiology

Meningiomas and nerve sheath tumors occur with about the same frequency in the adult spine [1]. Spinal meningiomas account for less than 25% of all primary spinal tumors and about 25% of all intradural spinal tumors [2–5]. They are far less frequent than intracranial meningiomas, accounting for only 1.2–12.7% of all meningiomas [6–8]. These data are confirmed by a recent epidemiological study of 1709 spinal meningiomas reported in the large prospective Surveillance, Epidemiology, and End Results database, which represented 30.7% of all primary intradural spinal tumors and 7.9% of all meningiomas [9]. This proportion increases in patients with type 2 Neurofibromatosis (NF2). For patients with NF2, approximately 10% of meningiomas requiring resection are located in the spine [10, 11]. Mautner et al. found spinal meningiomas in one-third of patients with NF2 [12]. In the general population, most meningiomas are discovered in patients aged between 60 and 80 years [6, 8, 13–17]. However, as expected, spinal meningiomas may present earlier in patients with NF2.

Spinal meningiomas affect women in 75–85% of cases [18] with a female-to-male ratio of 4:1 [6, 14] compared with a 2:1 ratio for intracranial meningiomas [19]. In the case of intracranial meningiomas, this discrepancy in the incidence between the sexes has been attributed to hormonal effects in women [20, 21] based on the strength of evidence of progesterone and estrogen receptors frequently observed at histological examination [22, 23], as well as reports of an association between meningioma and breast cancer [23] or tumor growth and pregnancy [22]. Moreover, as noted by Schaller [24], this female predisposition is not observed in children; in

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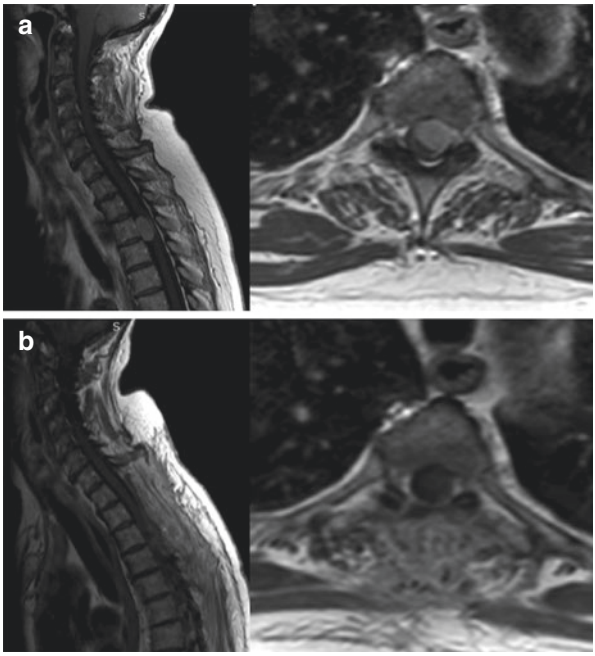

Fig. 9.1 Thoracic spinal meningioma. (**a**) Preoperative MRI T1-weighted post-contrast left sagittal and right axial images showing a spinal meningioma with left anterolateral attachment between the third and fourth thoracic vertebra. (**b**) Postoperative T1-weighted post-contrast left sagittal and right axial MRI of thoracic spinal meningioma showing total tumor resection

fact, there is a slight male preponderance before puberty. The location of spinal meningiomas is also different depending on sex [25] and occur with the highest frequency (80%) in the posterior, posterolateral, or lateral thoracic region (Fig. 9.1a,b, and Fig. 9.2a,b), followed by the anterior cervical region (15%) and infrequently in the lumbosacral region (5%) in women [14, 26]. For men, 50% of spinal meningiomas are found in the thoracic region and 40% in the cervical region [27].

Furthermore, differences have been found between ethnic groups with spinal meningioma/intradural nerve sheath tumors having an equal one-to-one ratio (1:1) in Western populations but not in Asian populations, which had a one-to-four ratio (1:4) [28].

In addition to increasing age, the most consistent factor associated with the risk of meningioma is exposure to ionizing radiation with a latency period that can be long (19–35 years) [29–31].

9.2 Pathology

Meningeal tumors are referred to as meningiomas, which is the term proposed originally by Cushing. Cushing and Eisenhardt described the removal of a spinal meningioma as “one of the most gratifying of all operative procedures” [32] about

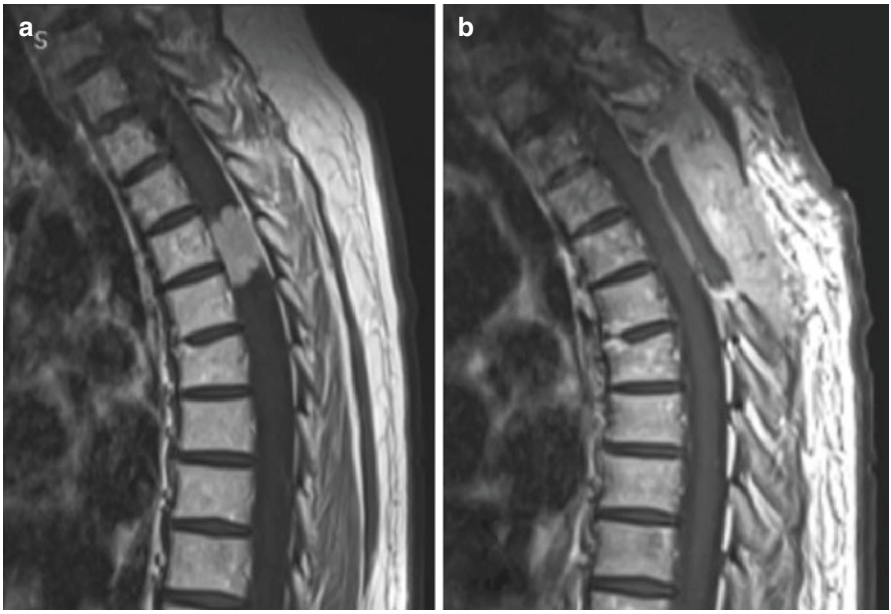

Fig. 9.2 Thoracic spinal meningioma. (**a**) Preoperative T1-weighted post-contrast sagittal MRI showing a bilobular thoracic spinal meningioma. (**b**) Postoperative T1-weighted post-contrast sagittal MRI of thoracic spinal meningioma showing total tumor resection

50 years after Horsley first removed a meningioma compressing the spinal cord in 1888 [33, 34].

Spinal meningiomas arise from arachnoid cap cells within the dura mater [35]. They are typically solitary and slow-growing with a lateral expansion into the subarachnoid space [17], well-circumscribed, and non-invasive into normal tissue [26, 27, 36]—they do not generally seed other parts of the central nervous system or body regions [36]. Multiple spinal meningiomas have been associated with NF2 [37]. Meningiomas may exert considerable compressive forces on the spinal cord [38]. Unlike intracranial meningiomas, spinal meningiomas do not penetrate the pia with the exception of en plaque or infiltrating meningiomas, which have a more extensive tumor matrix and infiltrate the surrounding structures [16, 39]. Hydrosyringomyelia can occur in rare cases of intramedullary meningioma [40]. Spinal meningiomas are entirely intradural, but about 10% may be both intradural and extradural, or purely extradural [41]. Because of the different criteria applied in published studies for describing the relationship of the tumor to the spinal cord, the distribution of the site of tumor origin appears to be heterogeneous [6, 8, 13–17, 42]. The tumor rarely completely encases the spinal cord [43, 44].

Spinal meningiomas can appear macroscopically smooth and fibrous or variegated, fleshy, and friable. Histologically, the majority of spinal meningiomas are Grade I (benign biotype) according to the World Health Organization (WHO). This category comprises—in order of frequency—the psammomatous, meningothelial,

transitional, and fibroblastic subtypes [13, 17, 26, 45]. The rare histological variants of WHO Grade II (clear cell and chordoid) and III (anaplastic) show a high risk of local recurrence and an aggressive biological behavior [46]. Calcified cases are uncommon and account for only 1–5% of all spinal meningiomas in the literature [47]. Calcified lesions are more likely to adhere to nerves and surrounding tissue, especially the dura, and can be classified according to their microsurgical appearance as microcalcified (non-visible calcifications), macrocalcified (visible calcifications), and ossified (totally calcified) [48]. The presence of hematopoietic elements within the tumor is very rare with only four case reports of this occurrence [49–52].

Several receptor types may play a role in pathogenesis, primarily progesterone and estrogen receptors [22, 23], but also peptidergic, growth factor, and aminergic receptors [46].

From a genetic point of view, spinal meningiomas and intracranial meningiomas have been historically treated similarly, but recent genetic information may change this paradigm. Sayagues et al. described a higher predominance of single tumor cell clones (monosomy 22) in spinal meningiomas whereas intracranial varieties exhibit more heterogeneous chromosomal aberrations associated with the presence of multiple tumor clones [45]. Other studies have demonstrated complete or partial loss of chromosome 22 in more than 50% of patients with spinal meningiomas [53, 54].

9.3 Clinical Features

A delay in the diagnosis of the spinal meningiomas is frequent; the mean time between the onset of symptoms and surgical treatment is 1–2 years [6, 15–17]. The heterogeneous clinical presentation of these tumors before appropriate imaging investigations are performed might explain the delay. Focal pain is the most common presentation of spinal meningioma [26, 27, 55], and typically precedes progressive segmental sensory or motor root deficits, both of which suggest cord compression. Chronic compressive myelopathy mechanically damages neural tissue and its vascular supply, which leads to ischemia [38]—corticospinal tract compromise is the earliest manifestation of compression. Physical examination may reveal decreased segmental deep tendon reflex and asymmetric muscle tone at later stages. Due to the apparent resistance of anterior horn cell columns to external compression stressors, lower motor neuron findings are a late observation [2]. In relation to their location, high cervical lesions may insidiously present as an occipital headache [26] and Brown-Sequard syndrome [18], whereas thoracic neoplasms typically present with visceral pathology [26]. Bowel and bladder dysfunction may also occur but less frequently. Before the era of magnetic resonance imaging (MRI), differential diagnosis included multiple sclerosis, syringomyelia, and pseudo-tumoral herniated discs with a significant misdiagnosis rate as high as 33%, according to Levy et al. [6].

9.4 Neuroimaging

Nowadays, MRI is the diagnostic tool of choice for spinal meningiomas [25]. In their study spanning before and after the advent of MRI, Klekamp et al. showed that MRI allowed a 6-month gain in diagnosis [16]. MRI defines tumor extension and tumor limits with surrounding neural structures, and is of paramount importance for preoperative evaluation, surgical mapping, confirmation of resection adequacy, and follow-up for tumor reoccurrence [14, 18, 26, 56]. As highlighted by De Verdelhan et al. in their comparison between MRI features of spinal schwannomas and meningiomas, meningiomas mostly show moderate and homogeneous signal intensity on T2-weigthed images and moderate and homogeneous enhancement after gadopentetic acid (Gd-DTPA) [57]. In the same study, they authors confirmed the importance of the well-known "dural tail" sign [58–60], and described the importance of coronal imaging for the identification of lateral tumors and sagittal images for anterior or posterior tumors. A peritumoral hypointense rim is often present around meningiomas and corresponds to a well-formed peritumoral cerebrospinal fluid (CSF) space [61]. Calcifications, when present, may produce a dark signal on T2-weighted images [62].

When MRI is contraindicated, myelo-computed tomography (CT) may be useful for identifying intradural pathology [2, 18]. Additionally, calcifications within meningiomas may be better seen on CT scans [26, 63]. Preoperative spinal angiography has been recommended by Roux et al. to locate precisely the anterior spinal arteries and detail tumoral vascularization, particularly as anteriorly located tumors corresponds to a greater surgical risk [17].

9.5 Surgical Treatment

Many classifications for spinal meningioma have been proposed to help guide the surgeon in choosing the best surgical approach and in understanding the relationship between the tumor and critical anatomical structures. Spinal meningiomas have been classified on the basis of their location of attachment. Either the posterior, lateral, or—rarely—anterior surgical approaches are used to remove this benign tumor [64].

9.5.1 Posterior Approach

Position is prone with the arms forward. After careful preoperative planning, a midline skin incision is performed extending two levels above and below the extent of the lesion. The paraspinal, intrinsic dorsal, and deep transversospinal muscles are separated subperiosteally on either side. Depending on tumor size, a monosegmental or multisegmental laminectomy is performed above and below the length of the

tumor. In the case of a lateral-sited meningioma, a hemilaminectomy wide-enough to allow safe removal can be performed. A partial facetectomy can be performed in order to increase the viewing angle. Pedicle removal is not performed in any case. The dura is opened along the midline and fixed to the sides. The dentate ligament section is usually required to facilitate spinal cord handling. Depending on tumor location (ie, ventral, lateral, or posterior to spinal cord), the spinal cord is usually displaced and/or rotated by the tumor. Tumor removal begins laterally where the tumor is attached to the dura, in order to minimize thermal injury to the spinal cord. The meningioma shrinks and is then debulked in order to widening surgical field. After tumor removal and careful hemostasis, the dura is coagulated in all cases and primarily closed "watertight".

9.5.2 Pediculo–Transversectomy (Lateral Route)

The patient is positioned prone with the arms forward. After careful preoperative planning, a midline skin incision is performed extending two levels above and below the length of the lesion. Midline and paravertebral soft-tissue dissection is then carried out to expose the spinous process, lamina, and facet joints. The paraspinous muscles are further dissected free and reflected laterally to expose the medial transverse process and facet joint. A high-speed drill is then used for posterior laminectomy and unilateral superior/inferior medial facetectomy and pediculotomy, without removing the ribs or transverse processes. Durotomy is performed laterally to the lesions. The range of drilling of the medial facet and the number of pedicles drilled is determined by lesion location. The pedicle is removed in all cases to protect the spinal cord—the rotation of the spinal cord is performed with guidance from neurophysiological monitoring to prevent spinal cord injury. The dentate ligament is cut. After gentle rotation of the spinal cord and obtaining wide operative fields by using a transpedicular approach, tumor removal can be performed. An ultrasonic aspirator is used for internal decompression to prevent spinal cord injury. The tumor attachment is meticulously coagulated after tumor removal. No posterior fixation with spinal instrumentations is performed [65].

9.5.3 The T–Line

In 2016, Tachibana et al. proposed the T-line concept, which utilizes lines to decide the best surgical approach for anterior spinal meningiomas [66]. An axial-view MRI is needed to make the measurement. First, the tangent of the tumor and the spinal cord is marked on the image with a line (T-line 1), followed by marking the bisected line of the facet on the dominant side of the tumor (T-line 2) (Fig. 9.3a). Spinal meningioma cases can then be divided into 2 groups: the T-line (+) group and the T-line (−) group. In the T-line (+) group, the point of intersection between T-lines 1 and 2 is located on the posterior side of the lamina. In these cases, there is enough

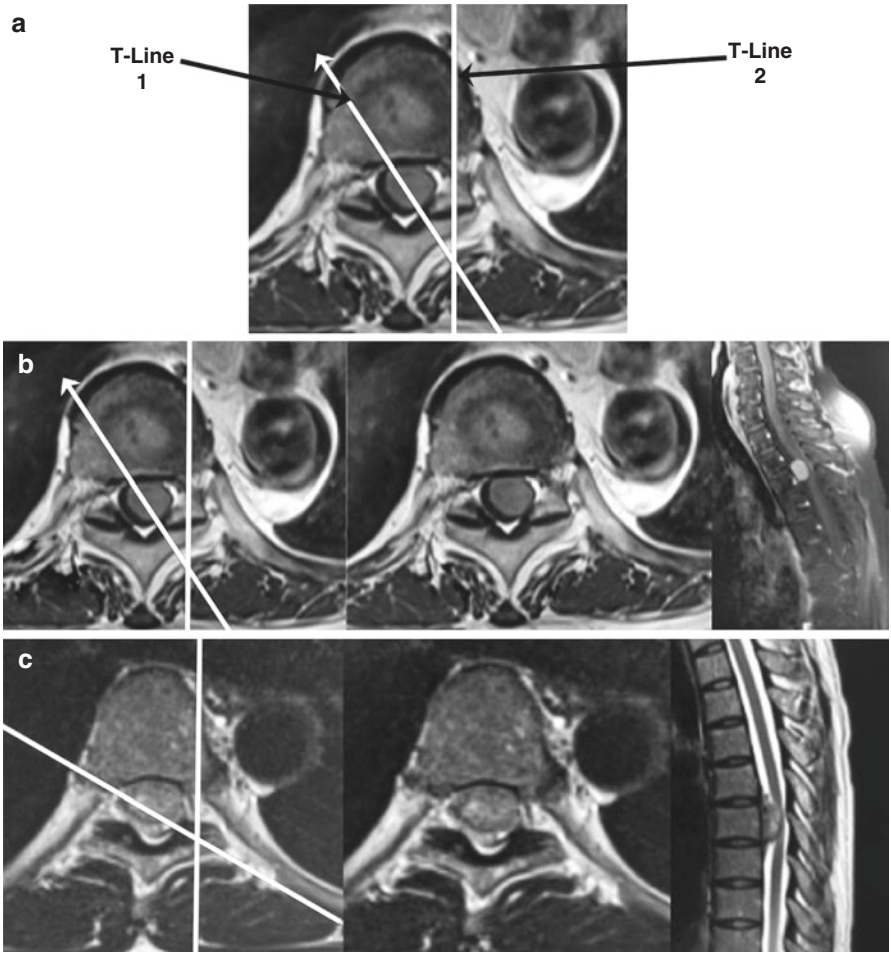

Fig. 9.3 Demonstration of the T-line concept. (**a**) The intersection of the tangent of the tumor and the spinal cord described as T-line 1 and the bisected line of the facet on the tumor dominant side as T-line 2. (**b**) T-line (+) showing the point of the intersection located on the posterior side of the lamina, which should be excised via the posterior approach. (**c**) T-line (−) showing the point of the intersection on the anterior side of the lamina, which should be excised via the posterolateral approach. (Originally published in Tachibana et al. (2016); reprinted with permission)

space to allow tumor excision using the posterior approach with laminectomy and one-half facetectomy (Fig. 9.3b). In the T-line (−) group, the point of intersection is located in the anterior side of the lamina. In these cases, there may not be enough space for the posterior approach and the tumor requires excision via the posterolateral approach. When the tumor is located anteriorly to the spinal cord, the point of intersection of T-line 1 and 2 is located on the anterior side of the lamina, and these cases are classified as T-line (−) (Fig. 9.3c).

9.5.4 Anterior Approach

Meningiomas located ventrally to the spinal cord in some circumstances should be approached by an anterior access. While the anterior approach to cervical spine is a standard procedure for a neurosurgeon, the anterior approach to the thoracic column represents a challenging option. Intradural extramedullary lesions arising in a purely ventral location (with severe spinal cord compression and significant bilateral ventral tumor extension, but without spinal cord rotation or lateral displacement) can be difficult to perform a safe removal using either a posterior or posterolateral exposure. Heavily calcified or densely fibrotic lesions not amenable to internal decompression can also prove challenging. Until recently, ventral or ventrolateral approaches to intradural pathologies were used infrequently [67, 68]. Mistrust of these approaches is due to a deep surgical field with problematic ventral epidural bleeding, limited lateral access, risk of CSF fistulas, and the usual requirement for spinal reconstruction and stabilization. Despite this, there are a few cases for which an anterior approach is required and consists of a vertebral corpectomy. The basic surgical technique requires the use of a high-speed drill to perform the decompressive corpectomy and the posterior longitudinal ligament should be excised. The decompression extends rostrally and caudally through the disc space and laterally to the uncinate processes. The width of the corpectomy usually ranges from 15 to 20 mm. After vertebral body removal, the longitudinal ligament and dura mater are opened and the meningioma is removed through microsurgical technique; finally, a fibular allograft is used to reconstruct the corpectomy defect. An anterior segmental plate is secured using screws into the upper and lower cervical vertebral body.

9.5.5 Operative Technique

Regarding the surgical strategy for spinal meningioma, there is no consensus about whether Simpson grade I resection achieves better long-term clinical outcome than Simpson grade II resection. When feasible, Simpson grade I removal should be the aim in all cases of spinal meningioma because it may be advantageous for achieving better long-term recurrence-free survival. However, if the dural attachment is located ventrally or laterally, a safely repairable dural section takes priority over radical excision of the dural attachment, preventing iatrogenic refractory CSF leakage or neurological worsening during dural repair [69]. The tumor recurrence rate after complete resection (Simpson grades I and II resection) is 9.7% as reported by Nakamura [70], and the recurrence rate increased progressively with the length of follow-up after complete resection (Simpson grades I and II) with 0%, 3.2%, and 8% for 5, 10, and 15-year follow-up, respectively. In this series, all the patients who developed recurrence had undergone Simpson grade II resection. The authors stated that the conclusion regarding the correlation between Simpson grade II resection and a low tumor-recurrence rate is open to question, based on studies with a postoperative follow-up of less than 10 years. Moreover, the tumor recurrence rate in

patients younger than 50 years at the time of the initial surgery was significantly higher than in those who were aged 50 years or older.

CSF leakage (and less frequently anterior cervical pseudomeningocele) can be a problem with anterior approaches for intradural pathology. In addition to meticulous dural closure using a synthetic dural substitute, a spinal drain should also be placed for 3–5 days for continuous drainage (10 cc/h).

Internal debulking is not feasible for a hard tumor, which should be removed without suction or ultrasonic aspirator. Surgical removal should be performed to achieve early dissection and devascularization of the mass that might be "en bloc" prior to the removal. According to Alafaci et al. [71], the metaplastic pattern of ossified meningiomas determines fibrotic or calcific transformation of the arachnoid membrane, eliminating the arachnoid dissection plane. The absence of a safe dissecting plane between the tumor and pia mater needs a meticulous microsurgical dissection between the pia mater and the tumor surface to obtain "en bloc" tumor removal. The ultrasonic surgical aspirator should be used to accelerate tumor debulking while also keeping in mind that its use can result in neurovascular damage. In our experience, especially in the case of hard meningiomas, the use of the ultrasonic surgical aspirator for hard tissue facilitates the internal decompression reducing stretching maneuvers of neural tissue [48].

9.6 Complication Avoidance

The specific risks related to meningioma surgery are CSF leakage and neurological deficits, which are most frequently associated with cases of ossified meningiomas, anterior dural attachment, and tumors infiltrating the spinal cord. Ruggeri et al. [48] described a univariate analysis that showed a statistically significant relationship between improvement of neurological status and the degree of ossification of meningiomas. Specifically, they found a direct relationship with microcalcified meningiomas, and an inverse relationship with ossified meningiomas. No relationship was observed between neurological status improvement and patient age, length of clinical history, or the site of the lesion within the vertebral canal. Moreover, calcified meningiomas can be more safely approached by laminectomy instead of a hemilaminectomy because it offers a wider operative field for better manipulation of neural tissue, especially in the thoracic spinal cord, which is more susceptible to damage than the cervical cord and lumbar spinal roots. Motor and somatosensory evoked potentials always provide guidance in all procedures, especially in spinal calcified meningiomas and anterior located ones, and the use of neurophysiological monitoring is strongly recommended.

The median mortality rate of surgical cases of spinal meningiomas is 1% (range, 0–4%). Postoperatively, median non-neurological and neurological morbidity rates are 4% (range, 0–24%) and 6% (range, 0–21%) of patients, respectively [71]. Since meningiomas arise from the dura that covers the spinal cord tissue, safe dissection allows separation of the tumor and complete resection in 82–98% of patients [17].

9.7 Conclusion

Cushing and Eisenhardt defined the removal of a spinal meningioma as "one of the most gratifying of all operative procedures." In the last few decades, a better understanding of the relationship between patient status and the outcome of the tumoral pathology, location and ossification, improvements in neurophysiological monitoring and neuro-anesthesia, as well as the development of innovative variations to the traditional approaches to spinal cord tumors have significantly improved the surgical management of spinal cord meningiomas.

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Spinal Schwannomas

10

Madjid Samii and Mario Giordano

10.1 Introduction

Spinal schwannomas are the most common nerve sheath tumors of the spine [1]. They are slow-growing benign tumors, typically encapsulated, and composed entirely of well-differentiated Schwann cells. In the vast majority of cases, schwannomas are solitary and sporadic, while multiple schwannomas are associated with neurofibromatosis type 2 (NF2) and schwannomatosis [2]. The incidence of spinal schwannoma is around 0.3–0.4/100,000 each year either in solitary or syndromic form. Most of clinical and surgical series show similar data about spinal schwannoma epidemiology—males and females appear to be equally affected, and the onset can be between 25 and 60 years with a prevalence in the fourth and fifth decade even if it can occur at any age [3, 4]. However, in one of the largest series reported by Hirano and colleagues and including 678 spinal tumors [5], there is a slight prevalence of male (1.3:1) and the onset is reported most frequently between 50 and 59 years. Approximately 90% of cases are solitary and sporadic and 4% arise in the setting of NF2. Of the 5% of schwannomas that are multiple but not associated with NF2, some may be associated with schwannomatosis.

10.2 Etiology

Spinal schwannomas belong to the larger category of nerve sheath tumors along with neurofibromas. They are different in etiology, localization, and histology. Whereas schwannomas are encountered in patients with and without NF2, neurofibromas are

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found in patients with NF1, an autosomic dominant disease linked to a genetic defect located on chromosome 17 [6]. NF2 is an autosomic dominant disease related to a genetic defect located on chromosome 22, which causes the loss of merlin protein (ie, the NF2 gene product). The phenotypic expression of NF2 gene changes among patients, resulting in variable clinical courses, while genotypic subtyping has shown no evidence of utility in terms of further prognostic information [7]. About 90% of patients with NF2 present spinal tumors in their life; among these patients, schwannomas are the most common. Of course, vestibular schwannomas, ependymomas, astrocytomas, and meningiomas can be found in these patients [8]. For this reason, they should undergo magnetic resonance imaging (MRI) scans of the spine almost every year in order to detect the tumors at their earliest stages [9].

Multiple schwannomas, also called schwannomatosis, can occur in patients without NF, but these tumors do not currently have a known genetic base [2].

10.3 Histology

Histologically, we can distinguish conventional schwannomas and other variants, such as the cellular schwannoma—which shows similarities with malignant peripheral nerve sheath tumors—or melanotic schwannoma, containing cytoplasmic melanin bodies. Less common variants are the psammomatous and plexiform schwannomas.

Conventional schwannoma is composed entirely of neoplastic Schwann cells other than inflammatory cells, which may be focally numerous. There can be two basic architectural patterns found in varying proportions:

- **Antoni A Pattern:** Hypercellular, composed of compact areas with interwoven bundles of long, spindly, and elongated Schwann cells with occasional palisading nuclei and Verocay bodies. This pattern is prevalent in NF2 patients.
- **Antoni B Pattern:** Less cellular, composed of stellate-shaped cells, dispersed in a loose eosinophilic matrix with variable lipidization [10, 11].

The vascularization of schwannomas is typically composed of thick-walled vessels, alternating with dilated vessels surrounded by small hemorrhages.

Regarding the immunohistochemistry profile, a typically diffuse S100 and collagen IV positivity is present, associated with an extensive SOX10 expression and a low Ki-67 proliferation index in the enlarged atypical cells. Malignant transformation is absolutely rare in conventional schwannomas, while it is more common in melanotic ones [2].

10.4 Macroscopic Aspect and Localization

Spinal schwannomas appear as smooth, globoid, well-defined, and encapsulated masses [1]. They do not enlarge the nerve but are suspended eccentrically from it and are separated from other rootlets. Most are entirely intradural, but 8–32% may

be completely extradural, 1–19% may be intra-extradural, and less than 1% are intramedullary. These rare cases are thought to arise from the perivascular nerve sheaths that accompany penetrating spinal cord vessels [12, 13].

In 6–23% of cases, spinal schwannomas may assume a characteristic dumbbell configuration extending through the dural root sleeve—they develop into an "hourglass" shape caused by the anatomic barrier encountered during growth, resulting in both intradural and extradural components. Most have a contiguous intraspinal, foraminal (usually narrower), and extraforaminal components. The widening of the neural foramen is a characteristic finding and mostly indicates the benignity of the lesion [14].

Spinal schwannomas arise in most cases from the dorsal rootlets as they develop from Schwann cells of a sensory nerve root [1]. These lesions can occur in any spinal region, but it seems they are more common in the lumbar and cervical tract. The reason for this feature could probably be explained by the anatomical characteristics of lumbar nerve roots, which run long distances from the conus to the foramina. On the contrary, transdural growth resulting in a dumbbell shape is common in the cervical tract because the intradural root segment is short. Rarely, schwannomas can be found strictly adherent or directly originating from the conus medullaris [12, 15, 16]. Asazuma and colleagues have developed a radiological-based classification specifically for dumbbell tumors in which they are distinguished on the basis of anatomic relationships with surrounding structures [14].

10.5 Clinical Presentation

Clinical presentation depends on tumor location and its anatomical relationship with the spinal cord and nerve roots. According to their benign nature, schwannomas can grow for a long time before resulting in any symptoms due to mass effect. Thus, they can be an occasional finding in 2–20% of cases with a consistent variability among different surgical series [11, 17]. The most frequent onset symptom is pain, particularly for sporadic schwannomas as reported in most series. Sensory deficits can also appear, like paresthesias. Less common symptoms are motor deficit or impairment of sphincter function. On the other hand, NF2 patients are more likely to develop neurological deficits than patients without NF2. For this reason in NF2 schwannomas, gait ataxia and other motor deficits resulted as the first symptoms followed by pain [12, 15, 16, 18, 19].

10.6 Surgical Treatment

Surgery is the gold standard treatment for symptomatic or growing spinal schwannomas. The goal is symptom relief and the prevention of recurrence. Recurrence is rare after total excision, except in neurofibromatosis, and can be achieved in most cases in total security [3, 13]. If this is not possible, due to the strict involvement of functional nerve roots, the fibrous capsule or a portion of the tumor itself can be left in order to preserve neurological function [1, 11]. The role of the fibrous

capsule in recurrences is uncertain, while subtotal resection predisposes the tumor to regrowth. Subtotal resection may be sufficient for a durable relief from symptoms, considering the benignity and the slow growth of schwannomas. However, sometimes section of the entire nerve root is required and may be performed without any postoperative deficit because the fascicles involved are nonfunctional in most cases, and their function is compensated by adjacent roots [12]. In case of C1–C2 schwannomas, more caution is needed for possible involvement of the vertebral arteries [20].

Radiosurgery is a possible alternative in selected cases, such as recurrences, incomplete resections or comorbidities that contraindicate surgical treatment [21].

Multiple surgical routes have been described:

- **Posterior Approaches:** The classical laminotomy (or laminectomy) is still the most used approach, except in case of dumbbell tumors with massive extradural components. A more invasive surgical approach may be needed for these tumors. So, if the tumor is located inside the spinal canal, a complete laminotomy spanning the length of the tumor has to be performed, including a half level exposure above and below the tumor level with partial facetectomy, if needed. Hemilaminectomy and interlaminar approach are options that can reduce postoperative pain and preserve spinal stability [22]. The dura has to be opened with a sharp incision in the midline in order to expose the spinal cord and schwannoma. If a portion of the lesion extends in the foramen, a horizontal incision following the root sleeve can be performed to obtain complete removal. Ventral tumors may need section of the dentate ligament to achieve a good visualization. Lumbar tumors can be covered by the cauda equina or conus medullaris; in these cases, nerve roots must be separated in order to get a better visualization [23]. When the tumor is exposed, it has to be dissected from the adherent anatomical structures, individuating the correct dissection plane. Usually, the arachnoid is strictly adherent to the tumor capsule. Once a safe entry zone is individuated, the tumor capsule is cauterized with bipolar forceps in order to lower the vascularity and shrink tumor size. If the nerve roots are suspected to be inglobated or strictly adherent to the tumor capsule, a nerve stimulator may be used in order to identify and spare functional motor roots. After the incision of the capsule, an ultrasonic aspirator may be used to internally debulk the tumor.
- **Anterior and Combined Anterior/Posterior Approaches:** The specific kind of approach is influenced by the surgeon's experience, and by the size and location of the paraspinal tumor component [24, 25]. Asazuma et al. recommended these approaches for dumbbell lesions in which the extraforaminal extension is massive, since the other types of dumbbell lesions can be managed through the classic posterior approach [14]. Furthermore, in rare cases dumbbell tumors infiltrate surrounding structures and cannot be encapsulated. Thus, this kind of approach is considerably associated with higher incidence of motor deficit, as it often necessitates resection of both nerve roots [26].

10.7 Personal Experience

Of our experience, including over 1400 cases of nerve sheath tumors, we analyzed our 40 most-recent cases of spinal schwannomas.

The average patient's age was 45 years (range, 10–80 years) with a sex distribution of 18 females and 22 males. The main clinical symptoms at admission were pain (65%), motor weakness (45%), and sensibility disturbances (27.5%). The distribution along the spine showed a predominance of the lumbar localization (42.5%), followed by the thoracic (32.5%) and cervical tract (25%). Regarding the extension of the lesion, the treated cases were harboring 62.5% intradural, 20% intra-extradural, and 17.5% paraspinal tumors [17]. In 10% of the cases, we dealt with giant schwannomas.

We treated spinal schwannomas in five cases affected by NF2. In 90% of the patients affected by NF2, spinal tumors can be found, and schwannomas are the most common. In such patients, the indication for surgical removal of the lesion should be evaluated very carefully. In fact, during routinely performed MRI controls of the spine, multiple tumors are detected; this should not imply an indication for surgery. These tumors can remain clinically silent for years and only one-third of them have been seen to cause symptoms.

For such reasons, indication for surgery should be given for lesions causing neurological signs and/or showing significant growth. Of the five treated cases affected by NF2, four underwent total removal while in one case there was a partial resection. These results show a more conservative strategy in such cases compared with non-syndromic schwannoma cases. In NF2 subjects, any nerve root can be affected at any time despite the radicality of the surgery Thus, it is mandatory to preserve functioning and not expose the patients to any risk of postoperative deficit.

In the non-syndromic cases, a total resection was obtained in 34 of the 35 cases. Subtotal removal was performed in one recurrent case due to the presence of tumor infiltration of the root that had evidence of motor function.

Regarding the postoperative outcome, we could achieve a resolution of the preoperative pain symptomatology in 85% and improvement in 15% of the patients at the first postoperative follow-up. There was a resolution of the preoperative weakness 66% and improvement in 22% of the cases, while the deficit remained stable in two patients affected by NF2.

We used different surgical approaches in relation to the extension of the lesion (Figs. 10.1, 10.2 and 10.3). The majority of the cases where treated with posterior approaches: 50% laminotomy, 25% hemilaminectomy, and 15% interlaminar approach. In the remaining 10% of the cases with an extended extradural portion, more complex approaches (anterior and lateral) were used. Regarding the postoperative complications, we had cerebrospinal fluid leak in two patients: it was solved with lumbar drainage in one case and required revision in the second case. Transient postoperative neurological deficits were present in 12.5% of the cases.

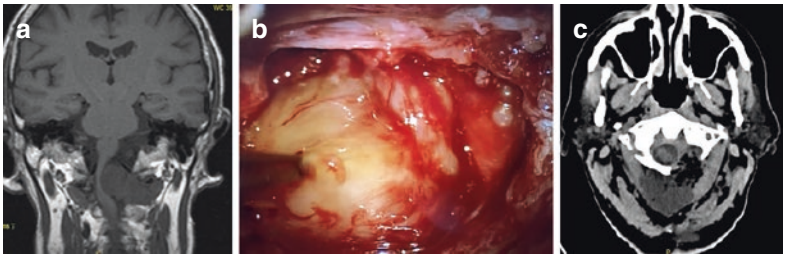

Fig. 10.1 (**a**) Coronal non-contrast T1-weighted MRI image showing a case of large intra/extradural schwannoma C2 on the left side in a 68-year-old patient with a 6-month history of pain and progressive tetraparesis. (**b**) Intraoperative image of the same case displaying the exposed schwannoma, which was removed via a C1 hemilaminectomy in a semi-sitting position. (**c**) Axial computed tomography scan performed on the first postoperative day demonstrating the left hemilaminectomy of the atlas and total removal of the lesion

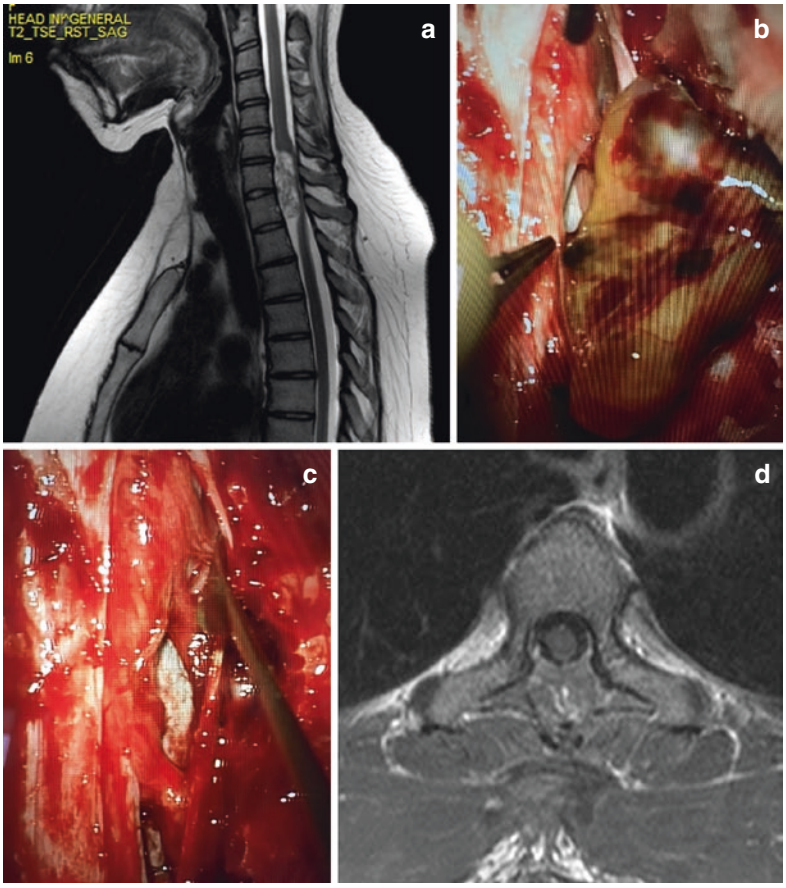

Fig. 10.2 (**a**) Sagittal T2-weighted MRI image of a 23-year-old patient harboring an intradural schwannoma at the C7–T1 level with intratumoral bleeding. The patient presented high grade paraparesis. (**b**) Intraoperative image of the patient showing the removal of the lesion via C7–T1 laminotomy. (**c**) Surgical site after tumor resection. (**d**) Postoperative axial T1-weighted post-contrast MRI image showing the complete removal of the schwannoma

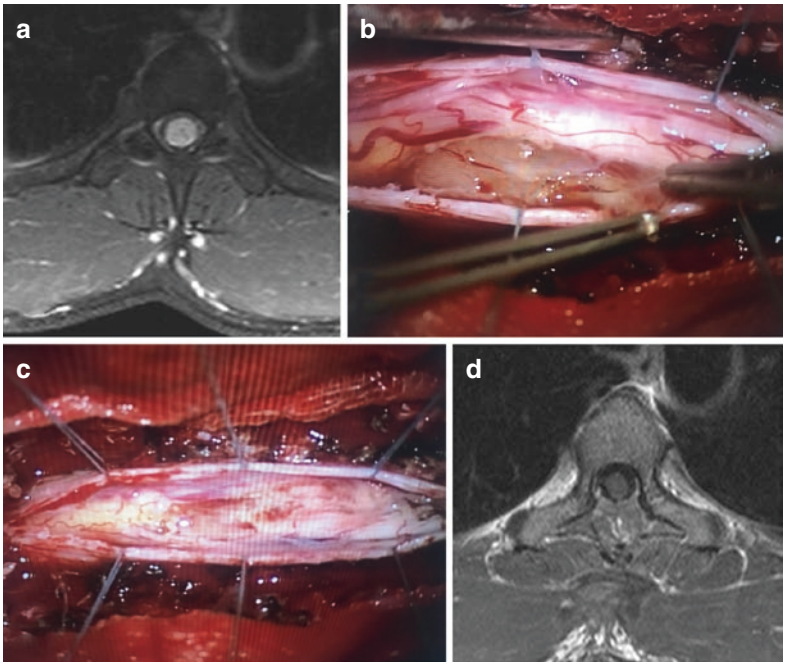

Fig. 10.3 (**a**) Axial T1-weighted MRI image with contrast media showing a T2–3 schwannoma in a 40-year-old man with weakness of the lower extremities due to the extreme compression of the spinal cord. (**b**) Intraoperative exposition of the lesion via T2–3 laminotomy. (**c**) Surgical site after removal of the lesion. (**d**) Postoperative axial T1-weighted post-contrast MRI image with contrast media demonstrating the total removal of the lesion

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Management of Intradural and Extradural Spinal Schwannomas

11

Alvin Y. Chan, Andrew K. Chan, Catherine A. Miller, Line G. Jacques, and Praveen V. Mummaneni

11.1 Introduction

Spinal schwannomas (also called neurilemmomas or neurinomas) are typically benign round encapsulated neoplasms of Schwann cell progenitors in the spine. Schwannomas grow as appendages to the parent dorsal nerve root and contain neoplastic Schwann cells [1, 2]. Schwannomas form two patterns that are classified as Antoni A (ie, highly cellular regions with closely packed elongated nuclei) or Antoni B (ie, poorly cellular and loosely packed regions) [3]. Spinal schwannomas are frequently intradural-extramedullary or extradural [1, 4], although there are rare examples in the literature of intramedullary tumors [5–7]. They are the most common nerve sheath tumors, which comprise roughly one-fourth of primary spinal tumors, and usually present in the fourth through sixth decades of life [4, 8]. Ninety-five percent of Schwannoma cases are believed to be sporadic [9], although multiple tumors can imply a syndrome [10]. The incidence is reported to be 0.3–0.5 per 100,000 individuals [11].

Schwannomas can also be categorized into variants, such as cellular, plexiform, or melanotic. Cellular schwannomas have higher cellularity and mitotic rates than other tumors, which may lead to more erosive localized damage without malignant potential [12]. Older data suggested that these tumors typically arise paravertebrally or from the pelvis [13]. Another form is described as plexiform, which are rarely found in the spine [14]. These tumors usually have Antoni A-type tissue, and are often dermal in younger patients [12]. Melanotic schwannomas are less common and pigmented with spindle and epithelioid cell morphology [12].

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Occasionally, patients will present with multiple schwannomas, which is typically syndromic (eg, neurofibromatosis type II [NF2] or schwannomatosis) [10]. NF2 and schwannomatosis can overlap in terms of phenotype or presentation but they are genetically and molecularly distinct [15]. NF2 is an autosomal dominant multiple neoplasia syndrome that is derived from a mutation to a tumor suppressor gene on chromosome 22 [16]. Patients develop tumors of the central nervous system, including bilateral vestibular schwannomas, as well as ophthalmic and cutaneous lesions [16]. Approximately two-thirds of NF2 patients have spinal tumors, which tend to be more aggressive than other forms of schwannoma [17, 18]. Conversely, schwannomatosis is described as a third form of neurofibromatosis and is defined by the development of multiple schwannomas without vestibular nerve involvement [19, 20]. It can be a sporadic entity, but it can also involve a familial genetic component, such as a mutation on the *INI1/SMARCB1* tumor suppressor gene [21].

We review the current management recommendations for treating patients with intradural or extradural spinal schwannomas with the aim to compile a resource of current evidence for these common tumors. Surgical approaches and strategies for intradural and extradural tumors are discussed, as well as other considerations related to management. Surgical pearls are also provided to help avoid common pitfalls.

11.2 Work–Up & Presentation

Diagnosing spinal schwannomas starts with taking a thorough history, conducting a thorough neurological exam, and electromyogram and nerve conduction velocity test data, if necessary. Furthermore, a neurogram can provide additional anatomical details on the relationship of the tumor, nerve root, and potentially the dura. The most common preoperative symptom for spinal schwannomas is localized pain with or without radiation [1, 11, 22, 23]. Other less frequent symptoms include sensory deficits in a dermatomal distribution, bowel or bladder incontinence, motor weakness, gait disturbances, or muscle atrophy [22]. Rarely, patients have presented with elevated intracranial pressure and associated bilateral papilledema [24].

Schwannomas are often asymptomatic and found incidentally on imaging. Their presentation can be diverse and unusual, but they typically have characteristic features. Schwannomas tend to be hyperintense on T2-weighted imaging and range from hypointense to isointense on T1-weighted imaging [2, 25]. The tumors often have heterogeneous enhancement. A study of 92 patients with schwannomas found that 55.4% of tumors showed fluid signal intensity on T2-weighted magnetic resonance imaging (MRI) and 58.7% showed rim enhancement on contrast T1-weighted imaging [26]. Imaging on computer topography (CT) often exhibits hypo-to-mild hyperdensity but may not be distinguishable from the spinal cord without intrathecal contrast [2]. Furthermore, spinal schwannomas can present with pedicle erosion and remodeling with a widened foraminal diameter [2]. Rarely, schwannomas will present with subarachnoid or subdural hemorrhaging [27, 28], which can be

Table 11.1 Summary of different potential surgical approaches and procedures depending on the spinal region and tumor location

Region	Tumor location	Approach and procedure
Cervical	Ventral (midline)	Anterior approach (eg, corpectomy) with or without posterior fusion
	Ventral (lateral)	Posterior approach (eg, laminectomy) or posterolateral approach (eg, facetectomy) with or without fusion
	Lateral recess	
	Dumbbell	
	Dorsal	
Thoracic	Ventral	Anterior approach (eg, thoracotomy with corpectomy and fusion)
	Lateral	Posterior-based approaches (eg, transpedicular, costotransversectomy and fusion)
	Dumbbell	
	Dorsal	Laminectomy or laminotomy with or without facetectomy and fusion
Lumbar/sacrum	Ventral	Laminectomy or laminotomy with or without facetectomy and fusion
	Lateral	
	Dumbbell	
	Dorsal	

challenging to diagnose [29]. The apparent diffusion coefficient (ADC) can also be useful in certain situations for assessing pre-operatively the benign nature of the tumor.

Different surgical approaches are summarized in Table 11.1.

11.3 Intradural Tumor Management

11.3.1 Intradural Extramedullary Tumors

Schwannomas are encapsulated tumors that splay rather than invade the dorsal sensory root. Intradural extramedullary tumors are the most common presentation, accounting for approximately two-thirds of all spinal schwannomas (Fig. 11.1) [11, 30, 31].

There are many surgical strategies that can be utilized, depending on tumor size and location [32]. In many cases, conventional posterior laminectomy or hemilaminotomy with tumor debulking may be sufficient to achieve gross total resection [22, 33]. Unilateral laminectomy has been shown to result in improved postoperative pain and adequate tumor debulking while maintaining regional stability [34]. In certain patients, minimally invasive options—like interlaminar approaches—may be employed [35, 36].

The location and size of the tumor may dictate the type of surgery indicated. For example, a retrospective review of 110 patients compared the outcomes (blood loss, hospital length of stay, pain scores) for patients who underwent a microsurgical laminectomy, hemilaminectomy, or laminectomy with pedicle screw fixation [37]. The results showed that hemilaminectomy was best suited for removal of cervical

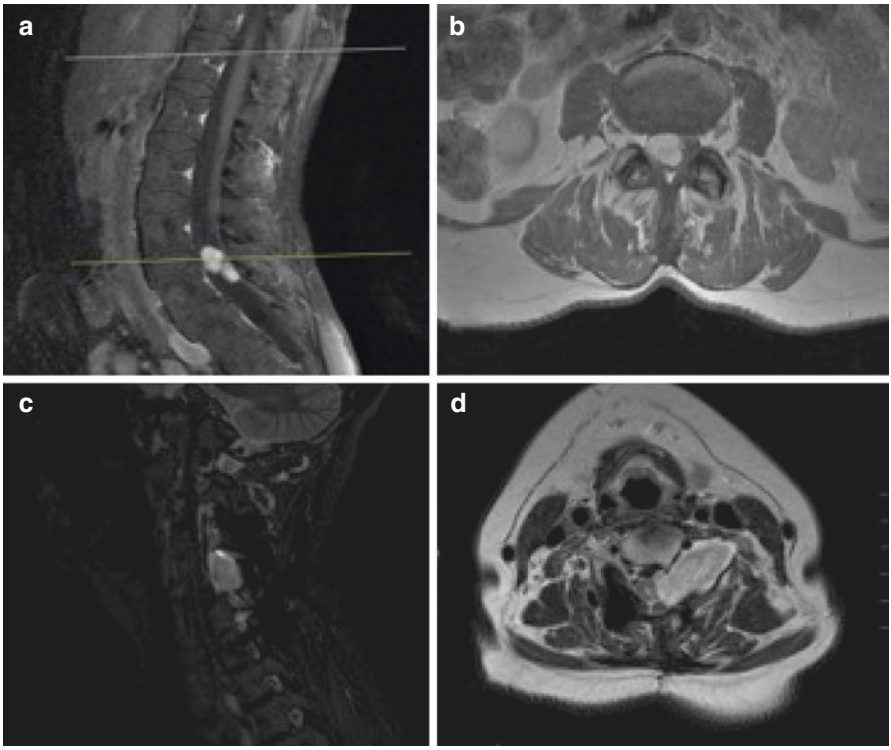

Fig. 11.1 Images showing two patients with intradural tumors. T1-weighted sagittal (**a**) and axial (**b**) images of a patient with an exclusively intradural tumor. Sagittal (**c**) and axial (**d**) images of a patient with both intradural and extradural schwannoma

tumors, laminectomy was best suited for removal of thoracic tumors, and laminectomy with pedicle screw fixation was best suited for removal of lumbar tumors. However, the benefits were minimal and thus appropriate judgment must be used when determining the correct approach and technique.

In some instances, an intradural schwannoma may be ventral to the cervical or thoracic spinal cord and cause compressive myelopathy. In the lumbar region and in select instances in the thoracic region, a posterior approach with only a laminectomy or a posterolateral approach that is medial to the paraspinal muscles is typically adequate for dorsally-located tumor debulking [38, 39]. For tumors in the cervical spine, the anterior approach may be more favorable for ventral canal tumors, given the inability to manipulate the cord [40]. An anterior cervical corpectomy with spinal arthrodesis and fixation has been used to treat a midline ventral intradural schwannoma [41]. Alternatively, a posterior facetectomy may allow for a posterolateral approach to a lateral recess tumor in the cervical spine (Fig. 11.2).

Gross total resection of schwannomas without severe neurological deficits is often achievable. For example, a study of 128 patients who underwent surgery for spinal schwannomas demonstrated that gross total resection was accomplished in

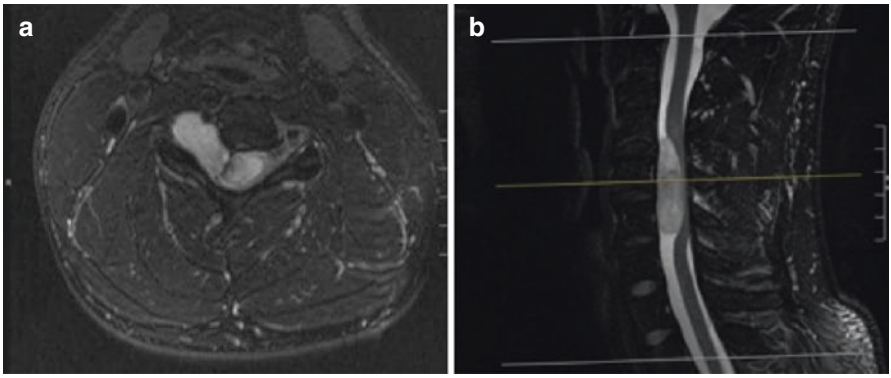

Fig. 11.2 T2 axial (**a**) and T2 sagittal (**b**) MRI images of a 27-year-old man with a dumbbell type schwannoma that extended through the C4–5 foramen. The tumor is amenable to a surgery utilizing a posterolateral approach and posterior facetectomy

97% of tumors [22]. Preservation of the spinal nerve root is feasible, but is sometimes sacrifice of the parent root is necessary to completely resect the tumor. Even when the nerve root is sacrificed, the neurological deficit may be minimal if the affected sensory nerve root only is transected [42]. Although the exact mechanism is unclear, the hypothesis is that as the tumor progresses, the nerve root is damaged and becomes dysfunctional, allowing muscles to be reinnervated by other nerve roots [43]. In support of this hypothesis, a study of 31 patients who required nerve root sacrifice for tumor resection at spinal levels critical for function (ie, C5–T1 and L3–S1) showed that postoperative disabling deficits were minimal, and that the spinal roots that produce the tumors were frequently nonfunctional at the time of surgery [22, 44]. Additionally, intraoperative neural monitoring or direct nerve root stimulation can be used as an adjunct to help assess whether sacrificing the nerve root will result in any postoperative deficit [23].

There may be specific risk factors that predict whether patients will have neurological deficits postoperatively. A study of 64 patients with solitary spinal intradural schwannomas (between T11 and S1) demonstrated that the absence of preoperative lower extremity pain, presence of either preoperative sensory or motor disturbance, or a tumor between T11 and L2 were more likely to have postoperative deficits after concurrent nerve root sacrifice than those without any of these risk factors [45]. Moreover, the authors found that the age, sex, duration of disease, the presence of diabetes, and the tumor length were not predictive of postoperative deficits.

11.3.2 Intramedullary Tumors

Intramedullary schwannomas are rare and represent approximately 1% of cases [1, 2, 11], which is not surprising considering their origin from Schwann cells located

outside the spinal cord. The exact pathogenesis of intramedullary tumors is unclear. A number of hypotheses have been proposed, including derivation from ectopic Schwann cells [46]. Complete resection is not always possible because these tumors can be infiltrative.

Due to the rarity of these tumors, there is no consensus on surgical approach or technique. A posterior approach with a laminectomy or laminotomy can be sufficient for adequate tumor debulking. However, it is crucial to determine the location of tumor origin to ensure a safe surgical corridor [47]. Lee et al. described a case series of ten patients with intramedullary tumors and argued that if the tumor originates from the dorsal root entry zone and not from within the spinal cord, then a myelotomy can be avoided [47]. If the tumor originates from a purely intramedullary location, typically a myelotomy must be performed.

11.4 Extradural Tumor Management

Extradural schwannomas are found outside the thecal sac and occasionally away from the nerve root (Fig. 11.3) [30]. They are relatively uncommon in comparison to intradural extramedullary tumors. Celli et al. sought to establish the clinical presentation, tumor characteristics, and surgical outcomes for extradural schwannomas [30]. They retrospectively reviewed 24 cases at their institution and found that the patients were predominantly women (71%) and tumors were more likely to develop in the cervical and thoracic spine [30]. On rare occasions, extradural schwannomas can develop within the vertebrae and grow into the spinal canal, causing cord compression [48].

Extradural schwannomas have traditionally been removed via an open midline posterior approach with a laminectomy or hemilaminectomy and potential fusion, depending on whether facetectomy is required to debulk the tumor [31, 49, 50]. This strategy is similar to intradural surgical techniques without durotomy and typically is adequate for gross total resection and alleviation of symptoms [11]. Conversely, recent studies have noted that a minimally invasive approach is possible for appropriate tumors with expandable tubular retractors (Fig. 11.4) [50, 51]. Standard microsurgical techniques similar to minimally invasive lumbar microdiscectomy are used [51]. The advantages of a minimally invasive approach include the following: (1) the avoidance of fusion due to lack of facetectomy and iatrogenic spinal instability; (2) less tissue destruction; and (3) less blood loss [51]. Figure 11.5 demonstrates a tumor that is amenable to gross total resection via a minimally invasive spine surgery technique. A potential disadvantage to minimally invasive techniques is there is minimal potential for tumor mapping. Therefore, not all tumors are amendable to minimally invasive techniques, and surgical judgment should be utilized when determining whether an open or minimally invasive approach is appropriate.

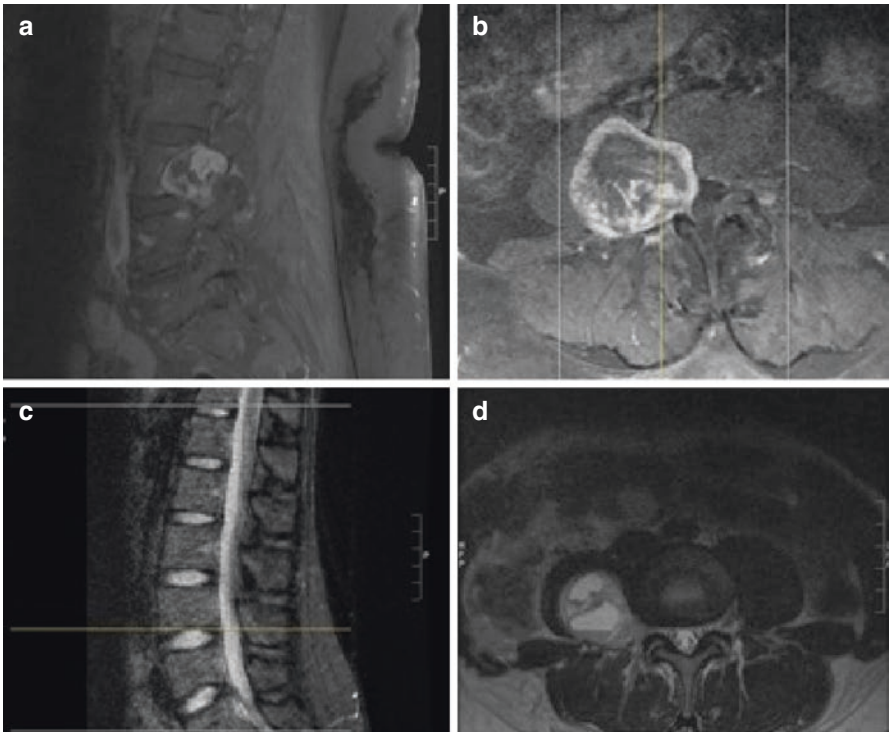

Fig. 11.3 Images showing two patients with extradural schwannomas. Sagittal (**a**) and axial (**b**) MRI sequences of a patient with lumbar right-sided extra-dural schwannoma. Sagittal (**c**) and axial (**d**) views of a right-sided schwannoma invading anteriorly

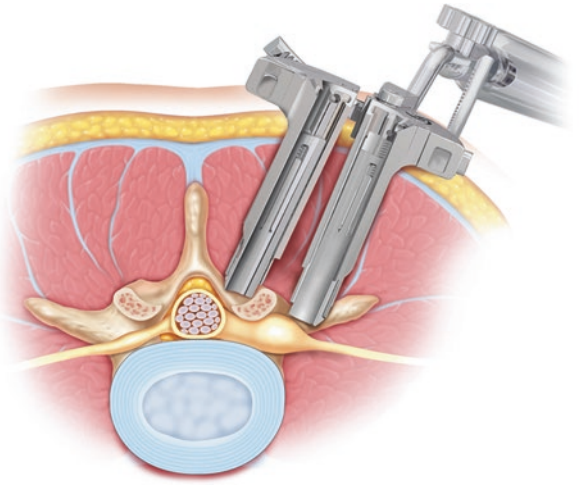

Fig. 11.4 Illustration of a minimally invasive spine surgery approach with an expandable tubular retractor. (Originally published in Lu et al. J Neurosurg Spine 2009 [50]; reprinted with permission)

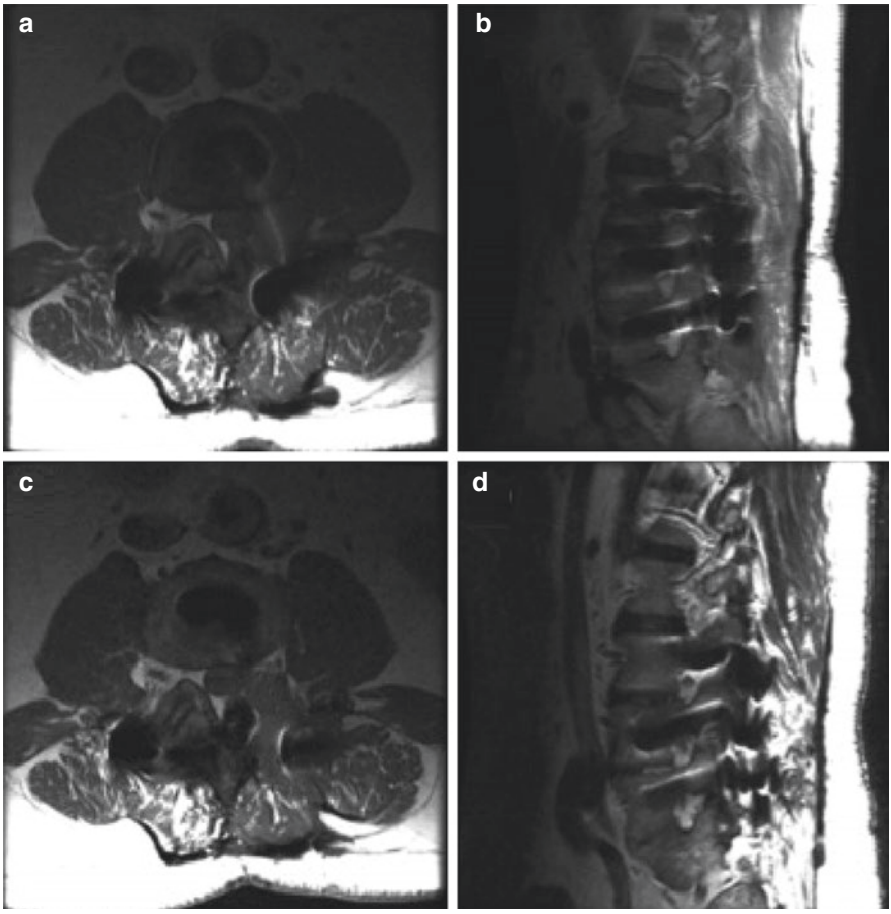

Fig. 11.5 Images showing the results of a minimally invasive approach with an expandable tubular retractor to resect a left L3–L4 schwannoma found 2 years after a spinal fusion. By using a tubular retractor placed via a Wiltse approach, we did not have to remove any of the hardware. Preoperative axial (**a**) and sagittal (**b**) MRI imaging. Postoperative axial (**c**) and sagittal (**d**) images following gross total resection of tumor. (Originally published in Lu et al. J Neurosurg Spine 2009 [50]; reprinted with permission)

11.5 Other Considerations

11.5.1 Dumbbell Tumors

Schwannomas can take the form of a "dumbbell" shape, which is a term to describe a tumor that is split into two different spaces (eg, a tumor that is both intradural and extradural). Dumbbell schwannomas are typically found in the cervical spine [1, 10]. A study of 118 spinal dumbbell tumors found that 18% of schwannomas were

at the C2 nerve root, which was the highest incidence of any nerve root [49]. Dumbbell schwannomas can be destructive to the vertebra and incorporate multiple nerve roots; therefore, some studies recommend removal as soon as identified regardless of whether or not the patient is symptomatic [52].

Although spinal dumbbell tumors are not particularly rare [49], they present surgical challenges because of the unique exposure required. In the cervical spine, a posterior approach can be used, especially if the foramen is involved. A study of 41 cases of dumbbell schwannomas in the subaxial cervical spine found that gross total resection with minimal postoperative neurological deficit was possible, if the extraforaminal component was smaller than 5.4 mm in its longest diameter [53]. Gross total resection is possible by using a modified posterior midline exposure, followed by a single-sided laminectomy and facetectomy, which gives access to the intraspinal, foraminal, and extraforaminal spaces for optimal tumor removal [54]. Others advocate use of a posterior approach to resect as much tumor possible while leaving the foraminal portion unresected with the goal of preservation of the facet joint [55]. The rationale is to maintain low recurrence rates while minimizing potential complications from facet disruption. Dumbbell tumors have been removed through a hemilaminectomy with or without facetectomy and possible fusion, depending on assessment of stability [49]. The use of microsurgical or endoscopic techniques for transforaminal resection may help preserve stability and joint integrity, precluding the need for a fusion [56].

When debulking a dumbbell tumor, it is beneficial to start with resection of the extradural component. The invagination of the dural ring may resemble intradural extension during the operation, but there may not actually be any intradural component [57]. By debulking the extradural portion initially, the dural ring can be carefully examined for intradural extension before the dura is opened. Schwannomas are encapsulated tumors, which allows for potential removal without sacrificing the nerve root or undertaking an unnecessary durotomy.

11.5.2 Sacral Schwannoma

Tumors in the sacrum are rare and often asymptomatic but can present with a variety of neurological deficits like bowel or bladder dysfunction (Fig. 11.6) [58]. Only approximately 50 sacral schwannomas have been described in the literature [59]. Indeed, these tumors can become massive with expansion into the spinal canal and pelvis before causing severe-enough symptoms for patients to seek evaluation. Their size can make them difficult to manage [58]. MRI is often required to make a diagnosis because radiograph can be inconclusive [60]. The rarity of these tumors has made surgical management somewhat controversial, as aggressive resections may lead to a low chance of recurrence, but a high probability of neurological deficits [60, 61]. Therefore, conservative management may be more appropriate in some circumstances and surgical judgment should be utilized.

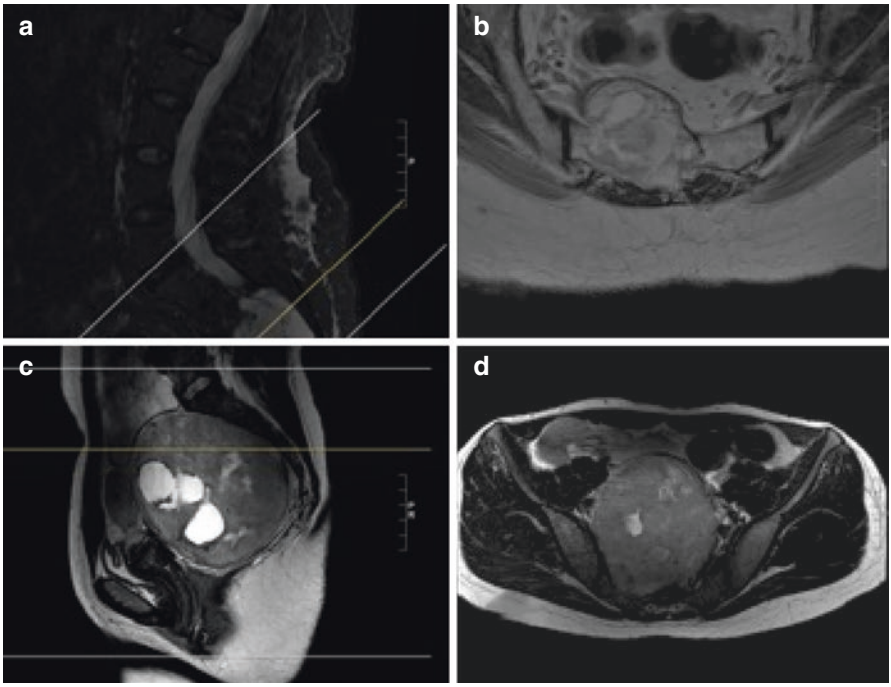

Fig. 11.6 MRI sequences of 2 patients with large sacral tumors. Sagittal (**a**) and axial (**b**) images of a large right-sided sacral tumor from the first patient. Sagittal (**c**) and axial (**d**) images of a giant sacral schwannoma

11.5.3 Intraoperative Neural Monitoring

The use of intraoperative neural monitoring is important for appropriate surgical management as it has become standard of care for resecting these tumors. Recent guidelines have been outlined for surgery on the spinal column and cord [62]. Specifically, multimodality intraoperative monitoring (MIOM) (eg, somatosensory and motor evoked potentials) is recommended to assess spinal cord integrity with motor evoked potentials being superior to somatosensory evoked potentials for assessment of spinal cord integrity. In our experience, intraoperative neural monitoring can also help with diagnosing whether the nerve root is involved or if the spinal cord is damaged prior to resection. Monitoring also helps avoid functional motor fibers during the procedure.

11.5.4 Recurrence

As with other benign tumors, gross total resection of spinal schwannomas is curative while subtotal resection permits possible recurrence. The rate of recurrence in spinal schwannomas is roughly 5% at 2 years postoperatively [23, 63]. Schwannomas

have a wide variability in growth rate and can increase in size by 5% annually [64]. A retrospective analysis of 169 patients with spinal schwannomas found that the risk factors for recurrence were higher number of spanned levels, increasing tumor size in the cranial-caudal direction, and tumor location in the cervical or sacral regions [63]. However, residual tumor size may not correlate with the rate of recurrence. A study of 27 patients found that postoperative residual mass did not correlate with significant tumor regrowth at 2-year follow-up. Alternatively, in this cohort, tumors that had a high Ki-67 labeling index value—a cellular marker for proliferation—were more likely to recur than those with low values [65]. In another study of 32 patients with giant spinal schwannomas (defined as tumors extending at least 2 vertebral levels intraspinally or 2.5 cm extraspinally), those who underwent gross total resection were less likely to have tumor recurrence compared with patients who underwent subtotal resections [66].

11.5.5 Complications

Resection of spinal nerve sheath tumors is safe with respect to major morbidity and mortality, but the complication rate is relatively high. A study of 199 patients who underwent resection for spinal nerve sheath tumors, including 163 schwannomas, described the complication rate as 32% with new or worsening sensory deficits as the most frequent complication [67]. Another study of 187 cases of spinal schwannoma described the late complication rate as roughly 21% [11]. Severe pain, spinal deformity, and spinal arachnoiditis (ie, pain disorder derived from the arachnoid) were the most common complications. Furthermore, cerebrospinal fluid leak is a possible complication, especially in cases with dumbbell schwannomas.

11.6 Conclusion

Spinal schwannomas are relatively common primary encapsulated nerve sheath tumors. The main presenting symptom is pain, although other complaints are possible, such as neurological deficits. We described the typical surgical approach for intradural and extradural tumors. Often, a posterior open midline incision followed by laminectomy or hemilaminotomy/hemilaminectomy with or without facetectomy and fusion is necessary for gross total resection—the mainstay of curative treatment. Subtotal resections can lead to recurrence, although the rate of recurrence is relatively low. Common complications include worsening sensory deficits or severe pain.

11.7 Surgical Pearls

- Intraoperative monitoring can help distinguish whether the associated nerve root can be sacrificed without postoperative motor deficits. However, it is important to note that potential sensory or pain deficits cannot be detected this way.

- Intramedullary schwannomas are exceedingly rare and may not require myelotomy, if the origin of the tumor is the dorsal root entry zone.
- Extradural tumors and intradural extramedullary tumors in certain instances can be reached via a minimally invasive approach with tubular retractors, although nerve monitoring is very limited with this approach.
- Dumbbell schwannomas should be resected extradurally first and then intradurally; resection in this order will spare the need for durotomy in case there is not actually an intradural portion of the tumor.
- Intraoperative neural monitoring is important for diagnosing nerve root involvement or spinal cord damage, as well as helping to avoid damaging functional motor fibers.

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Spinal Cord Tumors in Neurofacomatosis

12

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12.1 Introduction

Neurofacomatosis (phakomatoses) are a group of neuro-oculocutaneous disorders characterized by involvement of structures that arise from the embryonic ectoderm—thus, the central nervous system (CNS), skin, and eyes. The phakomatoses concept was formulated in 1923 by an ophthalmologist Van Der Hoeve to describe three disorders (neurofibromatosis, tuberous sclerosis, and von Hippel-Lindau syndrome), according to their ophthalmologic manifestations (Greek *phakos* means birthmark) [1, 2]. However, it has been subsequently noted that mesodermal and

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endodermal tissues are also involved. A number of genetic and acquired diseases come in this category and may affect one or more organ systems. They tend to form tumors in various organs, particular the nervous system. Now neurofacomatosis are also termed as "neuroectodermatoses" or "neurocutaneous syndrome."

Intramedullary spinal cord tumors are rare. They account for only 4–6% of all CNS tumors [3]. In this chapter, we mainly survey the neurocutaneous tumor syndrome and intramedullary spinal cord tumor associated with the three major neurofacomatosis: Neurofibromatosis type I (NF1), Neurofibromatosis type 2 (NF2) and von Hippel-Lindau syndrome (VHL). Table 12.1 lists the summary of neurocutaneous tumors and intramedullary tumors associated with all neurofacomatosis.

12.2 Neurofibromatosis Type 1

12.2.1 Epidemiology and Genetics

NF1, known as von Recklinghausen disease or peripheral neurofibromatosis, was first described by von Recklinghausen in 1882 [4]. It is the most common of the neurofacomatoses with a prevalence of 1 per 3000; it has equal sex distribution and no obvious ethnic predilection [5, 6]. NF1 is transmitted as an autosomal-dominant trait but half of patients get sporadic mutations without a family history of the disease [7]. Penetrance is nearly 100% by 8 years of age, whereas expressivity is extremely viable [8, 9].

The NF1 locus maps to chromosome 17q11.2 and consists of 57 constitutive exons spread over 350 kb of genomic deoxyribonucleic acid (DNA) [10]. Using cDNA-SSCP/HD analysis, Pros et al. identified 282 different mutations in 374 independent patients with NF1 [11]. The NF1 gene encodes for a 2818-amino-acid protein referred to as neurofibroma [12]. Neurofibromin plays a pivotal regulatory role in the Ras pathway of cellular proliferation. Loss of neurofibromin function will cause to excessive Ras activation and creating a tendency toward cell proliferation and tumor development [13]. Neurofibromin is expressed in many different cell types especially in Schwann cells and neurons [14]. Therefore, neurofibromin functions as a tumor suppressor gene with respect to neurofibroma and glioma formation [15, 16]. Recently, the mechanistic target of rapamycin (MTOR) pathway has also been implicated in NF1-related tumors [17].

12.2.2 Diagnostic Criteria and Screening

Diagnostic criteria are summarized in Table 12.2, which were outlined in an earlier National Institutes of Health (NIH) meeting (NIH Consensus Development Conference, Neurofibromatosis: Conference Statement, 1988) [18]. Two or more criteria must be present to establish the diagnosis. These criteria are extremely sensitive and specific for the disease, but genetic testing for confirmation is strongly recommended in controversial cases. However, DeBella et al. concluded that the

Table 12.1 Neurofacomatosis and Allied Tumors

Syndrome	Classic features	Associated tumor	Associated spinal cord tumor
Neurofibromatosis Type 1	Café au lait spots	Neurofibroma, Optic Glioma, Iris hamartoma	Intramedullary astrocytoma
Neurofibromatosis Type 2	Juvenile lens opacity	Vestibular Schwannoma, Meningioma, Spinal schwannoma and meningioma	Intramedullary ependymoma
Von Hippel-Lindau Disease		Retinal, cerebellar and spinal hemangioblastoma, Endolymphatic sac tumors Pheochromocytoma, Renal cell carcinoma	Intramedullary hemangioblastoma
Tuberous Sclerosis Complex	Cortical tubers, seizure, hypopigmented macules, autism, Shagreen patch	Angiofibroma, Renal angiomyolipoma, Subependymal giant cell astrocytoma, Cardiac rhabdomyoma	
Schwannomatosis		Cranial and spinal nerve schwannomas (except acoustic neuroma)	
L'hermitte-Duclos Disease	Seizure, CNS abnormalities	Cerebellar gangliocytomas	
Ataxia-Telangiectasia	Ataxia, Sclera telangiectasia CNS abnormalities	Leukemia, Lymphoma	
Li-Fraumeni Syndrome		Sarcoma, cancers of the breast, brain and adrenal glands	
Sturge-Weber Syndrome	Port-wine stain, seizure, glaucoma	Ipsilateral leptomeningeal angioma	
Maffucci's Syndrome	Hyperpigmented patches and nevi	Multiple enchondromas with secondary hemangiomas, Glioma	
Epidermal Nevus Syndrome	Seizure, CNS abnormalities	Patchy cutaneous hamartomatous lesions	
Neurocutaneous Melanosis	Pigmented cutaneous area	Leptomeningeal melanoma	
Klippel-Trenaunay-Weber Syndrome	Unilateral limb hypertrophy, Macrocephaly	Subcutaneous hemangiomas	
Incontinentia Pigmenti	Hypopigmented skin lesions, CNS abnormalities		
Cowden Disease	Seizure, CNS abnormalities	Multiple facial trichilemmomas	
Wyburn-Mason Syndrome	Retinal and cerebral arteriovenous malformation		

Table 12.2 Diagnostic Criteria for NF1

The presence of two or more of the following is diagnostic:
• ≥6 cafe´ au lait spots >5 mm in prepubertal individuals or > 15 mm in postpubertal individuals
• ≥2 neurofibromas of any type or 1 plexiform neurofibroma
• Axillary or inguinal freckling
• Optic gliomas
• ≥2 hamartomas of the iris (Lisch nodules)
• Distinctive osseous lesion (ie, sphenoid wing dysplasia or thinning of long bone cortex with or without pseudoarthrosis)
• First-degree relative with NF1

diagnosis of NF1 cannot always be made in young children using the NIH diagnostic criteria [8]. Modification of these criteria may be necessary for children under 8 years old.

The diagnostic and health supervision guidelines for patients with NF1 have been published by the Committee on Genetics of the American Academy of Pediatrics [19]. Screening magnetic resonance imaging (MRI), electroencephalogram (EEG,) and X-rays are no longer routinely recommended unless specific problems arise. Neurologic and ophthalmologic assessments, as well as blood-pressure monitoring (for pheochromocytoma and renal arterial abnormalities), are required. Behavior and development should be evaluated carefully, and formal neuropsychometric evaluation may be necessary if concerns arise. Genetic counseling and screening with targeted testing of the NF1 mutation identified in the patient should be considered in first degree relatives [18].

12.2.3 Neurocutaneous Tumor Syndromes and spinal tumors in Neurofibromatosis type 1

Symptoms within and between families can vary extremely, and signs generally develop by 10 years of age [18]. By puberty, more than 80% of NF1 patients develop neurofibromas that can be cutaneous, subcutaneous, or deep [8]. Plexiform neurofibromas can experience malignant transformation (Fig. 12.1). The incidence of optic pathway gliomas, brain stem gliomas, cerebellar gliomas, and meningiomas is increased in patients with NF1 [20]. A prospective study of NF1 cancer incidence in the United Kingdom (UK) showed NF1 carries a 2.7-fold increase in overall risk of cancer, with a cumulative risk of a malignancy at 20% by age 50 years [21].

Spinal neurofibromas: Spinal neurofibromas (Fig. 12.2) are benign tumors of the peripheral nerves, originating from the nerve sheath, and generally encasing the nerve roots as a result of an asymmetric growth pattern [22, 23]. Their common anatomical locations are intradural extramedullary, and dumbbell type. Familial

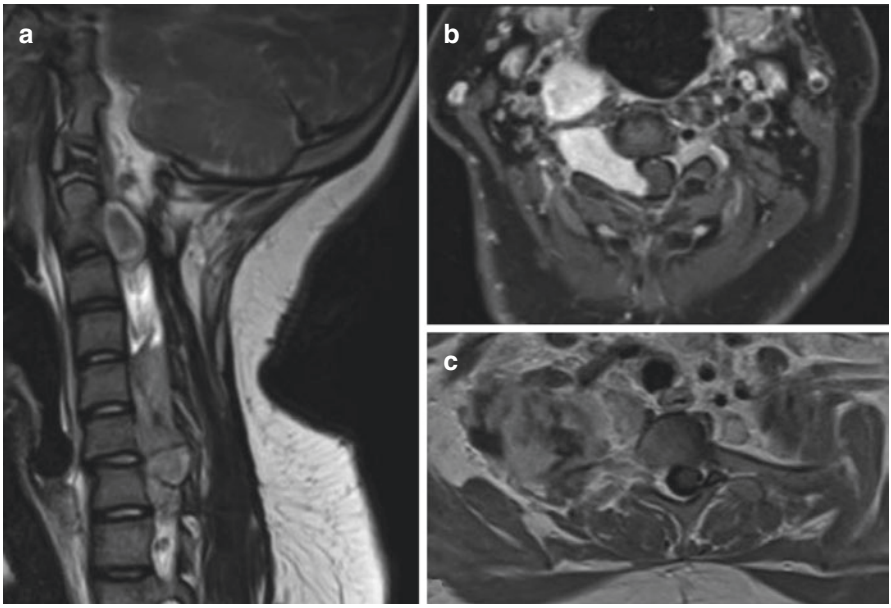

Fig. 12.1 Sagittal (**a**) and axial (**b**, **c**) MRIs of plexiform neurofibromas undergoing malignant transformation

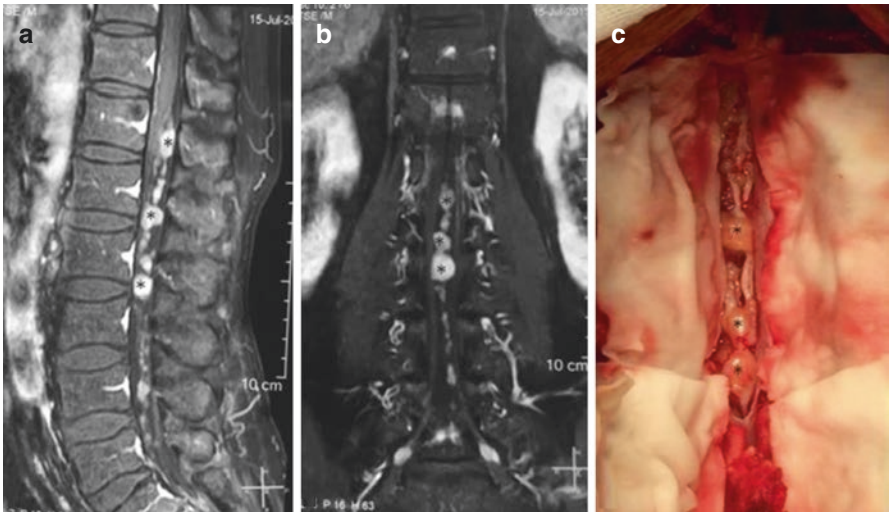

Fig. 12.2 Sagittal (**a**) and coronal (**b**) MRI with gadolinium identifies multiple lesions in the lumbar spinal canal. Intraoperative view of the neurofibromas (**c**)

spinal neurofibromatosis is an alternate form of neurofibromatosis that is classified by numerous neurofibromas symmetrically affecting the whole axial spine [24, 25]. Spinal cord compression is seldom found but can occur [23]. So far, the largest systematic study by Nguyen et al. that describes spinal MRI findings of patients with NF1 and associated symptoms demonstrates that 80% of patients with NF1 had spinal neurofibromas, with ascending frequency from 70% in patients younger than 10 years to 80% in patients aged 10–18 years to 89% in individuals older than 18 years of age [22]. Meanwhile, symptoms are reported among 60% of patients at presentation. At baseline, 34% of patients had MRI changes consistent with spinal cord compression that was most prevalent at the cervical (43%) and lumbar (40%) spine region. Some of the patients with progression of their spinal neurofibromas developed cord compression. Paraspinal plexiform neurofibromas (PNs) were present in 79% of patients, of which 88% had accompanied spinal neurofibromas. However, other reported frequency of asymptomatic spinal neurofibromas on MRI ranges from 13% in children to 40% in children and adults with NF1. The higher incidence of spinal neurofibromas as described in the study by Nguyen et al. probably results from a more severe phenotype patient cohort and its clinical trials nature.

Surgical resection is a safe and effective treatment for spinal nerve sheath tumors. Approximately 30% of patients developed a postoperative complication, most commonly new or worsening sensory deficits. Complications were more common in cervical and lumbosacral tumors but had no association with patient age, clinical presentation, symptom duration, tumor size, or tumor pathology. Intradural and dumbbell tumors were associated with higher rates of cerebrospinal fluid (CSF) leak, pseudomeningocele, and wound infection. Complications are an inevitable consequence of spinal nerve sheath tumor surgery given the intimacy of these lesions with functional neural elements. There was no difference in the use of intraoperative neuro-monitoring when comparing cases with surgical complications and those without. However, the use of neuro-monitoring was associated with a significantly higher rate of gross-total resection.

Plexiform neurofibromas: PN is another tumor type that can be found in up to 50% of patients with NF1 who undergo an MRI [26]. PNs occur along any peripheral nerve but if located in the paraspinal area, they can grow and extend laterally along the spinal nerves with or without involvement of the neural foramina [27, 28].

12.2.4 Spinal Cord Tumor in Neurofibromatosis Type 1

Gliomas are often associated with NF1, most being low-grade. They mainly involve the optic pathways—especially in children [29, 30]—and only 1% are found in the spinal cord [18]. The incidence of intramedullary gliomas in NF1 patients may be far more than their sporadic counterparts according to similar works [31]. So far, there are several case series reporting intramedullary gliomas in NF1 patients. Lee et al. reported 3 intramedullary astrocytomas with NFI (1 low grade astrocytoma and 2 anaplastic astrocytomas) [32]. On pathologic

examination, most are pilocytic astrocytomas (PAs) World Health Organization (WHO) Grade I [33]. However, patients with NF1 may also develop diffusely infiltrating astrocytomas (DAs) (WHO grades II–IV), particularly with an onset later in life [34]. Rodriguez et al. included 100 patients with NF1: there were four intramedullary astrocytoma cases, two PAs, and two low-grade astrocytoma, subtype indeterminate (LGSI) [35]. The prognoses of the PA and LGSI gliomas overall were generally favorable.

Pilomyxoid Astrocytoma (PMAs) usually occur in young children and are frequently located in the hypothalamic/chiasmatic region. They are seldom found in the spinal cord. Spinal PMAs affect pediatric age group more than adult patients with a female preponderance, mostly the cervical and thoracic spinal regions. Most of the lesions are intramedullary with only one case report being an intradural extramedullary lesion [36]. The association of intramedullary PMA with NF1 is even less common. Dunn-Pirio et al. reported so far the first case of a spinal cord PMA in an adult patient with NF1 [37]. The patient underwent a partial surgical resection of the spinal cord tumor followed by adjuvant carboplatin 560 mg/m^2 every 4 weeks. Radiation was avoided due to risks associated with NF 1. Single agent carboplatin was effective and well-tolerated.

Ependymomas have been reported with a higher incidence in NF2 rather than in NF1 and are preferentially located in the spinal cord [38]. Ependymoma with NF1 has rarely been reported, not to mention spinal cord ependymoma with NF1. To date, only four cases of ependymoma with NF1 have been reported in English literature, and only 2 of them were spinal cord ependymoma with NF1: thoracic cord ependymoma (WHO II) in a 5-year-old boy and 1 cervical spinal cord ependymoma in a 49-year-old female [39, 40]. There were no differences found between ependymomas in NF1 patients and those found in their sporadic counterparts in terms of clinical course. Therefore, the management modality is similar with total surgical resection remaining the treatment of choice whenever possible. Moreover, as NF1 is a multisystem disease, the cooperation between multidisciplinary clinicians and scientists is essential.

12.3 Neurofibromatosis Type 2

12.3.1 Epidemiology and Genetics

NF2 is significantly less common than NF1 with an incidence of 1 per 33,000 [41]. Although the disease is classified as "neurofibromatosis," neurofibromas are relative infrequent. Actually, NF2 is a unique clinical and pathological entity, entirely distinct both phenotypically and genotypically from NF1. The hallmark of NF2 is the development of bilateral vestibular schwannomas (VS). It is an autosomal dominant inheritance pattern with nearly 100% penetrance, although 50% of patients have sporadic mutations [42]. Affected patients with no gender predilection typically present in late adolescence; those who present in childhood often have atypical and more severe clinical manifestations [43].

The NF2 gene maps to the long arm of chromosome 22 (22q11.1-22q13.1), which encodes a 595-amino-acid protein referred to as merlin or schwannomin [44]. Merlin is a cytoskeletal protein that appears to play a role in the control of cell growth, affecting signaling pathways connected with contact inhibition and tumor suppression [45]. Merlin is widely expressed in Schwann cells, arachnoid cells, and the ocular lens. The gene product is considered to be a tumor suppressor and regulator of Schwann cell and arachnoidal cell proliferation [46]. Merlin functions as a tumor suppressor gene with respect to schwannoma and meningioma formation [42]. Some genotype-phenotype correlations have been identified with NF2. Missense or splicing mutations tend to predict milder disease than do mutations that lead to protein truncation [47]. Somatic mosaicism for NF2 gene mutation may produce localized disease severity [42]. Therefore, genetic testing for NF2 is valuable in some cases for diagnostic purposes.

12.3.2 Diagnostic Criteria and Screening

There are multiple diagnostic criteria for NF2. The most recent and sensitive criteria to be used are Baser criteria or Manchester criteria, which have been shown to have a sensitivity of 79% and a specificity of 100% [48]. The criteria are shown in Table 12.3.

Accepted criteria for NF2 screening include having a first-degree relative with NF2, the presence of VS before the age of 30 years, the presence of meningioma before the age of 20 years, the presence of cutaneous schwannomas, and the

Table 12.3 Diagnostic Criteria for NF2 (Manchester Criteria)

The presence of two or more of the following is diagnostic:
Bilateral vestibular schwannomas
• First-degree family relative with NF2 and unilateral vestibular schwannoma or any two of the following: – Meningioma – Schwannoma – Glioma – Neurofibroma – Posterior subcapsular lenticular opacity
• Unilateral vestibular schwannoma and any two of the following: – Meningioma – Schwannoma – Glioma – Neurofibroma – Posterior subcapsular lenticular opacity
• Two or more meningiomas and unilateral vestibular schwannoma, or any two of the following: – Schwannoma – Glioma – Neurofibroma – Posterior subcapsular lenticular opacity

presence of multiple spinal tumors [49]. The NF2 screening includes detailed personal and family history, cutaneous and ocular examination, and MRI of the neural axis. For patients with a confirmed diagnosis of NF2, regular following should consist of annual hearing test, brainstem auditory evoked potential response, visual exam, and dermatologic exam. MRI of neural axis should begin at age 10, repeated every 2 years up to age 20, and then repeated every 3-to-5 years afterward [42]. Closer follow-up is required for patients in whom lesions are identified.

12.3.3 Neurocutaneous Tumor Syndromes and spinal tumors in Neurofibromatosis type 2

Patients with NF2 harbor a wide spectrum of nervous system tumors, including cranial (vestibular, facial, and trigeminal) and peripheral nerve schwannomas, as well as meningiomas and intramedullary ependymomas [50].

Vestibular Schwannoma. VS or acoustic neuromas are benign tumors that are pathognomonic for NF2 when present bilaterally. Bilateral VSs are seen in up to 95% of patients with NF2 (Fig. 12.3) [51]. VS cause the typical symptoms of hearing loss, tinnitus, and vestibular dysfunction. Hydrocephalus and brainstem dysfunction can result from mass effect in severe cases. Management options include observation, surgical resection, radiosurgery, or chemotherapy [52]. The decision to treat requires a consideration of the patient's age, medical condition, hearing status, neurological function, and size of tumor. Surgical timing presents challenges to neurosurgeons. Symptomatic and large tumors usually are treated surgically; however, the treatment of smaller bilateral tumors is less clear due to unpredictable tumor growth. Stereotactic radiosurgery also has been applied for local control [53]. Surgical approach and planning are required to take into account the likelihood of

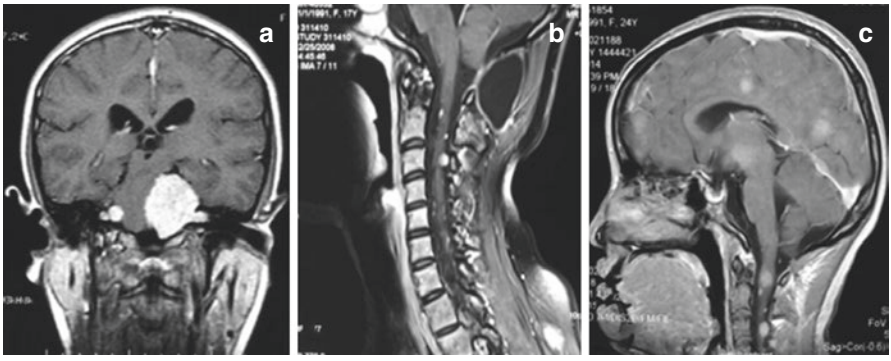

Fig. 12.3 The cranial (**a**) and cervical spinal cord (**b**) MRI of a 17-year-old girl with NF2, which clearly show bilateral vestibular schwannomas and multiple spinal schwannomas, respectively. Image from 7 years later (**c**), which shows multiple intracranial meningiomas and progress of the spinal schwannomas

preservation of hearing and whether the tumors are bilateral. In addition, VSs in NF2 are often multifocal and may grow to involve facial nerve fibers [42]. Therefore, microsurgical resection is associated with significant tumor recurrence in NF2 patients, as well as with high risk of hearing loss and facial dysfunction. Radiosurgery is a valuable alternative treatment offering tumor control or delaying the need for surgery; however, there is a price in terms of hearing function. These results may compare favorably with the progressive deafness associated with the natural history of the disease, or with surgery [53]. Targeted chemotherapy is currently being explored but the data are still lacking.

Intracranial meningioma. Meningiomas are the second-most common tumor associated with NF2. Intracranial meningiomas (Fig. 12.3) are observed in 45–58% of people with NF2, where spinal meningiomas are found in 20% of affected patients. Intracranial meningiomas tend to be multiple in number and often develop at a younger age than sporadic patient [47]. In the pediatric age group, meningiomas are often the first sign of NF2 [54]. Malis reported a series of 41 NF2 patients with long-term follow-up [55]. His series highlights the clinical burden of meningiomas in NF2. Most of the deaths in patients from NF2-related disease was attributable to overwhelmingly rapid growth of multiple meningiomas, not vestibular schwannomas [55]. Clinical symptoms from meningiomas are usually related to their size and location. Surgery remains the mainstay of treatment for growing and/or symptomatic meningiomas in NF2. Usually most meningiomas can be safely and fully resected. However, meningiomas involving the optic sheath and skull base are associated with higher rates of surgical sequela [56]. In situations where there is residual tumor from a partial resection, stereotactic radiosurgery has been used for local control [57]. At present, there are no defined medical treatments for NF2-associated meningiomas, and clinical studies using molecularly targeted drug therapies are currently being investigated [58].

Spinal schwannoma and spinal meningioma. Research has identified that NF2 patients have a predilection for multiple spinal nerve sheath schwannomas and spinal meningioma [59]. Spinal schwannomas are intradural, extramedullary neoplasms, arising from dorsal nerve roots (Fig. 12.3). In Malis's series treated over a 30-year period, he found that tumors of the spine were nearly as common as VS on MRI [55]. Among 41 NF2 patients, all of whom were initially referred due to bilateral VS, a total 99 extra-medullary spinal tumors were treated surgically. Of these, 58 were spinal schwannomas and 41 were meningiomas [55]. Previous reports have indicated that symptomatic spinal schwannomas in NF2 are likely to grow faster, more likely infiltrating nerve roots and progressing to serious deficits sooner [60]. Li et al. found that patients with NF2 were the youngest at the first spinal schwannoma operation and had the shortest duration of preoperative symptoms [61]. These intradural-extramedullary NF2 schwannomas did not have a preferred spinal location and only a slight predominance in the lumbar area [62]. Small cauda equina nodular schwannomas were common in NF2 (86.9%). They were usually small in size and showed a relatively stable behavior over time [63]. On the contrary, large extramedullary tumors (>5 mm) in NF2 were prone to progression. If small cauda equina nodules progressed into larger tumors, they would be difficult to treat

surgically. Meanwhile, most patients with NF2 tend to have significant problems related to bilateral vestibular schwannomas as well as other intracranial neoplasms. In such cases, a conservative approach is usually adopted towards these small spinal tumors. In addition, it was much more difficult to totally resect tumors in NF2 patients with higher rate of neurological deficits, and tumor recurrence [60].

For patients with NF2, approximately 10% of meningiomas requiring resection are located in the spine [64]. Spinal meningiomas is more prevalent in the female and elderly populations [65]. Early surgery remains the main treatment of growing and/or symptomatic meningiomas in NF2.

12.3.4 Spinal Cord Tumor in Neurofibromatosis Type 2

More than 75% of intramedullary spinal cord tumors associated with NF2 are ependymomas. Intra-medullary ependymomas are present in 33–53% of patients with NF2. Cervical cord and cervicomedullary junction are the most common location of involvement (Fig. 12.4) [55]. They are usually multiple and present with typical appearance of a "string of pearls" in neuroimaging, being hyperintense on T2, hypointense to isointense on T1, and mostly enhancing after contrast [62]. Clinical

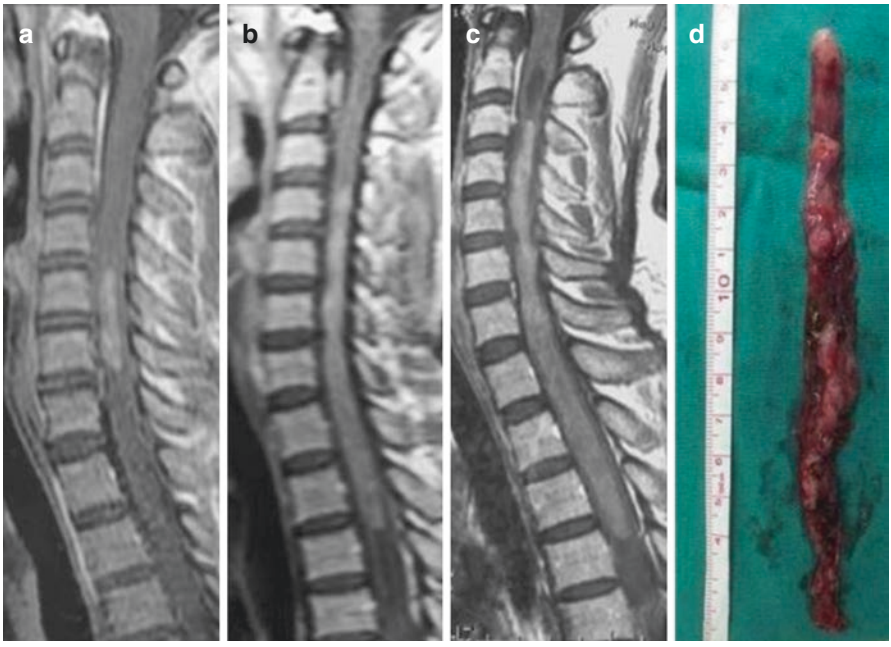

Fig. 12.4 The progress of a multiple-segment cervical intramedullary ependymoma with NF2. The spine MRI were taken on the year of 2005 (**a**), 2008 (**b**), and 2009 (**c**). The lesion was removed en bloc in 2009 (**d**)

signs and symptoms are variable and depend on the size and anatomic location of the tumor. In contrast to sporadic tumors, the majority of NF2-associated spinal tumors are asymptomatic. Accordingly, fewer than 20% of patients with these tumors are symptomatic. The most common symptoms of the patients with intramedullary spinal cord tumors are back pain, weakness, or sensory disturbances [66]. The management of NF2-associated ependymomas has not been firmly established. Although observation is often used to follow asymptomatic tumors, surgical resections are frequently effective and curative. Kalamarides et al. retrospectively reviewed two NF2 centers: Manchester, UK and Paris/Lille, France [67]. They found a significantly improved outcome in patients cared for in specialty centers. Spinal ependymomas produce morbidity. Surgery can prevent or improve this in selected cases but can itself result in morbidity. Surgery should be considered in growing/symptomatic ependymomas, particularly in the absence of overwhelming tumor load where bevacizumab is the preferred option [67].

The timing of the resection is best determined by detailed neurologic surveillance to assess for early onset of symptoms [68]. Because most NF2-associated spinal cord ependymomas are grade II tumors, gross total resection is often the curative (Fig. 12.4), with radiation therapy reserved for recurrent or residual tumors. WHO grade I myxopapillary ependymoma has also been reported in patients with NF2, and these tumors are usually treated with surgery alone [69]. Given that NF2 is a genetic tumor syndrome, there are concerns about the extra risks of radiation therapy in this patient cohort. For this reason, chemotherapy is the desirable choice for the patients with recurrent and unresectable tumors. The evaluation of molecularly targeted therapies for these tumors is currently ongoing. Small series of patients treated with bevacizumab have reported improvement with NF2-associated ependymomas [70].

12.4 Von Hippel-Lindau Disease

12.4.1 Epidemiology and Genetics

Von Hippel-Lindau (VHL) disease was attributed to Eugen von Hippel's descriptions of the retinal angiomatosis in 1904 and Arvid Lindau's descriptions of the hemangioma in the cerebellum and spinal cord in 1927 [71, 72]. The term von Hippel-Lindau disease was first used in 1936 and has been in common use since the 1970s. VHL is an autosomal dominant disease found in approximately 1 per 36,000 people [73]. It is familial in around 80% of cases, and the penetrance rate is up to 90% [74]. VHL is characterized by hemangioblastomas, usually involving retina, cerebellum, and spinal cord. It is also associated with non-CNS lesions, such as pancreatic neuroendocrine tumors, pheochromocytomas, renal cell carcinomas, endolymphatic sac tumors, and cystic tumors in multiple organs. Although VHL is grouped in the neurofacomatosis or neurocutaneous syndromes, it does not typically involve cutaneous manifestations, in contrast with other phakomatoses.

VHL disease as an autosomal dominant inheritance pattern is caused by loss of the tumor suppressor gene located at 3p25–26 [75]. The VHL gene encodes for a protein referred to as pVHL, which coordinates multiple aspect of the cell cycle and facilitates angiogenesis through regulatory control over hypoxia-inducible factor-1 alpha (HIF-1α) and hypoxia-inducible factor-2 alpha (HIF-2α) [76]. Dysfunction or absence of the pVHL leads to constitutive overexpression of HIF-1α and HIF-2α, which leads to increased level of vascular endothelial growth factor (VEGF) and other pro-angiogenic signals [76, 77]. These insults combine to cause the spectrum of tumors found in VHL disease.

12.4.2 Diagnostic Criteria and Screening

Clinical diagnostic criteria of VHL, summarized in Table 12.4, are used for referral to specialists for genetic counseling and testing. For individuals who have a family history of VHL, detection of only one type of tumor specific to VHL may be sufficient to make a diagnosis. For those patients without a family history of the disease, at least two types of VHL tumors should be identified to confirm a diagnosis [78, 79]. The definite diagnosis of VHL is typically confirmed by genetic testing to identify a germline mutation of the VHL gene.

The loss of vision is one of the more common presentations with VHL due to retinal hemangioblastoma (angiomas). Patients with cerebellar hemangioblastoma may present with ataxia, dysmetria, and coordination difficulties. Patients with spinal cord hemangioblastomas present with motor or sensory problems based on the tumor's location. Patients with pheochromocytomas can present with paroxysmal or sustained hypertension. Hearing loss is often associated with endolymphatic sac tumors.

Screening protocols have been developed for early diagnosis of typical lesions. The protocol includes annual ophthalmic examinations from early childhood, MRI of the head every 12–36 months from adolescence onward, ultrasound (or MRI) of the abdomen every 12 months, beginning at the age of 16 years. Annual blood pressure monitoring and 24-h urine studies for catecholamine metabolites should be considered in high-risk families [80]. Patients also need regular evaluations for

Table 12.4 Diagnostic Criteria for VHL

Without VHL family history: Present with two or more of the following characteristic lesions
With VHL family history: Present with one or more of the following characteristic lesions
• Spinal or cerebellar hemangioblastoma
• Retinal angioma
• Adrenal or extra-adrenal pheochromocytoma
• Renal cell carcinoma
• Multiple renal and pancreatic cyst

neurologic symptoms, visual impairment, and hearing loss. As a result, all patients with VHL require lifelong monitoring for associated tumors.

12.4.3 Neurocutaneous Tumor Syndromes in von Hippel–Lindau disease

The disease is classified into type 1, the result of a nonsense mutation or deletion, and type 2, the result of a missense mutation. Based on adrenal involvement and risk of pheochromocytoma, type 2 carries risk of pheochromocytoma and type 1 does not [81]. Type 1 typically carries high risk for renal involvement, high risk for CNS hemangioblastomas, and low risk for the development of pheochromocytomas [82].

Hemangioblastomas are the lesions most frequently observed in VHL disease. Sporadic hemangioblastomas tend to be solitary in older patients, whereas VHL disease-related hemangioblastomas tend to be multiple in young adults with mean age of 29 years [73]. Woodward et al. examined 188 patients with solitary hemangioblastoma and without VHL family history [83]. Of these, 5% were found to have germline mutations in the VHL gene, and another 5% ultimately progress to additional VHL-related lesions. VHL-related hemangioblastomas have been reported to harbor germline mutation (94%) and loss of heterozygosity (62%) at the VHL gene. Over 150 different germline mutations have been identified [84, 85].

Hemangioblastomas in retina and central nerve system. Retinal hemangioblastoma is one of the earliest manifestations of the disease, and it has been reported in early childhood [86, 87]. More than 50% of patients with VHL disease have retinal hemangioblastoma. The retinal lesion has the appearance of aneurysmal dilatation which will manifest to tortuous vessels and lead to retinal detachment with progressive vision loss [88]. Other VHL-associated hemangioblastomas are circumscribed vascular tumors usually found in posterior fossa (80%) and spinal cord (20%) and rarely in the cerebral hemispheres. These tumors usually are found in patients after the third decade of life. They are benign but become symptomatic due to mass effect caused by adjacent cyst progression or tumor hemorrhage. 80% of patients with hemangiomas in medulla or spinal cord are associated with syringomyelia [89].

VHL disease is suggested to account for approximately a third of patients with CNS hemangioblastomas. On the other hand, overall CNS hemangioblastomas occur in 60–80% of VHL patients [73, 90]. The growth of VHL associated hemangioblastomas in central nerve system is variable. Some tumors tend to grow rapidly and others remain quiescent even in the same patient. Surgery for hemangioblastomas in VHL disease in indicated for patients who become symptomatic. Radiological progression without symptoms should not be an absolute indication for surgical resection [91]. Radiation therapy, in particular radiosurgery, can provide sustained control in patients with multiple or surgically inaccessible solid hemangioblastomas. Radiosurgery does not control the growth of associated cysts [92].

Chemotherapy to date has not yielded good tumor control rates. Targeted therapy, such as vascular endothelial growth factor (VEGF) inhibitors, and gene replacement therapy are under investigation.

Renal cell carcinoma and pheochromocytoma in VHL. Renal cell carcinoma (RCC) is the most common malignancy in VHL patients occurring in 24–45% of cases. In contrast to sporadic RCC, VHL-related RCC tends to be multifocal, bilateral and highly recurrent, although its metastatic potential is low. It has a clear cell appearance and is an important cause of death in VHL patients [90, 93]. Once identified, surgery is the treatment of choice with partial nephrectomy or radio frequency ablation when there is limited tumor involvement. Total nephrectomy or even bilateral nephrectomy is reserved for those patients with extensive tumor involvement, recognizing that renal dialysis is possibly required after surgery to sustain life [94]. Although the risk of RCC varies in different subtypes of VHL disease, in the most common forms the lifetime risk is 70% with 40 years of age being the mean age at clinical diagnosis.

Pheochromocytoma is a rare tumor and is present in about 0.2% of patients presenting with hypertension [95]. The majority of pheochromocytomas are sporadic; however, 15–20% are inherited as a part of the familial disorder. Familial pheochromocytoma are associated with von Hippel-Lindau (VHL) disease and multiple endocrine neoplasia II (MEN II) [96]. VHL disease accounts for 50% of patients with apparently isolated familial pheochromocytoma and 11% of patients with an apparently sporadic pheochromocytoma [93]. Mean age at diagnosis of pheochromocytoma in VHL disease is around 30 years. Both adrenal and extra-adrenal pheochromocytoma can occur in VHL disease. Pheochromocytoma differ from hemangioblastoma and clear cell renal cell carcinoma in that they are not richly vascularized and they are involved in several other tumor syndromes [93]. Genetic testing for VHL gene and radiological screening tests may be considered to establish early diagnosis in other members of familial pheochromocytoma [97].

12.4.4 Spinal Cord Tumor in von Hippel-Lindau disease

VHL disease accounts for approximately 10% of patients with an intramedullary spinal hemangioblastoma. On the other hand, up to 25% of patients with intramedullary hemangioblastomas will have evidence of VHL [98]. The tumor tends to occur in dorsal or dorsolateral parts of the spinal cord with pial attachment. They show a cervical predominance when they occur in association with VHL and typically present with progressive sensory deficits or proprioceptive deficits. Patients with VHL tend to become symptomatic at an earlier age [99].

MRI is the diagnostic test of choice for intramedullary hemangiomas (Fig. 12.5). MRI findings demonstrate “flow-void” phenomenon that reflects prominent feeding arteries or draining veins. Heterogeneous enhancement pattern also represents a vascular tumor parenchyma, comprising closely packed blood vessels interspersed

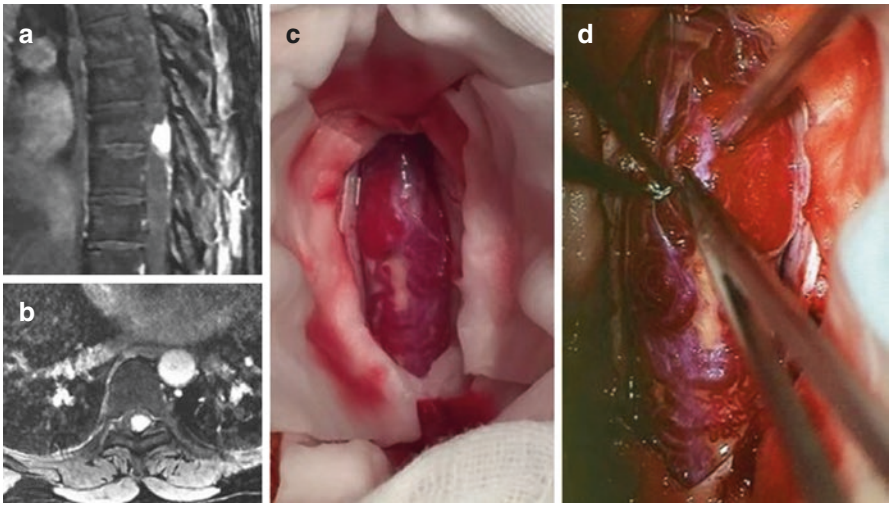

Fig. 12.5 Coronal (**a**) and axial (**b**) MRI with gadolinium identifying intramedullary hemangioblastomas of the thoracic spinal cord. Intraoperative view of the hemangioblastomas (**c**, **d**)

with stromal cells [100]. Regardless of tumor size, they are often associated with significant edema and syrinx formation [101].

Microsurgical resection is the primary treatment for intramedullary hemangioblastomas of the spinal cord (Fig. 12.5). The indications for surgical resection in the setting of sporadically occurring spinal cord hemangioblastomas differ from those occurring in VHL patients. Resection is necessary in patients with sporadic tumors both for diagnosis and to ameliorate symptoms. In the VHL patients with intramedullary hemangioblastomas, the surgical indications are based on the presence of symptoms and signs. Therefore, asymptomatic tumors may be followed clinically/radiographically and should be resected only when they become symptomatic. Preoperative spinal angiography can be of value prior to surgery in helping to determine the location and the nature of the feeding artery and delineate vascular supply [102]. Preoperative embolization may serve as an adjunct to surgery for those associated with arteriovenous shunt, for cord dysfunction related to venous congestion, or in cases harboring the risk of torrential intraoperative bleeding [103].

Clinical series have demonstrated that these lesions can be resected safely with preoperative neurological function serving as the best predictor of neurological outcome after surgery. Anatomically, hemangioblastomas arise from the pial layer and are considered juxta-medullary, but can exhibit an encapsulated component [104]. Surgical resection is complicated by the risk by of bleeding and local ischemia during surgery [105]. Complete resection is possible with the use of microsurgical techniques [106]. Targeted therapies, such as SU5416 (VEGF inhibitor), thalidomide, and bevacizumab (pan-VEGF inhibitor), have been reported to stabilize the disease in small case series [107–109].

12.5 Conclusion

Our understanding of VHL has come a long way since Van Der Hoeve described these three disorders (neurofibromatosis, tuberous sclerosis, and von Hippel-Lindau syndrome) according to their ophthalmologic manifestations in 1923, and the later discovery of the NF1, NF2, and VHL genes in the early 1990s. Now, advanced techniques of microsurgical technique and stereotactic radiosurgery set a high bar for tumor treatment. New targeted therapies are showing promise for CNS tumors arising in this population of at-risk individuals. However, CNS tumors, including spinal cord tumors associated with the neurofacomatosis, comprise a group of tumors that are histologically benign, but have significant clinical consequences. Multidisciplinary management with early diagnosis is the mainstay of management. Hopefully a more advanced understanding of the molecular mechanisms will translate to new targeted therapies or perhaps gene replacement therapies which will revolutionize the outcomes in this group of patients.

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Spinal Cord Astrocytomas

13

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13.1 Introduction

Astrocytomas are the most common intramedullary tumors in children and occur secondary to ependymomas in adults [1–3]. The great majority of patients with astrocytomas have solitary tumors [3]. However, intramedullary astrocytomas may be encountered together with other spinal tumors in patients with neurofibromatosis type 1 (NF-1) or type 2 (NF-2) [3]. Astrocytomas in adults carry a better prognosis then their pediatric counterparts [4]. They are often infiltrating tumors and radical resection is not always possible [3]. For the purpose of this chapter, we concentrated mostly on low-grade astrocytomas in adults.

Spinal cord astrocytomas have different biomarkers than supratentorial astrocytomas. The 2016 World Health Organization (WHO) classification of tumors of the central nervous system introduced a novel classification for astrocytomas. One characteristic of astrocytomas is a major restructuring of diffuse gliomas with incorporation of genetically defined entities [5, 6]. In the new classification, the diffuse gliomas include WHO grade II and grade III astrocytic tumors, grade II and III oligodendrogliomas, grade IV glioblastomas, as well as the related diffuse gliomas of childhood. WHO grade II diffuse astrocytomas and WHO grade III anaplastic astrocytomas are now each divided into isocitrate dehydrogenase (IDH)-mutant, IDH-wildtype and not otherwise specified (NOS) categories [5].

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This classification leaves the kinds of astrocytomas that have a more circumscribed growth pattern, and lack IDH gene family alterations and frequently BRAF alterations (pilocytic astrocytoma, pleomorphic xanthoastrocytoma) or TSC1/TSC2 mutations (subependymal giant cell astrocytoma) distinct from the diffuse gliomas [5].

13.2 Epidemiology

Intramedullary spinal cord astrocytomas account for 6–8% of all primary spinal cord tumors [7–11]. Low-grade histologic findings, which include diffuse and pilocytic astrocytomas, are more common (75–90%) than high grade findings, such as anaplastic astrocytomas and glioblastoma [7–11]. Patients present at an average age of 29 ± 18 years with an equal age distribution spanning from 1 week to 69 years [3]. According to the literature, the average patient history can last from 13 to 30 months [3], with a considerably shorter history for malignant astrocytomas compared with benign astrocytomas.

13.3 Molecular Biology and Biomarkers

Astrocytomas arise from glial cell predecessors that infiltrate the spinal cord. These tumors can be divided in subtypes following the new 2016 WHO grading scale: Grade I gliomas (pilocytic astrocytoma and subependymal giant cell astrocytoma), and diffuse astrocytomas (Grade II and Grade III [anaplastic astrocytoma] and Grade IV [glioblastoma multiforme] with their distinct subtypes) [5, 6] The term "low-grade" Astrocytomas is usually reserved for WHO I and II tumors.

Spinal cord diffuse astrocytomas (WHO Grades II and III) are known not to harbor IDH1/2 mutations as do many of their supratentorial counterparts, which suggests mIDH1-IHC may only rarely be of diagnostic help in the context of small biopsies from infratentorial and spinal cord tumors [12]. An H3F3A K27 mutation (histone K27 M-H3.3) was demonstrated in patients with pediatric and adult spinal cord astrocytomas [12, 13].

Spinal pilocytic astrocytomas constitute 90% of intramedullary spinal cord tumors in patients younger than 10 years and 60% of those in adolescent patients [14]. In the spinal cord, BRAF–KIAA1549 fusion genes are common in pilocytic astrocytomas [15]. Deletion of the tumor-suppressor gene cyclin-dependent kinase inhibitor 2A (CDKN2A, also known as p16) was shown as to be a common mutation in pilocytic astrocytomas with loss of heterozygosity (LOH) at 9p21 (which encompasses CDKN2A), or at 10q23 (which encompasses the phosphatase and tensin homologue gene) in 31.6% and 50.0% of pilocytic astrocytomas, respectively [16]. Further genes of interest in the molecular biology of spinal cord astrocytomas are CDKN2A, H3F3A (identified as epigenetic marker of midline or spinal GBM), NF-1, TP-53, ATR-X and PTEN [17].

13.4 Symptoms

Symptoms of astrocytomas of the spinal cord in adults are dependent on the location of the lesion, tumor growth pattern, tumor volume, and histological grade where low-grade lesions have longer history. Most common symptoms of intramedullary tumors are pain, gait ataxia, motor weakness, sensory deficits, dysesthesias, and sphincter problems [2, 4, 9, 18–26]. With malignant tumors, many patients complain about pain, gait ataxia, or motor weakness immediately [3]. A comparison of benign and malignant tumors revealed no significant differences in the clinical picture apart from the considerably shorter history for malignant tumors [3]. Sensory deficits showed negative correlation with survival [27], perhaps because these are less likely to prompt patients to seek medical care, compared with motor deficits, potentially delaying diagnosis and treatment and resulting in worse outcomes.

13.5 Diagnosis

Magnetic resonance imaging (MRI) of the spine with and without gadolinium in axial, coronal, and sagittal projections reveals precise spinal level with the upper and lower border of the tumor, demarcation toward the normal cord, and the orientation of the tumor within the cord, as well as the differentiation between solid tumor and the cyst and syrinx. The resectability of an intramedullary tumor cannot be always predicted by MRI [3]. The extension of the lesion on the sagittal plan calculated on preoperative MRI was reported to be the only predictive factor associated with the immediate postoperative outcome and the short-term follow-up [26]. Presence and pattern of contract enhancement uptake may differentiate between malignant and benign lesions [3]. If a recurrent tumor has to be operated on, functional X-ray may be helpful to evaluate for possible spinal instability, resulting from the previous operation. Furthermore, a computed tomography (CT) scan with bone window, including sagittal and coronal reconstruction, may be helpful to determine exposure of the “healthy virgin” dura, as it demonstrates bony landmarks for the dissection of epidural scar tissue [3].

Astrocytomas often take up contrast inhomogeneously on T1-weighted images. Cysts accompany these tumors less often—42.5% in one series [3]. On axial scans, astrocytomas are often eccentric and may transgress the pia mater to grow exophytically. Astrocytomas may torque the spinal cord and infiltrate spinal nerve roots. Some astrocytomas do not take up gadolinium at all. To determine the exact extension of an astrocytoma, T2-weighted images may be extremely helpful as they tend to show a better demarcation toward normal cord tissue than do T1-weighted images [3]. Specifically, astrocytomas tend to have slightly fewer well-defined margins and are more likely to be eccentrically located within the spinal cord. Lesions on the spinal cord appear as isointense or hypointense when viewed on Tl-weighted imaging, and as hyperintense on T2-weighted imaging; these lesions can be enhanced with contrast despite their low histological grade [7].

Cysts usually accompany high-grade astrocytomas [10]. In contrast to this, syrinx is more specific for low-grade astrocytomas. This could be due to the fact that low-grade tumors have fewer infiltrates than high-grade tumors, resulting in a greater impact on cerebrospinal fluid (CSF) flow [10]. Presence of syrinx and cyst has also been viewed as positive prognostic parameter by some authors [19, 21, 22, 28, 29].

Zhao et al. divided spinal cord astrocytomas according to axial diffusion tensor tractography (DTT) in 2 types [30]: Type I (infiltrative; stage IA with infiltration and stage IB with destruction) and Type II (with displacement; with cysts). Axial diffusion tensor tractography (DTT) showed reliable prediction of resectability in patients with cervical spinal cord astrocytomas with type II tumors being gross totally resected [30].

13.6 Treatment

For treating low-grade primary spinal cord gliomas, gross total resection is considered the best treatment and has an excellent local control rate [3, 31]. The "ideal" goal of treatment should be radical gross total resection of tumor while preserving and improving neurological function to normal. Figures 13.1, 13.2, 13.3, 13.4 and 13.5 show clinical examples of patients with low-grade astrocytomas treated by the senior author (KIA) with radical resection and improved and resolved neurological deficit. There is currently no gold standard treatment for malignant primary spinal cord glioma [10, 20, 32].

Table 13.1 summarizes the available literature on surgically treated spinal cord astrocytomas in adults (1992–2017). We included all studies reporting spinal cord astrocytomas with significant numbers of cases in the series (n > 20) and/or all studies with intramedullary spinal cord tumors that had a significant number of

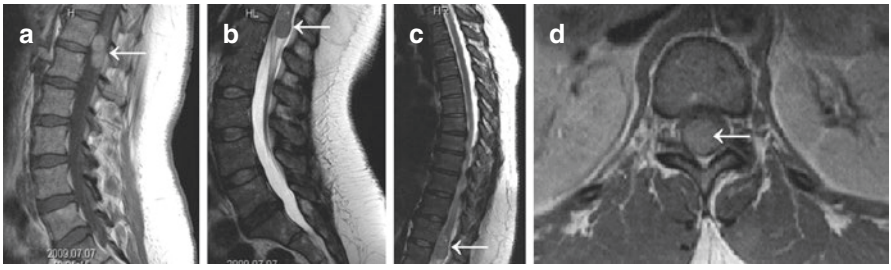

Fig. 13.1 Imaging of a 45-year-old female patient with severe low back pain, weakness of lower extremities, and perineal numbness. MRI of the total spine with and without contrast showed intramedullary lesion in T12–L1. (**a**) Sagittal T1-weighted post-contrast MRI of the lumbar spine shows well-demarcated homogenously enhanced intramedullary lesion (arrow). (**b**) Sagittal T2-weighted MRI of the lumbar spine. (**c**) Sagittal T2-weighted MRI of the lumbar and thoracic spine. (**d**) Axial post-contrast T1-weighted MRI showing the intramedullary tumor at T12. The lesion was resected and the pathohistological diagnosis showed the diagnosis of anaplastic astrocytoma (Grade III)

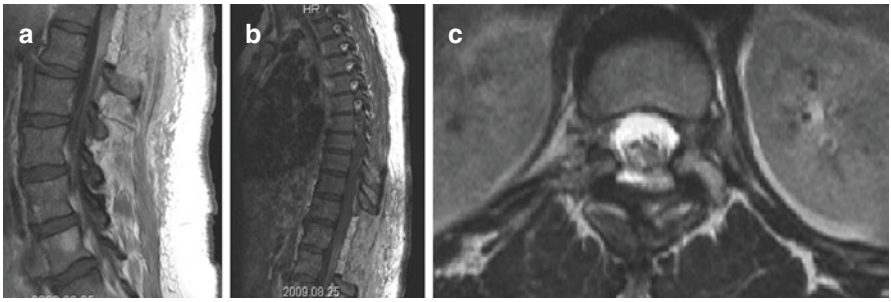

Fig. 13.2 Postoperative MRI of the spine with and without contrast showing the complete lesion resection. (**a**) T1-weighted post-contrast sagittal MRI of the lumbar spine. (**b**) T1-weighted post-contrast sagittal MRI of the thoracic spine. (**c**) T2-weighted axial MRI of the resection cavity at T12

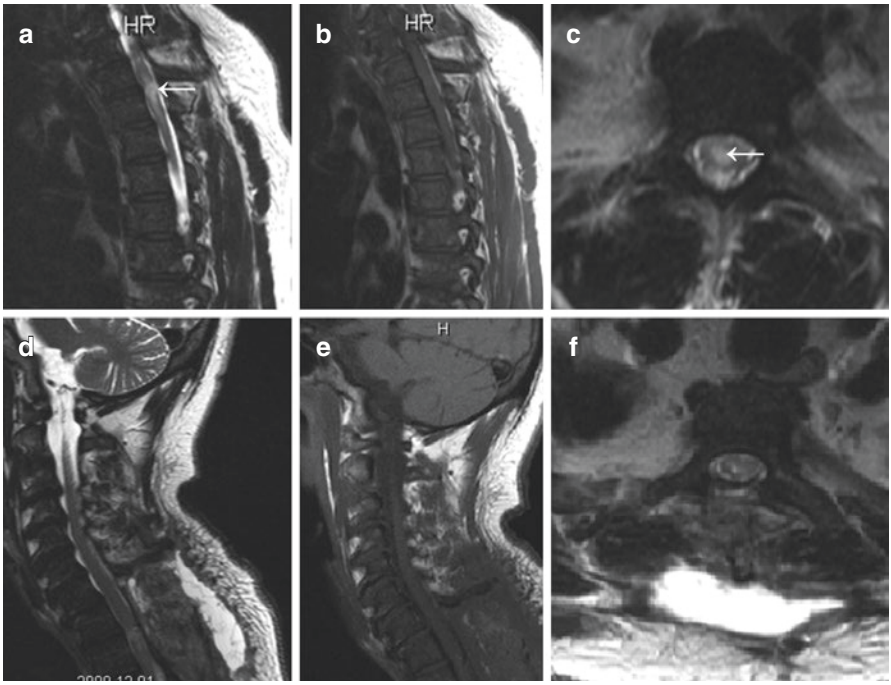

Fig. 13.3 Imaging of a 58-year-old male patient with history of weakness of lower extremities and sensory level at T1. MRI of the total spine with and without contrast showed intramedullary lesion in T1–T2 (arrow). (**a**) Sagittal T2-weighted MRI of the thoracic spine. (**b**) Sagittal post-contrast T1-weighted MRI of the thoracic spine. (**c**) Axial T2-weighted MRI of the intramedullary lesion at T1. The lesion was resected and the pathohistological diagnosis showed the diagnosis of low grade astrocytoma. (**d**) Sagittal T2-weighted MRI showing complete resection of the tumor. (**e**) Sagittal post-contrast T1-weighted MRI of the cervicothoracic spine. (**f**) Axial T2-weighted MRI showing the resection cavity

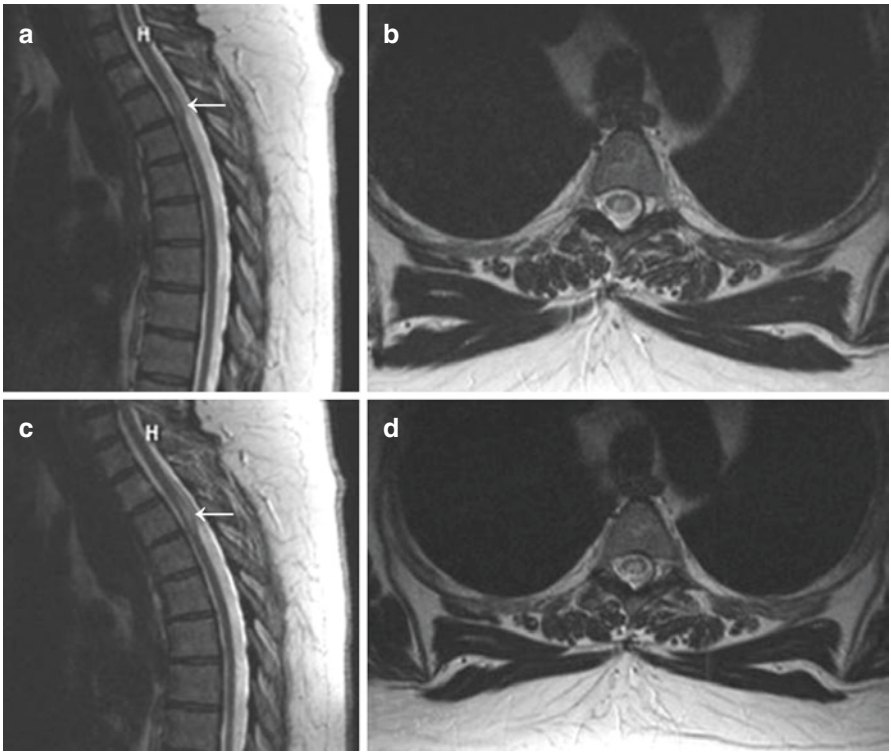

Fig. 13.4 Imaging of a 61-year-old female patient with diabetes and worsening gait. The patient was followed for years with an intramedullary lesion at T1. (**a**) Sagittal T2-weighted MRI of the thoracic spine showing the hyperintense intramedullary lesion at T1 (arrow). (**b**) Axial T2-weighted MRI of the thoracic spine at the same level. (**c**) Six-year follow-up showing growth of the lesion at T1 in sagittal T2-weighted MRI of the thoracic spine (arrow). (**d**) Axial T2-weighted MRI of the thoracic spine

astrocytoma cases. We also included studies with mixed pediatric and adult cohort of patients with spinal cord astrocytomas in which a significant percentage of adult cases were available.

We identified 20 large studies that evaluated surgical results of adult low-grade spinal cord astrocytoma treatment. There is not a single study that evaluated patients with only low-grade pathology; our literature review therefore includes studies that included more than 50% of patients with pilocytic astrocytomas and WHO Grade I and II tumors. Three of these studies included mixed cohorts of adult patients with intramedullary spinal cord tumors that included a significant number of astrocytoma cases [2, 11, 24, 31], and 1 study that evaluated a mixed cohort of adult and pediatric astrocytomas [3].

All of the studies were retrospective. The number of cases ranged from 23 to 136 [29, 33]. The largest study by Minehan et al. included 136 cases of adult spinal cord astrocytomas with mean age of presentation of 34.7 years [33]. This was also the

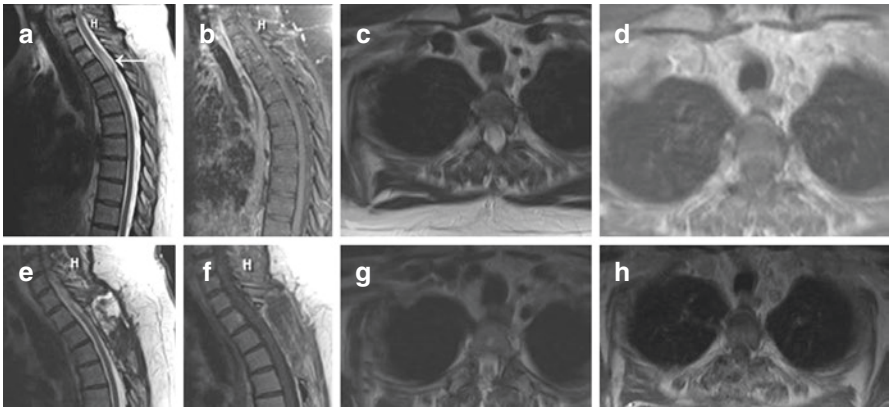

Fig. 13.5 Preoperative post-contrast MRI of the cervical and thoracic spine showing the intramedullary lesion at T1 (arrow). (**a**) Sagittal T2-weighted MRI of the cervicothoracic spine. (**b**) Sagittal T1-weighted post-contrast MRI of the cervicothoracic spine. (**c**) Axial T2-weighted MRI of the cervicothoracic spine. (**d**) Axial T1-weigted MRI of the thoracic spine, post-contrast. The lesion was resected, the pathohistological diagnosis showed low grade astrocytoma WHO Grade II. Post-operative MRI showed the complete resection of the tumor. (**e**) Sagittal T2-weighted MRI of the cervicothoracic spine. (**f**) Sagittal T1-weighted post-contrast MRI of the cervicothoracic spine. (**g**) Axial T2-weighted MRI of the cervicothoracic spine. (**h**) Axial T1-weigted MRI of the thoracic spine, post-contrast

only study with more than 100 cases. Mean age of presentation ranged from 28.3 years to 41 ± 17 years [27, 31]. Younger age was found to be associated with longer progression free survival and local control in 2 studies [34, 35]. There was no significant gender predisposition. There is a slight tendency toward tumor occurrence in the cervical and thoracic region compared with the lumbar spine.

There are currently no prospective studies that evaluate the outcome in patients with spinal cord astrocytomas. However, the current retrospective data allows for several conclusions to be made about surgical treatment. Although gross total resection is considered to be a gold standard for low-grade spinal astrocytomas and extent of surgical resection showed significant association with survival and reduces risk of disease progression [1, 4, 21, 24], studies of low-grade spinal cord astrocytomas are very heterogeneous concerning the treatment modality. In the largest study by Minehan et al., only 16% of patients underwent gross total resection, and only a further 25% underwent subtotal resection [33]. Gross total resection rates vary between 5 and 67% [36] with only 1 study that reported 100% gross total resection [8]. Ardeshiri et al. report 72.7% [37] and Fakhreddine et al. reported a 55% [27] rate of gross total resection, whereas remaining the studies report rates between 12% [18] and 30% [26].

Median overall survival for low-grade astrocytomas was reported between 91 and 156 months (7.58–13 years). Five-year survival for low-grade lesions (WHO Grades I and II) was between 54–78%, whereas the pilocytic astrocytomas examined in 3 studies had a longer median overall survival and 5-year survival up to

Table 13.1 Surgical series on spinal cord astrocytomas in adults 1992–present

Author and year	Patients (No.)	Age	Location	Histology	Resection	Adjuvant treatment	Neurological outcome	Surgical complications	Survival	Prognostic factors favorable for survival and neurological outcome
Epstein et al. 1992 [8]	25	30.2 mean age men, 29.6 mean age women	6 cervical, 11 thoracic, 10 cervico-thoracic	Group A: 19 low grade astrocytoma Group B: 6 anaplastic astrocytoma	Gross total resection in all cases	None	Group A: 12 unchanged, 3 improved, 2 worsened Group B: 4 declined, two remained unchanged	Not specified	Group A: 5/6 died; group B: 2/19 died Rest survived for mean of 50.6 months	Low grade histology
Huddart et al. 1993 [28]	27	Not specified	Not specified	Low grade and high grade astrocytomas	10 partial resection, 17 biopsy	Radio-therapy all patients	8 patients functional improvement, 15 were unchanged and 2 deteriorated	Not specified	Overall 5- and 10-year survival was 59 and 52%, and progression free survival was 38 and 26% at 5 and 10 years	Favorable functional status Low grade histology Female gender Presence of intramedul-lary cysts

Jyothirmayi et al. 1997 [29]	23	31 years	Cervical 5, cervicothoracic 4, thoracic 8, thoracolumbar 6	15 low grade, 6 high grade	Near total excision in 3, partial excision in 10 and biopsy in 10	Radiotherapy all patients	12 had improvement of neurologic status, 9 had stable status, and 2 deteriorated	Not specified	5-year overall survival was 79% for low grade tumors, 10 months for high grade tumors	Favorable functional status Low grade, female sex and intramedullary cyst correlate with PFS
Innocenzi et al. 1997 [38]	65	Median age 34.8 years	Cervical (12) 58% 72 Cervicothoracic and thoracic (45) Thoracic-lumbar (8)	WHO I 29, WHO II 26, WHO III 10 cases	GTR 10, STR 22, biopsy 23	Radiotherapy 20 patients	Not specified	Not specified	Grade I (pilocytic) median survival was 98 months with an actuarial survival at 5 years of 76%. Grade II median survival was 68 months and actuarial survival at 5 years was 68%. Grade III median 15 months	GTR longer survival compared to STR/partial resection Low histological grade and good preoperative and postoperative general condition favorable

(continued)

Table 13.1 (continued)

Author and year	Patients (No.)	Age	Location	Histology	Resection	Adjuvant treatment	Neurological outcome	Surgical complications	Survival	Prognostic factors favorable for survival and neurological outcome
Rodrigues et al. 2000 [34]	52	32 mean age	Cervical and/or thoracic spinal cord in 39 (75%) cases, and the cauda equina was involved in another 13 (25%) cases. The average extent of tumor was 4 vertebral bodies	Low-grade in 37 (71%) cases, intermediate-grade in 5 (10%) cases, and high-grade in 10 (19%) cases.	27 biopsy, 20 subtotal and 5 total resection	All patients radiotherapy, 6 chemotherapy	Stable functional status for 48 (92%) patients, improvement in 2 (4%) patients, and decline in 2 (4%) patients	Not specified	Five-year overall, cause-specific, and progression-free survivals were 54%, 62%, and 58%	Low grade histology age < 18 years, length of symptoms prior to diagnosis >6 months

Samii et al. 2007 [22]	65, 38 in adults with 42 operations	29 ± 18 years	18 tumors were located in the cervical cord, 32 in the thoracic, and 15 in the conus area; 31% had an associated syrinx.	27 grade I, 3 grade II, 9 grade III, 3 grade IV	18% complete resection 62% subtotal resection	9 underwent postoperative radiotherapy, 1 patient received chemotherapy, and 1 patient a combination of both.	Improvement 25%, stable and unchanged 58%, worsening of neurological status 17%	Permanent surgical morbidity in 14% of patients	Overall, 87% survived for 1 year and 63% and 57% survived for 5 and 10 years	Most important factor determining long-term outcome was the preoperative level of neurological function survival rates were influenced by local recurrences, histological grade (fig. 3.75), and patient age
Kim et al. 2001 [20]	28	36 years	The cervical cord was involved in 15patients, cervicothoracic in5, thoracic in 6 and thoracolumbar in 2	Low grade 18, anaplastic 3, GBM 7 cases	GTR in 3 patients, STR 6, partial removal in 14 and biopsy only in 5	19 radiotherapy	Not specified	Not specified	The median survivals of patients with low- and high-grade astrocytoma were 184 months and 8 months, respectively	Favorable functional status histological grade predictive of survival

(continued)

Table 13.1 (continued)

Author and year	Patients (No.)	Age	Location	Histology	Resection	Adjuvant treatment	Neurological outcome	Surgical complications	Survival	Prognostic factors favorable for survival and neurological outcome
Lee et al. 2003 [35]	25	40 years	6 cervical, 6 cervicothoracic, 24 thoracic and thoracolumbar	15 low grade (WHO I or II), 4 WHO III, and 6 specimens as high grade (WHO IV)	19 biopsy, 5 STR, and 1 had a GTR	22 radiotherapy, 13 chemotherapy	9 patients favorable and 13 unfavorable NF	Not specified	The actuarial OS rate at 5 years for favorable NF at diagnosis was 73%, compared to 22% for patients with unfavorable preoperative NF	PFS and LC were significantly better for young patients and those with lower tumor grade
Raco et al. 2005 [2]	202 patients with intramedullary tumor, 86 astrocytomas (42%)	Not specified	Not specified	27 grade I 41 grade II 18 grade III-IV	Grade I, 22 (81%) total and 5 (19%) partial resection Grade II 5 (12%) complete resection Grade III to IV no complete resection 61% (11 of 18 patients)	Not specified	Grade I: 26% (6 of 23 patients) had improved, 9% (2 of 23 patients) had worsened, and 66% (15 of 23 patients) remained 10% of grade II improved 61% (11/18) grade III-IV worsened	Not specified	Not specified	Low grade histology Complete resection Preoperative neurological status

Nakamura et al. 2006 [23]	30	Mean age 35 years	Cervical level in 13 patients, at the thoracic level in 16 patients, and at the conus medullaris in one patient.	18 low grade, 12 high grade	7 total, 8 partial resection, 15 biopsy	19 patients radiotherapy	Low grade 5 remained fair or better, high grade no change in all except two patients	5/18 low grade fair or better, 10/12 high grade aggravated or no change	The survival rate for all 30 patients with spinal cord astrocytoma was 68% at 5 years and 36% at 10 years	Low grade histology Thoracic region favorable
Abdel-Wahab et al. 2006 [21]	57	30 radiation group, 29 surgery-only group (mean age)	18 cervical, 16 thoracic, 1 conus, 22 overlapping, 2 not specified	Only 42% had review of grade by WHO criteria	13 patients complete resection	39 patients radiotherapy	Unknow for 34 patients; improved in 14, stable in 5 and worse in 4	Not specified	5-, 10 and 15 year survival: 59,53 and 32% Median PFS 44 months	Low grade histology Complete resection reduces risk of disease progression Radiation significantly reduced the risk of disease progression in low- and moderate-grade astrocytomas
Yang et al. 2009 [11]	174 patients, 62 astrocytomas		32 cervical, 30 thoracic	56 low grade, 6 high grade	Total 24, subtotal 22, 16 partial	39 radiotherapy	30 unchanged, 28 improved, 4 deteriorated	1 wound infection, 2 CSF fistulas with revision surgery	96 months follow up: 2/56 and all high grade died	Low grade histology

(continued)

Table 13.1 (continued)

Author and year	Patients (No.)	Age	Location	Histology	Resection	Adjuvant treatment	Neurological outcome	Surgical complications	Survival	Prognostic factors favorable for survival and neurological outcome
Minehan et al. 2009 [33]	136	34.7 20.7 years mean age	All but 2 lesions involved either cervical or thoracic level	69 had pilocytic and 67 had infiltrative astrocytoma	Incisional biopsy only (59%), subtotal resection (25%), and gross total resection (16%)	RT was administered to 102 (75%) of the 136 patients,	Not specified	Not specified	Patients with pilocytic tumors survived significantly longer than those with infiltrative astrocytomas (median overall survival, 39.9 vs. 1.85 years;	Pilocytic histologic type, diagnosis after 1984, longer symptom duration, younger age, minimal surgical extent, and postoperative radiotherapy
Fakhreddine et al. 2013 [27]	83	Mean age 28.3 years	56.1% cervical, 69.5% thoracic, 14.6% lumbar	Pilocytic group: 31 WHO grade I infiltrative group: 14 had grade II, 18 had grade III, and 18 had grade IV; 2 patients high-grade (III or IV)	Subtotal or total resection in 55.5%, rest biopsy	Chemotherapy 41.8% Radiotherapy 69.5%	Not specified Patients with infiltrative tumors were also more likely to present with motor deficits		5-year survival times for pilocytic 85.4% and infiltrative patients 36.4%	Tumor grade (pilocytic histology improved OS and grade II improved compared to III compare to IV) Chemotherapy improved PFS in infiltrative astrocytomas

Ardeshiri et al. 2013 [37]	22	16–75, one patient 7 years old	10 cervical 4 cervicothoracic, 5 thoracic, 3 thoracolumbar	15 WHO I 3 WHO II 4 WHO III	16 (72.7%) complete resection	None	Functional and neurological score unchanged in 13 and worse in 9 patients (Frankel score)	None	Follow up 21 months: 25% progression,15% progression, 60% unchanged, 1 died, 1 lost to follow up	Low grade histology cervical location
Klekamp et al. 2013 [31]	225 intramedullary tumors; type B (infiltrating; astrocytomas and gangliogliomas) 80	41+/−17 years	Not specified	Not specified	22.5% were classified as GTRs and 25.0% as STRs	Not specified	Permanent surgical morbidity 21%, 19.3% syringomyelia, 29.5% tumor hemorrhage,	15.9% in entire cohort, CSF fistula most common	Recurrence rate for benign in 10 years 28.8%, malignant 78.2%; GTR/STR 6.3%, partial resection+ biopsy 42.5%; survival not specified	Low grade histology Extent of resection Age correlate to postoperative morbidity

(continued)

Table 13.1 (continued)

Author and year	Patients (No.)	Age	Location	Histology	Resection	Adjuvant treatment	Neurological outcome	Surgical complications	Survival	Prognostic factors favorable for survival and neurological outcome
Babu et al. 2014 [18]	46	High grade 27.5, low grade 18.8 mean	Thoracic (47.8%), cervical (28.3%), cervicothoracic (15.2%), thoracolumbar (8.7%)	41.3% had pilocytic astrocytoma (WHO grade I), 21.7% WHO II, 19.6% WHO grade III), and 17.4% (GBM; WHO grade IV).	67.4% resection, of those 12.5% gross total; rest biopsy	Low-grade tumors: 34.5% and 51.7% received radio- or chemotherapy, respectively. High-grade: Adjuvant therapy94.1% and 88.2% being treated with radio- or chemotherapy	45.7% experienced new neurological deficits such as weakness, neuropathic pain, paresthesia/dysesthesia, ataxia, and bladder dysfunction; higher incidence of new deficits in resection cases than those who received biopsy only (54.8% vs. 26.7%); 37% worse than baseline	Number of complications increases with extent of resection	High-grade astrocytoma had a worse median survival time than those with low-grade tumors (28.1 mo vs. median not reached, $P < 0.0001$	High grade histology, tumor dissemination und multiple levels worse prognosis

Seki et al. 2016 [41]	33	Low grade 38.9 years, high grade 42.6 years	Low-grade SCAs cervicotho-racic spinal cord (40%), high-grade SCAs occurred most frequently in the thoracic spinal cord (38.5%)	20 low grade, 13 high grade	9 low grade GTR (27.3%)	Low-grade SCA, 15% chemo-therapy and 25% All high-grade radiation therapy, nine following chemo-therapy	51.5% showed deteriorated neurological status compared to preoperative baseline	Not specified	Median overall survival low grade 91 months, 78% at 5 years vs. high grade 15 months, 31% at 5 years	Low grade: GTR/STR related to better OS High grade histology and neurological status in final follow-up to be significant predictors of poor survival
Ryu et al. 2016 [10]	26	38.9 years mean age	11 cervical 8 thoracic 5 thoraco-lumbar 2 cervicotho-racic	14 high grade 8 low grade 2 cases of malignant transforma-tion	High grade biopsy or partial resection Low grade gross total or total resection	Radio-therapy for high grade tumors	Nurick grade: 58.3% of low-grade patients had a Nurick grade of 1, 2, or 3 85.7% of high-grade patients had a neurological grade of 4 or 5.	None	OS: Low grade 156.38 months High grade 12 months PFS: Low grade 138.85 months High grade 6.64 months	Low grade histology Ki-67 index

(continued)

Table 13.1 (continued)

Author and year	Patients (No.)	Age	Location	Histology	Resection	Adjuvant treatment	Neurological outcome	Surgical complications	Survival	Prognostic factors favorable for survival and neurological outcome
Parker et al. 2017 [26]	95 patients	35.6 years	Thoracic in 40%, purely cervical in 28.4%	Grade 1 in 35%; grade 2 in 35%; grade 3 in 22% and grade 4 in 8%	Complete removal in 29.5%	Not specified	During the early postoperative period (3 months) a worsening of functional capacity was observed in 18.4%	Not specified	Probability of survival at 5 years of 78.6% Survival at 10 years is to 76.8%	The preoperative neurological status is the only predictive factor for long-term follow-up

AA anaplastic astrocytoma, *Bx* Biopsy, *CSF* cerebrospinal fluid, *GBM* glioblastoma, *GTR* gross total resection, *KPS* Karnofsky Performance Score, *NF* Neurofibromatosis, *OS* overall survival, *PFS* progression free survival, *SCA* spinal cord astrocytoma, *STR* subtotal resection, *WHO* World Health Organization.

85.4% compared with infiltrative astrocytomas [27, 33, 38]. The strongest predicting factor of functional outcome is the preoperative neurological condition. Pathological grade (i.e., low-grade vs. high-grade), as well as favorable functional outcome, are the strongest predictors of increased survival. Most studies showed that more than 50% of the patients either remain unchanged or worsened following surgery. Adjuvant therapy was performed in most of the patient cohorts with rate of postoperative radiotherapy of 23–100% [3, 34], whereas most patients with higher grades underwent adjuvant radiotherapy or combined radiochemotherapy.

Postoperative neurological decline was reported in 21–57% of patients who underwent resection of the tumor [18, 19, 23, 35, 39]. Interestingly, the majority of series examining adult spinal cord astrocytomas do not specify operative complications, whereas postoperative worsening of deficits is more attributed to the infiltrative growth of the lesion or progression of the disease rather than to surgical events. It has been argued whether neurological decline in astrocytoma cases was a function of surgical resection or tumor growth. However, if the majority of neurological decline was observed at the patient's last clinic follow-up visit and not in the immediate postoperative period, tumor progression may be a possible mechanism of neurological decline [40]. Late morbidity was commonly observed in the form of neuropathic pain syndromes and rarely as a postoperative myelopathy [31].

13.7 Surgical Technique

The details of the surgical resection of a low-grade astrocytoma are demonstrated in our surgical videos (see online edition of this chapter). For the prone position, the patient is first anesthetized in the supine position on a bed or stretcher. To move the patient into the prone position, we use a log roll maneuver. Once the patient has been successfully turned, the head will face down in a head support device. The eyes should be gently taped shut and protected from any pressure. The patient's chin must be free of the table and frame. We prefer to use chest rolls in form of rolled sheets, as they are less traumatic to the breasts in female patients. The arms are positioned at the patient's side with the palms facing the patient and the thumbs down for the cervical and upper thoracic spine location. Anteroposterior cervical spine X-rays are helpful to determine levels in thoracic spine while lateral X-rays illustrate cervical and lumbar locations.

For lower thoracic and lumbar spine locations, we use a Jackson ("Carbon") table and arm-rests with paddings for elbows and axilla areas. To prevent nerve compression, appropriate supportive padding should be used as a general rule under bony surfaces where superficial nerves are known to travel. The armpits, elbows, and hands are padded. The patient's feet should be kept off the bed surface to prevent pressure sores. Padding should be placed under each patella of the knee joints. A pillow should be placed under the ankle joints to elevate the foot to relieve tension on the sciatic nerve and to prevent the toes from resting on the operating room table mattress. Once the positioning is completed, we determine the correct spinal level under fluoroscopic control [3]. Lateral views are more helpful in cervical and

lumbar locations, while anterior-posterior views are more commonly used in thoracic spinal locations. Electrodes for spinal neurophysiologic monitoring are usually placed before turning the patient prone.

We utilize Yasargil bipolar forceps with different progressive lengths and different tip sizes, which we use commensurate with intraoperative distances and surgical situation. Also, we use Yasargil controlled suctions of different sizes with which we can dial the strength of the suction according to intraoperative needs. Micro scissors of different sizes—straight and curved with blunt and sharp tips in different lengths—are used according to intraoperative situation and tactic.

The exposure of an intramedullary tumor is done usually from the posterior-dorsal aspect of the spinal cord with the patient in the prone position. A midline incision is performed in the fascia and the paravertebral spinal muscles are usually split bilaterally from spinous processes and laminas of spine. Small laminotomy [3] or conventional laminectomy can be performed. We recommend laminectomy in the thoracic and lumbar spine when the tumor is confined to 1 or 2 segments. In the cervical spine, a classical or open-door laminoplasty may be the method of choice, particularly if dealing with 3 or more levels or in younger patients. In tumors extending on more than 2 segments, especially in transitional areas (e.g., between cervical and thoracic spine, or thoracic and lumbar spine), additional stabilization may be considered.

The dura is opened in the midline and tacked to the surrounding muscle tissue with dural tacking sutures, usually 4-0 Nurolon (Ethicon, Somerville, NJ). The arachnoid is opened separately with micro scissors or micro knife, and delicately freed from the posterior or lateral spinal cord, keeping it intact for closure at the end of surgery. Ligaclips are applied to hold the arachnoid membrane to the dura. In most instances, the myelotomy is done in the midline. One exception from this rule may be when the lesion is located in 1 dorsal column and is apparent on the surface without any cortical mantle on one side of the spinal cord. Recognition of the midline to perform the myelotomy may be difficult because the spinal cord is frequently rotated and enlarged with loss of definition of the posterior median sulcus. In that situation, recording of sensory-evoked potentials or utilization of the intraoperative ultrasound is helpful to ensure staying on the median sulcus when separating both posterior columns.

If the tumor is located laterally, the dorsal root entry zone may be used for entry. We recommend opening through the posterior median sulcus over the entire length of the tumor (retraction and opening of the dorsal columns as if they were “pages of a book”) as the first step of dissection. This can be done with micro knife or micro scissors to cut the pia mater with the remainder of the cord splitting between the dorsal columns performed usually with blunt instruments, such as utilizing opening spring of Yasargil bipolar forceps. This maneuver is continued to expose the rostral and caudal aspects of the tumor. Next, we use 6-0 Prolene sutures (Ethicon, Somerville, NJ), which we anchor to the edges of the pia mater and suspend to the dura in order to keep the cord open (i.e., “like the book”) and reduce the micro trauma to the cord due to repeated dissection. This maneuver minimizes manipulation of the spinal cord during tumor removal, protects the lateral spinal cord

surfaces from micro injury, and may later facilitate the determination of tissue planes considerably after the tumor has been debulked. The tumor micro dissection in latero-lateral direction rather than superior-inferior direction minimizes micro trauma to the spinal cord and enables easier creation of the tumor-spinal cord margin by sharp dissection. Micro dissectors can also be used for this purpose.

Tumor size reduction may be achieved by either coagulation or debulking of the tumor. Tumor debulking relieves possible mass effect on the surrounding spinal cord tissue, allowing a certain degree of functional recovery. Any lateral dissection attempted at the beginning of debulking carries the risk of applying a lot of pressure to the surrounding cord. Debulking can be done with tumor forceps, sharp dissection, or ultrasound aspiration.

Once sufficient debulking or shrinking of the tumor has been achieved, the tumor margins should be dissected toward the surrounding cord. Often, the tumor infiltrates the spinal cord and searching for a plane that does not exist may represent a risk. In that case, preoperative recording of motor-evoked potentials (MEPs) compared with intraoperative MEPs may be essential for preserving neurological functioning and patient quality-of-life. With infiltrating tumors, debulking is continued as long as the surgeon can remain safely inside the tumor, assess the interface between the tumor and the normal spinal cord tissue, and then attempt to create a sharp margin between the two. Fine forceps, micro-dissectors, or sharp dissection with micro scissors or micro knife can be used to create a margin at the interface between the tumor and the normal spinal cord tissue. However, astrocytomas may be diffusely infiltrating tumors. Therefore, the identification or creation of cleavage planes may be difficult and should be done with the aid of intraoperative use of neuro-monitoring and ultrasound and substantial clinical and operative experience and judgement. The intraoperative finding of a clear tumor plane of resection carries positive prognostic significance. In tumors with ill-defined margins and/or the inability to create them, an ultrasonic aspirator can be used to debulk the mass. Tumor feeding vessels may come from all angles and will not originate from the anterior spinal artery as regularly as in the case of ependymomas. As long as the tissue appears pathologic, debulking can be continued. In some cases, a clear dissection plane can be followed all around the tumor or in most places.

Hemostasis is achieved using bipolar coagulation and surgically as well. Pial closure is done with 7-0 Prolene sutures, and arachnoid closure is done by approximating the edges with bipolar coagulation. Dural closure is performed with 4-0 Neurolon stitches with application of previously harvested fat graft in prevention of cerebrospinal fluid-leak [42].

13.8 Surgical Complications

Complications of the surgery may include cerebrospinal fluid fistula, pseudomeningocele, intraoperative bleeding, spinal cord infarction, epidural hematoma, operative spinal cord injury and edema, immediate postoperative worsening of the neurological deficits, respiratory failure, and wound infection [11, 40]. An overall

rate of permanent surgical morbidity in intramedullary tumors ranges between 18% and 34.6% [31, 36]. It has been reported that the incidence of acute perioperative neurological decline in patients with intramedullary spinal cord tumors increases with patient age, but improves to baseline in nearly half of patients within 1 month. Long-term improvement in motor, sensory, and bladder dysfunction may be achieved in a slight majority of patients, and occurs more frequently in patients in whom a surgical plane can be identified [43].

Cerebrospinal fluid fistulas are a common complication [31]. These fistulas may be avoided by using a tight running suture of the dura and fat graft, and tight sutures of the muscular layers, which appear to be the strongest barrier against cerebrospinal fluid [31, 42]. We use 4-0 Nurolon stitches for dural closure, checking for possible cerebrospinal fluid leak by using a Valsalva maneuver exercised by an anesthesiologist and applying previously harvested fat graft from the abdomen for watertight suture [42]. This fat graft utilization helps prevent pseudomeningocele and also epidural hematoma formation by eliminating the "dead space" created after laminectomy and also negative pressure that may favor cerebrospinal fluid leak.

In patients undergoing a second operation on a tumor, the muscles may be atrophic from the previous operation and may no longer provide a good barrier against leakage. Transient neurological deficits are not uncommon. Postoperative sensory deficits may be a consequence of the myelotomy required to reach an intramedullary tumor [31]. The longitudinal extent and, thus, the length of the myelotomy were found to correlate with postoperative sensory dysfunctions in several studies [31, 44]. Postoperative tethering can be seen in up to 37% of postoperative MRIs [31], but only about 5% of these patients developed clinical signs of myelopathy unrelated to tumor progress [31]. Nine out of 15 patients in one series experienced immediate worsening of neurological status postoperatively with an increased paresis and aggravated sensory deficit in which MRI was uneventful in all of these cases [44]. New neurological deficits, especially ataxia, could improve over time [42]. In their series, Klekamp et al. reported that long-term morbidity affected 3.7% patients with a postoperative myelopathy related to cord tethering at the level of surgery, and 21.9% in the form of neuropathic pain syndromes [31]. The rate of postsurgical cord tethering could be lowered significantly by using pial sutures after tumor resection. Neuropathic pain syndromes were more common after surgery for tumors with associated syringomyelia or those located in the cervical cord [31].

Complications associated with prone position may include ophthalmic injury and pressure injuries [45]. Ophthalmic injuries include retinal artery occlusion, corneal abrasion, and ischemic optic neuropathy with postoperative visual loss [46]. Pressure injuries include pressure necrosis of the skin, contact dermatitis, tracheal compression, salivary gland swelling, mediastinal compression, visceral ischemia, peripheral vessel occlusion, and limb compartment syndromes. Deep venous thrombosis (DVT) with venous air embolism (VAE) may also occur in patients in the prone position with the reported range of 10–25% [47]. Complications due to anesthetic technique include dislodgement of the endotracheal tube, which can be prevented with use of non-kinking endotracheal tube [48].

13.9 Extent of Resection

Gross total resection is a gold standard in surgery of low-grade astrocytomas. Extent of surgical resection shows a significant association with survival and reduces risk of disease progression [1, 4, 21, 24]. It is mainly reserved for pilocytic and for WHO Grade II tumors [3, 22]. Low-grade astrocytoma complete resection rates vary between 5% and 67% [36] (Table 13.1). One large study on surgical treatment of intramedullary spinal cord tumors showed that an intraoperatively identifiable tumor plane and decreasing tumor size were associated with gross total resection independent of histological tumor type [43].

Various studies reported postoperative neurological decline in 21% to 57% of patients who underwent resection of the tumor [18, 19, 23, 35, 39]. The most important factor in predicting gross total resection are preoperative neurological status or high preoperative McCormick grade [31]. Other strong predictors were adult age, a high spinal level, presence of a syrinx, and first surgery on the tumor. The remaining factors predicting gross total resection were benign histological grade, no arachnoid scarring, a short preoperative history, and an experienced surgeon [31].

Increasing rates of complete resection in patients with intramedullary astrocytomas might be the result of a combination of increased surgical experience, refinements in surgical techniques and the routine use of electrophysiological monitoring during surgery, which encourage the surgeon to a more radical approach [37].

13.10 Specific Surgical Aspects

13.10.1 Management of Blood Pressure during Spinal Surgery

Keeping normovolemia is mandatory to avoid intraoperative hypotension [49]. The prone position during spinal surgery is associated with reduced stroke volume, cardiac index, raised central venous pressure, and low blood pressure [46]. It is important to maintain euvolemia and monitor fluid responsiveness by pulse pressure variation and stroke volume variation [50]. An arterial line is also recommended as a means to monitor real-time blood pressure as well as monitor of intravascular volume (central venous or pulmonary artery catheter). Moderate degrees of hypotension (80–90 mmHg systolic, 20–30% below baseline) are efficacious at reducing blood loss in patients with major spinal surgery, and safe in any patient without specific risk factor [51].

13.10.2 Intraoperative Ultrasonography and Ultrasound-Based Neuronavigation

The first reports on the application of US-based neuronavigation systems in spinal cord surgery showed good utility of this method in guiding the surgical resection [52, 53]. However, its application has been shown to be useful only in resecting extramedullary tumors as the implementation of 3D sonography in intramedullary

tumors would be possible after the elimination of motion artifacts caused by respiration [54]. Use of non-navigated intraoperative ultrasonography with use of high-frequency linear probes (10–12 MHz) was beneficial in confirmation of tumor location and extension, planning myelotomy, and estimation of degree of resection of the intramedullary tumors. They were particularly helpful in guiding the approach to redo surgeries for recurrent spinal cord tumors [55].

13.10.3 Intraoperative Monitoring

Modern surgery of spinal cord astrocytomas is performed with neuro-monitoring. The preservation of MEPs correlates closely with postoperative motor function. A decline of 50% or more in MEPs amplitude is a warning sign that the tumor is almost infiltrative [56]. Setting the critical point to loss of MEP waveform and a 50% reduction of the D-wave yields better surgical outcomes compared with changes in SSEPs, which means surgery should be abandoned when these values are reached [57]. Suspending surgery when the waveform becomes aggravated and recontinuing later when the waveform has improved or abandoning the resection altogether when the waveform becomes multiphasic again or is lost leads to better postoperative outcomes in gait of patients with intramedullary spinal cord tumors [58]. Furthermore, neuro-monitoring assists in various steps of the surgical resection, even at the beginning of the surgery in finding the midline, which can be displaced by large and cystic tumors [56]. Real-time monitoring with constant free-running electromyography is also performed intraoperatively, which is useful for monitoring nerve root irritation and compression [58, 59]. Again, neuro-monitoring is a great and important intraoperative tool, but the final judgement on the extent of surgical resection, intraoperative maneuvers, and tactics rests on shoulders of an operative neurosurgeon.

13.10.4 Fluorescein Guided Surgery

Several studies suggested that the use of 5-ALA (5-aminolevulinic acid) fluorescence could be beneficial, especially in intramedullary gliomas [60]. Bright intraoperative fluorescence marking the border between the tumor and the spinal cord tissue was shown with use of fluorescein in pilocytic astrocytomas but was absent in Grade II astrocytomas [61]. This study showed that gadolinium uptake in T1-weighted MRI sequences could be shown intraoperatively as a fluorescent mass, using SF (salt mass of fluorescein) with a dedicated filter in the surgical microscope [61].

13.10.5 Postoperative Instability of the Spine

Laminoplasty is a safe method that preserves spinal stability and can be used in patients with tumor extension of 2 or more levels [44, 62]. Laminoplasty and

laminectomy were associated with similar functional outcome scores in one study [44]. It has been assumed that adult patients with astrocytomas are at low-risk for postoperative kyphoscoliosis following laminectomy [7]. Laminoplasty for the resection of intradural spinal tumors was not associated with a decreased incidence of short-term progressive spinal deformity or improved neurological function [63]. However, it may be associated with a reduction in incisional cerebrospinal fluid leak [63].

13.11 Surgical Outcome and Survival

We differentiate 2 types of outcome in the surgery of spinal cord astrocytomas: *surgical outcome* and *overall outcome.* Surgical outcome assesses the following: A) The neurological status after the surgery by noting deficits, or using Nurick Grade, McCormick Scale, or Frankel scale), B) Extent of resection, and C) complication rate. *Overall survival* is influenced mainly by the histological type of the tumor. Table 13.1 summarizes the most important surgical series of the spinal cord astrocytomas.

13.11.1 Surgical Outcome

Over the course of the past 30 years preoperative diagnostics, surgical technique, and intraoperative neuro-monitoring has significantly developed so that the reported results of surgical outcome show significant positive trends. Permanent surgical morbidity has now been reported between 14 and 21%, and most studies show that more than 50% of patients either remain unchanged or worsen following surgery (Table 13.1). The strongest predicting factor of functional outcome is the preoperative neurological condition [36, 64]. The timing of surgery is one of the crucial points for good outcome; these lesions should be operated before neurological deterioration occurs [56, 65].

13.11.2 Survival

Survival rates were shown to be influenced by histological grade, local recurrences, and patient age [3, 66]. One study reported a median survival time for pilocytic astrocytomas of 39.9. years [33]. Median overall survival for low-grade astrocytomas was reported between 91 and 156 months (7.58–13 years). Five-year survival for low-grade lesions was between 54–78%, whereas high-grade astrocytomas had overall survival between 9 months and 1.85 years (Table 13.1).

Pathologic grade is the strongest prognostic factor of overall survival and progression free survival in spinal cord astrocytoma [9, 10, 20, 21, 28, 29, 39]; however, it is not always concordant with biologic behaviors [10, 21]. Studies have shown more favorable outcome for low-grade tumors when compared with high-grade tumors,

one of which showed increased survival rates for Grade III tumors compared with Grade IV tumors [39]. Furthermore, increased survival was shown in patients with favorable functional neurological outcome [19, 20, 28, 29, 35, 39].

Some studies stated that neither progression-free intervals nor survivals were influenced significantly by the amount of resection, provided that a "good" reduction of tumor volume to decompress the spinal cord was achieved [3, 8, 19, 20, 43, 67]. Given that low-grade astrocytomas were more likely to be grossly or totally resected than high-grade astrocytomas, surgical extent of resection alone may be a too simplistic as a prognostic factor [10].

Gender and race seem not to significantly influence survival [9, 19–21, 34, 35]. Female sex was found to influence 5-year overall survival and progression-free survival in two studies [28, 29]. In contrast, one population-based analysis showed male sex to be predictive of favorable outcome [4, 68]. Most studies so far fail to find correlation of age to survival [21], although Sandler et al. found patients with tumor recurrence to be older [69], and Lee et al. reported that older age adversely affects local control, progression free survival and overall survival [35]. Only one series showed correlation of cervical location of the tumor with better functional outcome [37] while two studies have shown positive correlation of thoracic region with survival [9, 23]. Increased survival in patients with longer history was reported only in two studies [9, 34].

13.12 Recurrence and Malignant Transformation

Evaluation of tumor recurrence rates for astrocytomas revealed low spinal level, malignant grade, and adult age as important independent predictors. Recurrence rate of astrocytomas after 10 years is between 42 and 48% [31, 40]. The rates correlated with the histological grade and the amount of tumor resection. One series showed the recurrence rate of 6.3% after gross total resection or subtotal resection within 10 years, whereas partially resected or biopsied tumors recurred at a rate of 42.5% over the same time period [31]. Malignant transformation to anaplastic astrocytoma or to glioblastoma with extraneural metastases has been described [10, 28, 70].

We recommend postoperative follow-up after 3, 6, and 12 months post-surgery with MRI of the spine with and without contrast followed by yearly MRI evaluations. A postoperative regular follow-up for low-grade lesions is mandatory for at least 10 years due to the risk of recurrence [26].

13.13 Adjuvant Treatment

13.13.1 Radiation Therapy

The value of postoperative radiotherapy for low-grade astrocytomas remains controversial. The postoperative course of incompletely removed low-grade astrocytomas is considered by most neurosurgeons as being so benign that radiotherapy

could be withheld and repeated surgeries undertaken [4, 27, 70]. A great number of low-grade astrocytomas remain stable over years, if not decades, without any adjuvant therapy [56]. Samii et al. advise radiotherapy for patients with WHO Grade III and IV tumors only [3]. Following radical resection, reserving radiotherapy for recurrent disease may be a reasonable option [8, 67]. In some series [69], overall survival of high-grade patients who had undergone radiation therapy was shorter than that of those who had not [10, 69]. The major factor influencing long term clinical course and survival is the histological grade and not the mode of treatment [28]. Addition of radiotherapy can be can be rationalized because the predominant pattern of failure is local [34]. Postoperative radiotherapy for intramedullary astrocytomas may be recommended for temporary local control [28] since radiation has been shown to significantly reduce the risk of disease progression in low and moderate-grade astrocytomas [21] and to improve survival in infiltrative astrocytomas [33].

13.13.2 Chemotherapy

As malignant tumors in this localization are very rare, hardly any single institution acquires enough patients to perform an appropriate prospective study [28, 32]. Survival benefits of temozolomide (TMZ) after radiotherapy in patients with malignant primary spinal cord tumors were shown in small series with fewer than 25 patients [32, 71]. Chemotherapy was significantly associated with improved progression free survival, yet not overall survival [27]. Chamberlain et al. showed that TMZ, when has modest efficacy as reflected in progression free survival (18-month progression free survival, 41%, 24-month progression free survival, 27%) and median survival (23 months) for recurrent adult spinal cord astrocytoma who already underwent surgery and radiotherapy [71]. One study showed that in patients with infiltrative astrocytomas, chemotherapy was significantly associated with improved progression free survival but not overall survival [27]. Other studies showed that additional chemotherapy did not lead to extended survival in high grade astrocytomas [39, 70].

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Spinal Cord Hemangioblastomas

14

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14.1 Introduction and Demographics

Hemangioblastomas are histologically benign but highly vascular tumors of the central nervous system (CNS) that can be either sporadic in nature, or in association with von Hippel-Lindau (VHL) syndrome. If VHL is present, the lesions can be multiple and distributed throughout the CNS. A recent meta-analysis of the available literature found that 60% of hemangioblastomas are sporadic in nature and 40% are associated with VHL [1].

Hemangioblastomas are classified as Grade I tumors according to the World Health Organization classification system [2, 3]. The most common location of occurrence is the posterior fossa [4], followed by the spinal cord [5]. Spinal cord hemangioblastoma is rare, accounting for only 2–6% of overall spinal cord tumors; however, they are the third most common primary spinal cord tumor following astrocytoma and ependymoma [6–10].

Spinal hemangioblastoma has been shown to have a male predominance with male-to-female ratios ranging from 1.6:1 to 5:1 in the literature [1, 10, 11]. Patients with

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sporadic hemangioblastoma typically present in the fourth decade of life, and those with VHL-associated hemangioblastoma present in the third decade of life [1, 10–12]. Spinal hemangioblastoma is most commonly found in the dorsum of the cervical spine, followed by the thoracic spine, and—more rarely—the lumbar spine [3, 9, 12–14]. This pattern is likely due to the distribution and quantity of embryonic precursor cells [15–17]. Some reports have shown that spinal hemangioblastomas associated with VHL have a tendency to be present in the caudal spine, compared with sporadic hemangioblastomas [14].

14.2 Histopathology

All cases of VHL-associated hemangioblastoma—and about 50% of sporadic tumors [14, 18, 19]—are due to a malfunction of a tumor suppressor gene: VHL. This gene is located on chromosome 3p25-p26 and encodes pVHL, a protein that helps contribute to the formation of the ubiquitin ligase complex that downregulates hypoxia-induced growth factor (HIF-1). HIF-1 is a transcription factor that modulates the expression of growth factors, such as vascular endothelial growth factor, erythropoietin growth factor, and numerous other growth factors [20]. Some sporadic cases have been attributed to gain-of-function mutations of HIF-1 [21]. The above pathophysiology helps explain the polycythemia encountered in 10% of the patients with VHL.

Microscopically, these histologically benign lesions are composed of a vascular plexus surrounded by stromal cells, which have been shown to be the neoplastic cell of origin [19, 22].

Macroscopically, these tumors are well circumscribed and often in close proximity to the wall of a cyst. They are beefy red in appearance due to their vascular nature and are in striking contrast to their surrounding neural tissue. Lonser et al. [23] has shown that convective extravasation of plasma from the hemangioblastoma is the cause of the edema and subsequent cystic structures associated with these tumors.

14.3 Clinical Presentation

The clinical presentation of spinal cord hemangioblastoma is dependent on the size and location of the tumor, and its effect on the spinal cord by direct growth of the tumor, edema, or an associated cyst or syrinx. The symptoms often include motor weakness in the form of hemiparesis, quadraparesis, or paraparesis at presentation. Sensory abnormalities and pain are often present and related to the dermatomes associated with the tumor or associated cyst and syrinx.

The presentation of patients with these tumors is often delayed due to their slow growth rate and indolent progression to clinical symptomatology [9]. Occasionally, asymptomatic patients have spinal hemangioblastoma lesions incidentally discovered on medical imaging.

The most devastating sequela of hemangioblastomas is hemorrhage and acute motor paresis [10], which can result secondary to bleeding from a spinal

hemangioblastoma. Additionally, lumbago, radiculopathy, and headache can occur due to subarachnoid hemorrhage secondary to this rare event [5, 24].

14.4 Von Hippel–Lindau Disease Considerations

It is estimated that 10–40% of patients with hemangioblastomas harbor the genetic abnormalities of VHL disease [15]. The manifestations of VHL can include hemangioblastomas of the CNS and retina, endolymphatic sac tumors, pheochromocytomas, epididymal cystadenomas, and visceral cysts that commonly involve the kidneys and pancreas and are at increased risk for malignant transformation into carcinoma [25]. VHL is related to a germline mutation on the short arm of chromosome 3 (3p25.3) that is responsible for a tumor suppression gene inherited in an autosomal dominant fashion [26, 27]. Erythropoietin and vascular endothelial growth factor (VEGF) have been shown to be upregulated in hemangioblastomas and are likely related to the pathogenesis of these tumors [28]. Sporadic hemangioblastoma can also be associated with de novo mutations of the VHL gene [17].

The criteria for diagnosis of VHL are a positive family history and the presence of concomitant hemangioblastomas, *or*—in the absence of a family history—2 hemangioblastomas of the CNS, or 1 hemangioblastoma of the CNS and 1 of the following tumors: renal cell carcinoma, visceral cyst, pheochromocytoma, or a definitive mutation found in the VHL gene [4, 18]. It is recommended that all patients with spinal hemangioblastoma have undergo screening for VHL, which often includes entire neuraxis imaging, dedicated abdominal imaging, and fundoscopic eye examinations [3].

Most recommendations in the literature advocates only to operate on symptomatic VHL patients; however, some authors advocate for resection of asymptomatic lesions, which have shown progression and growth with impending neurological sequelae [18]. No study has shown a difference in outcome following surgical resection between VHL -associated and sporadic hemangioblastoma [29, 30]. However, since there is currently no curative treatment for VHL, a strategy of symptomatic palliation is followed and aggressive surgical resection of the lesions should be avoided as the extent of resection is less important than preservation of motor function [31].

14.5 Radiologic Presentation

Magnetic resonance imaging (MRI) remains the most important diagnostic tool for hemangioblastomas (Figs. 14.1 and 14.2). The tumor nodule is hypointense on T2 weighted images. It enhances, homogenously or at times inhomogeneously after contrast application. Usually, there is associated cyst that has the cerebrospinal fluid (CSF) density. Finally, associated spinal cord syrinx may extend rostrally well beyond the location of the tumor nodule.

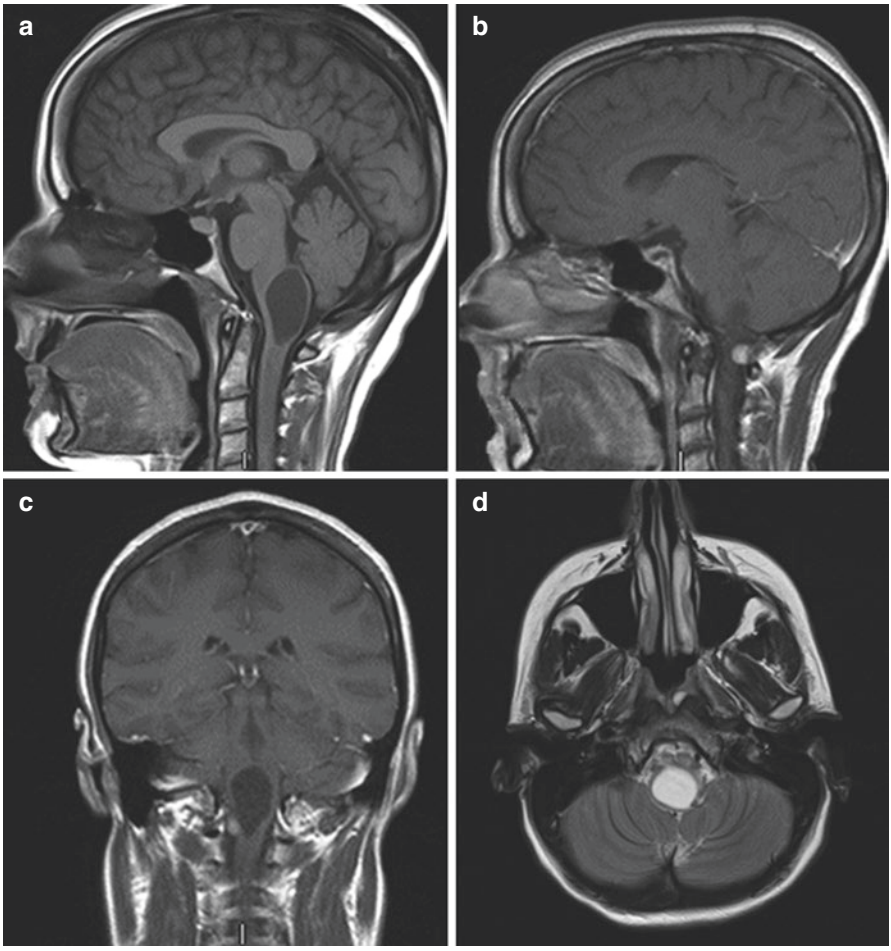

Fig. 14.1 Medulla oblongata/brain stem hemangioblastoma (Patient 1: VHL disease, female patient operated by the senior author, KIA) [57]. (**a**) Preoperative MRI of brain. (**b**) Sagittal pre-contrast T1- weighted MRI showing medulla oblongata cyst. (**c**) Sagittal post-contrast T1-weighted MRI showing enhancing nodule. (**d**) Coronal post-contrast T1-weighted MRI showing enhancing nodule and adjacent cyst. (**e**) Axial T2-weighted MRI showing medullae oblongata cyst

We always obtain plain X-rays in anterior-posterior, lateral, flexion and extension to evaluate spinal alignment and stability for preoperative surgical planning.

14.6 Surgical Management

Due to the slow growth rate and benign characteristics of hemangioblastomas, asymptomatic patients with spinal hemangioblastoma may be observed initially— especially in the setting of VHL—in order to avoid an excessive number

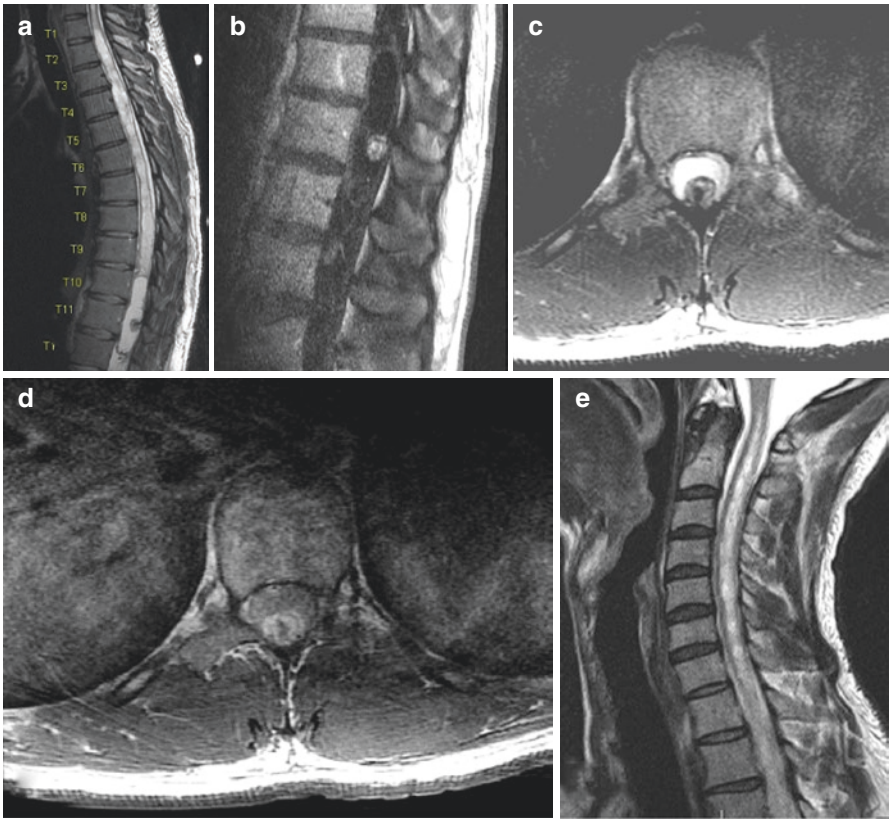

Fig. 14.2 Thoracic spinal cord hemangioblastoma (Patient 2: non-VHL disease, male patient operated by the senior author, KIA) [58]. (**a**) Preoperative MRI of spine. (**b**) T2-weighted sagittal MRI showing holocord spinal syrinx (above the lesion) and hypointense spinal cord hemangioblastoma at T11 surrounded by cyst. (**c**) T1 post-contrast sagittal MRI showing enhancing tumor nodule. (**d**) T2-weighted axial scan showing a tumor nodule. (**e**) T1 post-contrast axial MRI showing an enhancing tumor nodule. (**f**) Sagittal T2-weighted MRI showing syrinx extension to the brain stem

of surgical interventions [3, 17, 24]. Sporadic tumors not associated with VHL are curable by complete surgical excision, and are often present with symptoms that necessitate surgery. The current National Comprehensive Cancer Network guidelines suggest that primary spinal tumors undergo observation if they are asymptomatic, and undergo microsurgical resection if symptomatic [3, 18, 21, 32].

The goal of surgical treatment is complete removal of the tumor. Treatment of an associated cyst is usually not necessary as most improve with time with removal of the tumor [9, 33, 34]. The associated cystic cavity collapses upon nodule resection and pial opening. Additionally, associated edema and cord swelling usually resolves with time, following complete surgical excision [1]. The approach is often dependent upon the location of the tumor within the spinal canal. The posterior midline

approach with spinal laminectomy (or laminoplasty) and complete resection of the tumor is the most common and recommended approach [30].

The resection of a spinal hemangioblastoma should follow several surgical principles:

- Avoid entering the tumor nodule and causing significant hemorrhage
- Keep manipulation of neural tissue at a minimum and avoid any spinal vasculature not involved with the tumor nodule
- Use circumferential dissection in the plane between the tumor nodule and gliotic spinal cord
- Look for the junction of normal glistening white spinal cord pia and the sunset orange-yellow pia of the hemangioblastoma nodule with the microsurgical opening of the pia
- Treat the tumor like an arteriovenous malformation with low intensity bipolar coagulation of afferent vessels leading to the tumor nodule, and coagulate vessels close to the tumor in order to avoid damage to the spinal cord; coagulate the efferent veins last
- Shrink the nodule (if necessary) with low intensity coagulation

Due to the vast majority of spinal cord hemangioblastomas being located in the dorsum of the spinal cord, we describe our posterior approach to these tumors. Those tumors located anterior to the dentate ligament may be approached using an anterior or anterolateral approach.

Our surgical technique (senior author, KIA) (Figs. 14.3 and 14.4) involves prone positioning of the patient with laminectomies performed to provide exposure about 1–2 cm above and below the tumor. If tumor location involves cervical-thoracic or cervicolumbar junction, posterior sublimation should be considered. In younger patients and/or patients with tumor spanning several levels, laminoplasty should be considered. Ultrasound may be used to distinguish the tumor location once laminectomies are performed to aid in determining if further removal of the bone is needed. Bleeding from the edges of the bone laminectomy is easily controlled using Gelfoam Powder (Pfizer, New York, NY). We utilize Yasargil bipolar forceps with different, progressive lengths and different tip sizes which we use commensurate with intraoperative distances and surgical situation. Also, we use Yasargil controlled suctions of different sizes, where we can dial the strength of the suction according to intraoperative needs. Micro scissors of different sizes, straight and curved, with blunt and sharp tips in different lengths are used according to intraoperative situation and tactic.

The dura is incised in the midline with care to preserve the arachnoid plane. Retaining sutures are then placed to fasten the dura to surrounding soft tissues. The arachnoid membrane is opened (Figs. 14.3a and 14.4a) and retained to the dura using Ligaclips (Ethicon US, LLC, Somerville, NJ). An operative microscope is used to identify and dissect the hemangioblastoma nodule and free it from the supplying vessels. It is not necessary to enter the cyst cavity, if one is present, as complete tumor removal will eliminate and collapse the syrinx cavity.

The vasculature (perforators) that abuts the tumor margin is coagulated at low intensity with bipolar cautery; bipolar power is usually at 20–25 watts (Figs. 14.3b

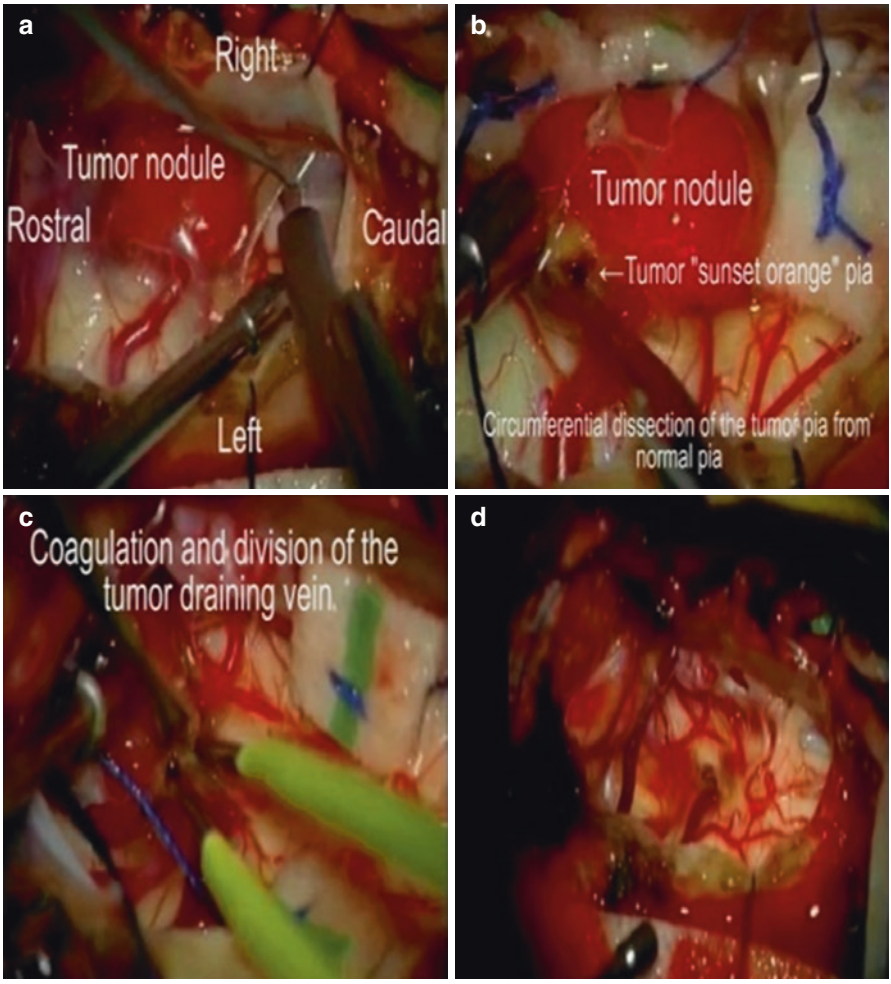

Fig. 14.3 Intraoperative microsurgical pictures of Patient 1 [57]. (**a**) Opening of arachnoid membrane. (**b**) De-vascularization of tumor nodule by coagulation of arterial feeders and division of the "sunset orange" pia of the nodule from white, "glistening" pia of the medulla. (**c**) Final coagulation of the tumor nodule draining vein before its division and delivery of the nodule. (**d**) Postoperative view of medulla oblongata after tumor nodule resection

and 14.4c). Care is taken to avoid violating the tumor capsule as this could cause unexpected bleeding. The pia is incised at the tumor margin to identify the gliotic plane between the tumor nodule and the spinal cord. There is often the clear margin between the white, glistening pia of the normal spinal cord and the orange-yellow pia of the tumor nodule. The pia is opened right at the junction between the 2.

The nodule is then circumferentially dissected using bipolar forceps and micro scissors to coagulate and divide the arterial feeder vessels that enter the tumor nodule. The draining vein of the nodule is kept intact until the very end, much like

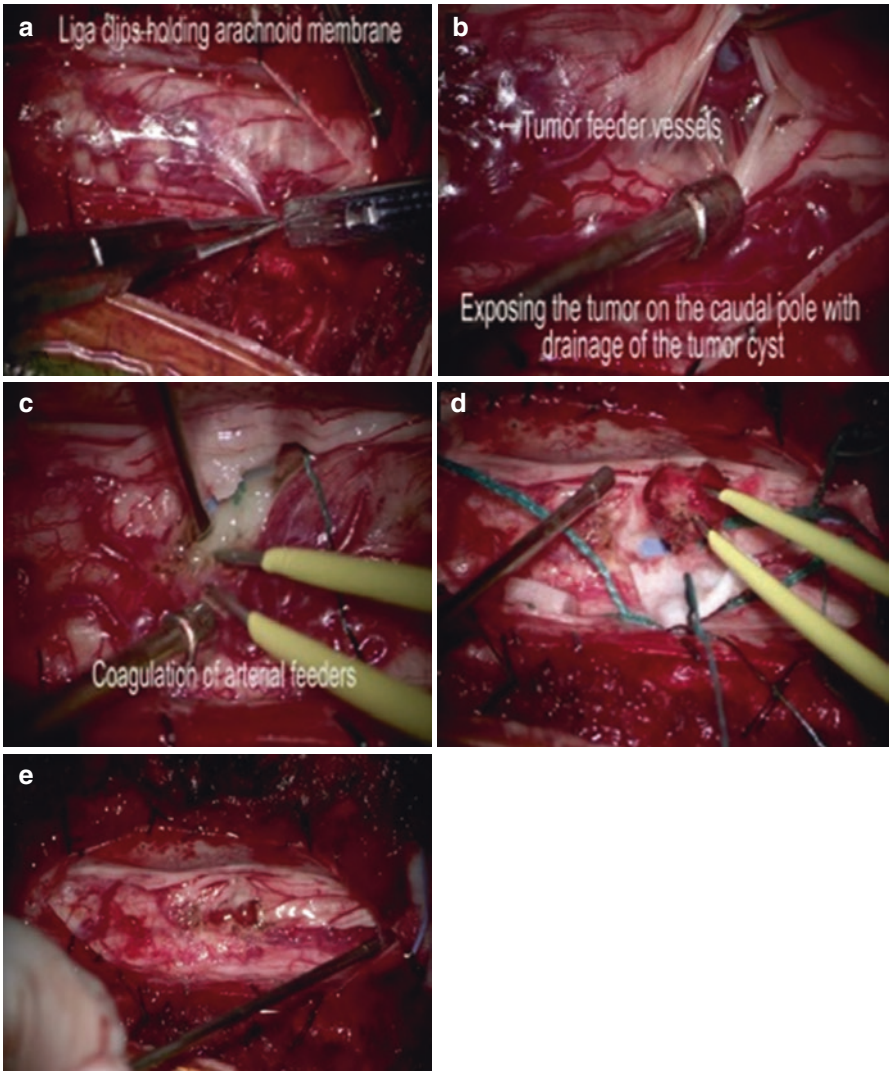

Fig. 14.4 Intraoperative microsurgical pictures of Patient 2 [58]. (**a**) Dura is opened. Arachnoid membrane tacked up to the dura with small Ligaclips. (**b**) Midline myelotomy below the tumor nodule with draining of the adjacent cyst. (**c**) Coagulation and division of arterial feeders to the nodule. (**d**) Delivery of the tumor nodule after coagulating and dividing the draining vein. (**e**) Spinal cord after tumor resection

resection of an arteriovenous malformation (Figs. 14.3c and 14.4c–d). Dynamic retraction can be performed by gentle use of the suction accompanied by microcotton pledgets as needed. Sensory nerve rootlets embedded in the tumor may be incised at thoracic levels; however, every effort should be made to preserve all neural tissue. Hemostasis is obtained using bipolar cautery (Figs. 14.3d and 14.4e).

The dura is closed in a simple running continuous watertight fashion and the remainder of the wound is closed in the standard fashion. We use a layer of fat tissue harvested from abdominal site at the beginning of surgery to cover the dura, obliterate any remaining "dead space," and avoid cerebrospinal fluid leak or pseudomeningocele formation [7]. Figures 14.3 and 14.4 show intraoperative photographs of surgical removal of hemangioblastoma while Figs. 14.5 and 14.6 show postoperative MRIs; Videos 14.1 and 14.2 also shows tumor removal.

We strongly recommend—and agree—with the literature that advocates for the routine use of neurophysiological monitoring during any surgery that involves the spinal cord by using somatosensory evoked potentials (SSEPs), motor evoked potential (MEPs), and nerve action potentials (NAP) stimulation [9, 36]. Additionally,

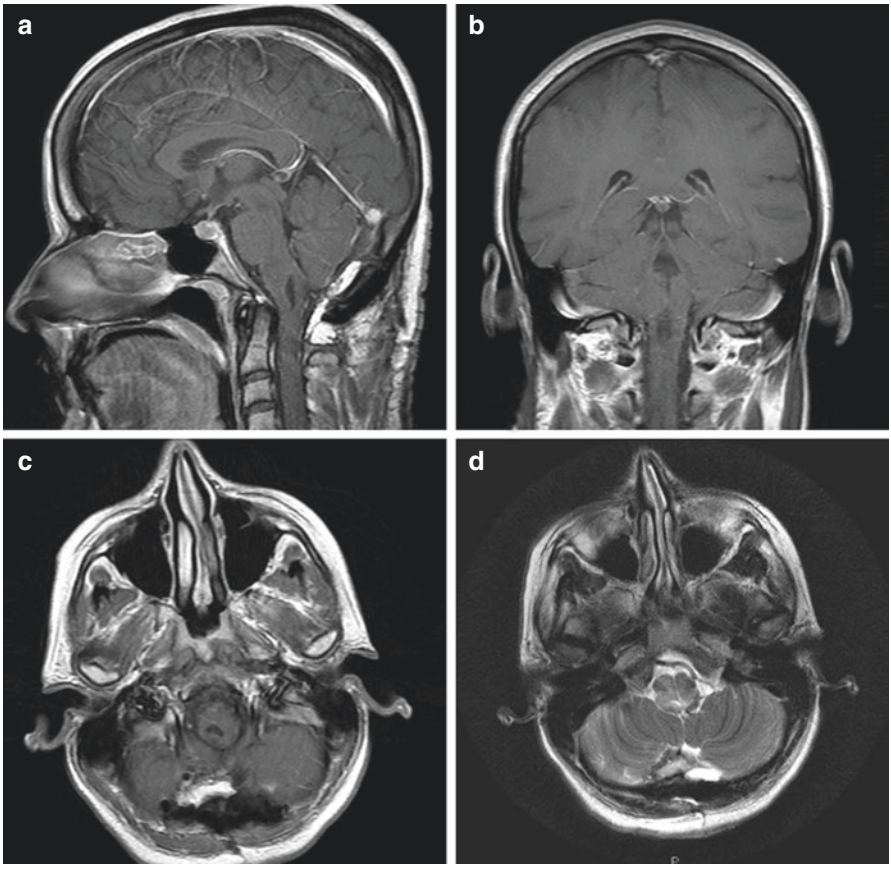

Fig. 14.5 Postoperative MRI of brain of Patient 1 [57]. (**a**) Post-contrast sagittal T1-weighted MRI showing cyst collapse after nodule resection. Note the fat graft dorsal to the dura to avoid CSF leak or pseudomeningocele formation. (**b**) Post-contrast coronal T1-weighted MRI showing cyst collapse after nodule resection. (**c**) Post-contrast axial T1-weighted MRI showing cyst collapse after nodule resection. Note the fat graft dorsal to the dura to avoid CSF leak or pseudomeningocele formation. (**d**) T2-weighted axial MRI showing cyst collapse after nodule resection

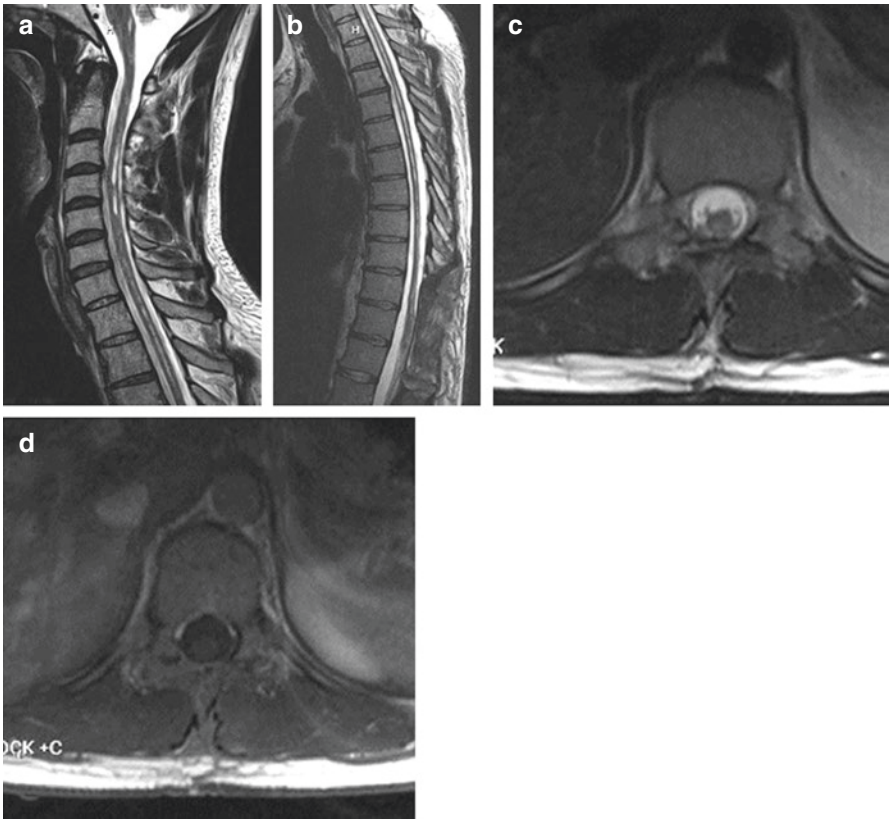

Fig. 14.6 Postoperative MRI of brain of Patient 2 [58]. (**a**) Sagittal T2-weighted MRI of cervical spine showing syrinx collapse after tumor resection. (**b**) Sagittal T2-weighted MRI of thoracic spine showing syrinx collapse after tumor resection. (**c**) Axial T2-weighted MRI showing postoperative thoracic spinal cord after tumor resection. (**d**) Axial T1-weighted post-contrast MRI showing postoperative thoracic spinal cord after tumor resection

temporary artery clipping of the main feeding artery when coupled with SEPs and MEPs can provide additional information to the surgeon on the safety of sacrificing vessels that are adjacent to and supply the tumor in order to facilitate safe removal of the nodule [37].

There are several common types of hemangioblastomas described that have special relevance to the technical aspects of surgical excision (Table 14.1).

14.7 Considerations in Pregnancy

The progression or presentation of spinal hemangioblastomas is known to occur during pregnancy and may be due to the increased blood volume and changing hormonal milieu [11, 38, 39]. Surgical resection has been noted to be the preferred

Table 14.1 Types of spinal hemangioblastoma and preferred approaches[a]

Type	Details	Surgical approach
Dorsal intramedullary	Most common; covered by a layer of pia mater and requires a midline myelotomy; located near dorsal nerve root entry zone.	Posterior approach Midline Myelotomy
Ventral intramedullary	Rare; outcomes worse due to difficulty of surgical excision.	Anterior or anterolateral approach [35]
Exophytic	Reaches the surface and can be directly removed; obviates the need for a midline myelotomy.	Posterior approach
Intradural Extramedullary	Does not have a direct attachment to cord parenchyma; can be directly removed.	Posterior approach
Extradural	Commonly arises from spinal nerves.	Posterior approach

[a]Adapted from Sun et al. [1].

treatment in order to prevent progression of neurological deficits, and has been noted to be safely performed in the second and third trimesters without increased risks of abortion or preterm labor. However, it is advisable to postpone surgery until after delivery with close observation of the patient and the patient's neurological condition, if clinically appropriate.

Careful consideration should be taken to prevent radiation to the fetus from diagnostic or intraoperative tests [39–42]. It is advised that a team-based approach with obstetric, anesthetic, and neurosurgical physicians should be used in the care of these patients.

14.8 Medical Management

Several medical therapies have been evaluated in the literature for treatment of difficult to resect spinal hemangioblastoma. Bevacizumab is a monoclonal antibody that blocks angiogenesis due to its effect on vascular endothelial growth factor A. There have been case reports of bevacizumab treatment causing significant tumor regression in a patient with an unresectable spinal cord hemangioblastoma [43]. Thalidomide has recently been shown to be effective in some cases of unresectable hemangioblastoma [44, 45]. However, the role of adjuvant chemotherapy in the treatment of hemangioblastoma remains controversial [2].

14.9 Radiosurgery

There have been reports of patients with spinal hemangioblastomas being treated with radiosurgery for unresectable tumors. However, radiosurgery has been reported to be associated with unfavorable outcomes, such as radiation necrosis, and often does not address the underlying symptom-causing syrinx [2, 46].

14.10 Preoperative Embolization

Preoperative embolization has been used in some reports in the literature to decrease vascularity. However, this often does not completely address the vascularity of the tumor and often requires super-selective catheterization, which can place the normal spinal parenchyma at risk and is usually not needed for complete resection [11]. It is, therefore, not used in the majority of patients undergoing surgical excision [37, 47–49], and in our opinion is mostly unnecessary.

14.11 Outcomes

The first excision of a spinal cord hemangioblastoma was described by Schultze in 1912 [20]. The neurological morbidity of spinal cord tumor surgery was poor until improvements in microsurgery and imaging arrived in the 1960s and 1970s [49–53]. We have compiled a summary of the available data in the literature showing outcomes of surgical resection of spinal hemangioblastomas in Table 14.2.

14.11.1 Neurological Outcome

Tumor location and size have been shown to affect outcome, with larger ventral and ventrolateral tumors associated with worse surgical outcomes [17, 30]. The McCormick functional status scale (Table 14.3) has been used in the literature to grade the neurological outcome of intrinsic spinal cord tumor surgery [54].

This scale, while not validated, has been used extensively in research of spinal cord tumors and hemangioblastomas. Several studies have shown that preoperative neurological status has a tendency to predict the postoperative neurological status of patients following resection of hemangioblastoma [31]. Microsurgical removal of tumors can result in favorable neurological outcomes, if good technique is applied and the conditions of the tumor are favorable (i.e., location, size, vascularity, and plane between tumor and spinal cord). The majority of patients operated on remain neurologically stable with a small subset who undergo neurological deterioration in the intraoperative period, but who eventually improve over time [17]. While not common, permanent neurological deterioration does occur and is often related to larger tumors that are not located in the dorsum of the spinal cord. Table 14.2 describes the outcomes of all of the case series that we could find available in the English literature as of October 2017.

14.11.2 Tumor Recurrence

Tumor recurrence can be due to either regrowth of new tumor, incomplete resection, or growth of new tumors in both VHL associated and sporadic hemangioblastoma. Young age, short duration of symptoms, multiple CNS tumors, and having VHL

Table 14.2 Literature review on studies evaluating spinal cord hemangioblastoma (both sporadic and VHL)

Authors (Year) Location Study Type	Patients (No.)	Treatment	Outcome	Follow up	Findings
Browne TR (1975) USA Retrospective cohort and literature review	N = 85 Male = 42 Female = 38 VHL: 36 (33%) Male = n/a Female = n/a	71 patients underwent surgeries, 7 patients had surgery followed by radiation, and only 2 received radiation therapy	Not formally documented	Not formally documented	Symptoms persisted with incomplete resection whereas complete resection caused almost complete resolution of symptoms. If incompletely resected, symptoms eventually recurred even if the cystic component had been removed with radiation for the residual tumor.
Guidetti B (1979) Italy Retrospective cohort	N = 6 Male = 3 Female = 3 VHL: 0 Male = n/a Female = n/a	6 patients underwent 6 surgeries	1 patient had intra-operative cardiac arrest and died after 24 h. 5 patients (83%) improved neurologically with phased return to work.	Mean, 28.5 (range, 2 months–11 years)	Patients undergoing complete surgical resection showed good neurological recovery compared with those who had incomplete resection or palliative procedures. Total removal is possible if a good plane is found between the tumor and the cord.

(continued)

Table 14.2 (continued)

Authors (Year) Location Study Type	Patients (No.)	Treatment	Outcome	Follow up	Findings
Pluta RM (2003) USA Retrospective cohort	N = 8 Male = 6 Female = 2 VHL: n/a Male = n/a Female = n/a	9 patients underwent surgery for ventral tumors: A posterior approach was selected to treat 5 patients (laminectomy and posterior myelotomy in 4 patients, and the posterolateral approach in 1 patient); an anterior approach (corpectomy and arthrodesis) was selected to treat the remaining 3 patients.	Immediately after surgery, the ability to ambulate remained unchanged in patients in whom an anterior approach had been performed, but deteriorated significantly in patients in whom a posterior approach had been used, because of motor weakness (4 of 5 patients) and/or proprioceptive sensory loss (3 of 5 patients). This difference in ambulation remained significant 6 months after surgery.	Mean for anterior approach, 28 +/− 9.2 months Mean for posterior approach, 79.6 +/− 38.6 months	The presence of an intraspinal syrinx should not influence the choice of surgical approach used to remove ventral spinal hemangioblastomas. In selected cases, the immediate and long-term results are appreciably better when surgery is performed using an anterior approach rather than a posterior or posterolateral approach.
Lee DK (2003) Korea Retrospective cohort	N = 14 Male = 11 Female = 3 VHL: n/a Male = n/a Female = n/a	14 patients underwent surgery with pre-operative angiography performed in 11 and pre-operative embolization performed in 4.	In 4 patients with preoperative embolization, intraoperative bleeding was minimal and total resection was possible. In 3 of 4 patients without total resection, their functional outcomes were aggravated postoperatively. At the last follow-up 8 patients were improved, 3 were stationary, and 3 deteriorated. All patients who showed improvements underwent total resection.	Mean, 47 months.	Total resection resulted in a better outcome. Preoperative embolization could be effective in the reduction of intraoperative bleeding and facilitate total resection with an improved surgical outcome.

Lonser RR (2003) USA Retrospective cohort	N = 44 VHL:44 (100%) Male = 26 Female = 18	44 patients with VHL underwent 55 operations with resection of 86 spinal cord hemangioblastomas.	84% of patients remained at the same McCormick grade, 7% improved (1 grade), and 9% worsened (1 or more grades) as of the final clinical assessment.	Mean, 44 months	Surgery improves McCormick status but having a ventral or ventrolateral lesion and the lesion being larger than 500mm^3 is associated with poor outcomes. The presence of a syrinx does not influence outcomes and the removal of a tumor associated with a syrinx leads to its resolution, alleviating the need for entering the syrinx, and doing so has strongly been discouraged.
Lonser RR (2005) USA Description of surgical technique	>190 operations (almost all were VHL patients)	More than 190 operations using microsurgical technique for resection	n/a	n/a	Hemangioblastomas, in contrast to other spinal cord tumors, are benign tumors that can be excised en bloc. Their technique uses administration of steroids at induction, a direct posterior approach to the tumor, ultrasound-guided identification of tumor site, development of a precise dissection plane, and relatively bloodless surgical field with no need to enter the syrinx associated with the tumor.

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Table 14.2 (continued)

Authors (Year) Location Study Type	Patients (No.)	Treatment	Outcome	Follow up	Findings
Biondi A (2005) France Retrospective cohort	N = 4 Male = 2 Female = 2 VHL: 1 Male = n/a Female = n/a	4 patients with lower spinal hemangioblastomas underwent embolization followed by surgery.	Embolization caused no permanent complications, although 1 patient with a cauda equina hemangioblastoma mildly worsened after the endovascular procedure, but recovered before surgery. At surgery, the tumor was completely removed in all cases. At 1-year postsurgical follow-up, 2 patients recovered completely from neurologic deficits, and 2 showed significant recovery.	Mean, 3.5 years	Pre-op embolization ensures less blood loss and easier manipulation of the tumor. It is therefore a useful procedure in aiding surgical resection.
Sharma BS (2007) India Retrospective cohort	N = 22 Male = 13 Female = 9 VHL:3 Male = n/a Female = n/a	22 patients underwent surgery	20 patients (91%) showed post-operative improvement or stability in their neurological deficits.	Mean, 4.6 years	Microsurgical resection is the treatment of choice even in the presence of gross pre-op neurological deficits.
Na JH (2007) Korea Retrospective cohort	N = 9 Male = 4 Female = 5 VHL: 5 Male = n/a Female = n/a	9 patients underwent surgery	All patients showed improvement or stability in their neurological deficits and there were no complications.	Mean, 22.4	Complete microsurgical resection in all cases of spinal hemangioblastomas provided good post-operative outcomes, and syrinxes associated with these tumors spontaneously resolved post-operatively.

Na JH (2007) Korea Retrospective cohort	N = 9 Male = 4 Female = 5 VHL: 3 Male = 2 Female = 3	9 patients underwent surgery	All patients remained stable post-operatively at 6-month follow-up whereas 3 (33%) improved by 1 grade at final follow-up with the remainder staying at their pre-operative grade. There were no complications or post-operative worsening of neurological symptoms.	Mean, 22.4 months	The posterior approach is safe and effective. Postoperatively, edema and syrinx resolved spontaneously. For early diagnosis and family consultation, the VHL mutation analysis was useful in patients with family history and in those with multiple hemangioblastomas.
Bostrom A (2008) Germany Retrospective cohort	N = 23 Male = n/a F:n/a VHL: 8 (35%) Male = n/a Female = n/a	23 patients underwent surgery	18 patients remained neurologically stable and 5 patients improved post-operatively. There was 1 case of tumor recurrence (even though the patient improved post-operatively) and 1 case of cerebrospinal fluid leak.	6 months	DSA is mandatory for pre-operative work-up, and en bloc resection by occlusion of the arteries and using bipolar coagulation is crucial. Radiographic progression and/or symptomatic progression prompts resection in VHL patients, but radiographic progression is a rarely-used an indication for surgery in patients with sporadic hemangioblastomas.

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Table 14.2 (continued)

Authors (Year) Location Study Type	Patients (No.)	Treatment	Outcome	Follow up	Findings
Shin DA (2009) Korea Retrospective cohort	N = 20 Male = 12 Female = 8 VHL: 2 (10%) Male = n/a F:n/a	20 patients underwent 24 operations	18 (90%) patients remained at the same grade or improved post-operatively; 2 patients progressed to a higher grade post-operatively; 5 had recurrence, 3 of whom had revision; 1 had radiation and 1 was observed.	Mean, 5.6 years	Pre-operative motor weakness and paraesthesia are more commonly present in those with cystic components; syrinxes shrank in 86% after tumor removal. En bloc resection is the fundamental surgical principle, aided by the tumor having a well-defined capsule.
Mandigo CE (2009) USA Retrospective cohort	N = 15 Male = 7 Female = 8 VHL: 4 Male = n/a Female = n/a	15 patients underwent 17 surgeries for the removal of 18 hemangioblastomas	1 patient worsened by 1 grade post-operatively; 1 improved by 1 grade; all others (87%) stayed at the same grade.	Mean, 35 months	Pregnancy can exacerbate the symptoms of these tumors—But microsurgical en bloc resection remains the treatment of choice in all cases. A technique that has been perfected over almost a century, it causes minimal blood loss and most importantly, minimal neurological morbidity.

Clark A.J (2010) USA Retrospective cohort	N = 20 Male = n/a Female = n/a VHL: 11 (55%) Male = n/a Female = n/a	20 patients underwent surgery, 5 of whom had additional intra-operative temporal artery occlusion with concurrent neuromonitoring.	Of the 20 patients, 5 improved, 13 remained stable, and 2 worsened. Of the 5 treated with TAO, 2 improved, 3 remained stable, and none worsened. Median McCormick's functional grade of patients treated with TAO was II and improved to I after the operation, whereas the grade of those not treated with TAO remained unchanged at II.	Mean, 19 weeks	Temporary arterial occlusion with concurrent neuromonitoring is a fast, safe, and efficient method that may assist the surgeon in difficult cases in differentiating tumor vessels from those supplying the spinal cord.
Mehta GU (2010) USA retrospective cohort	N = 108 Male = 57 Female = 51 VHL: 108 (100%) Male = 57 Female = 51	108 patients underwent 156 operations for resection of 218 spinal cord hemangioblastomas.	At 6-month follow-up, patients were stable or improved after 149 operations (96%) and worse after 7 operations (4%). The proportion of patients remaining functionally stable at 2, 5, 10, and 15 years' follow-up Was 93, 86, 78, and 78%, respectively.	Mean, 7 years +/− 5 years	Ventral or completely intramedullary tumors were associated with an increased risk of post-operative worsening. Symptom progression and not radiological progression alone should prompt surgical resection in VHL patients, which is a strategy that permits long-term stability of neurological status in most cases.

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Table 14.2 (continued)

Authors (Year) Location Study Type	Patients (No.)	Treatment	Outcome	Follow up	Findings
Kim TY (2012) Korea Retrospective cohort	N = 12 Male = 9 Female = 3 VHL: 12 (100%) Male = 9 Female = 3	12 patients with 24 spinal cord hemangioblastomas were divided into 3 treatment groups: Group 1 (13 tumors), asymptomatic tumors at initial diagnosis followed with serial imaging studies; group 2 (4 tumors), asymptomatic tumors at initial diagnosis that were subsequently resected; and group 3 (7 tumors), symptomatic tumors at initial diagnosis, all of which were resected.	7 tumors exhibited symptoms when diagnosed, and 17 did not. Among these 17 tumors, 9 tumors (53%) were ultimately resected. The 5 asymptomatic patients (42%) were McCormick grade I and remained at the same grade post-operatively. Among the symptomatic patients, 3 showed a 1-point reduction in functional status (25%), and 1 worsened from grade 1 to grade IV (8%).	Mean, 49.3 months	VHL patients with a large tumor and an extensive syrinx were at a greater risk of neurological deficits, some of which may be irreversible. Thus, the functional outcomes of patients with a large tumor are affected more by the presence of neurological symptoms and deficits than by the tumor volume itself, and thus resection of significantly large asymptomatic tumors might bring about better outcomes.
Harati A (2012) Finland Retrospective cohort	N = 17 Male = 10 Female = 7 VHL: 11 Male = N/A Female = N/A	17 patients underwent microsurgical resection of 20 tumors.	No patient had neurological decline on long-term follow-up. Among the patients with VHL, 5 patients with pre-operative sensorimotor deficits showed improvement of their symptoms but never regained full function. One patient who presented with tetraplegia remained the same.	Mean, 57 months	Asymptomatic patients with VHL benefit from early resection as well as those with a tumor size larger than $55mm^3$.

Park C.H (2012) Korea Retrospective cohort	Total: 16 Male = 12 Female = 4 VHL: 4 Male = n/a Female = n/a	16 patients underwent 30 operations; of these, 10 patients had pre-operative angiography and 3 had pre-operative embolization.	10 patients had total resection whereas 6 had subtotal resection. Postoperatively, improvement was noted in 18.7%, stability in 56.3%, but 25% were worse. Stable postoperative neurological functions were found in 83% of patients with preoperative McCormick grade I, and total resection was achieved In 75% of these patients.	Mean, 90 months	Capsule of the tumor is fragile, which is why pre-operative angiography is mandatory for knowledge of feeders and to avoid intra-operative bleeding and subtotal resection. In addition, the feeding artery should be dissected before the draining vein is coagulated. Preoperative mild deficit and fastidious microsurgical technique are associated with favorable outcomes, whereas age over 70 is a predictor of poor outcome. There is no correlation between postoperative functional outcomes and other variable factors, such as tumor size or location, the extent of resection, the recurrence or progression of the lesion, and the number of repeated surgeries. In addition, a non-aggressive surgical approach is the optimal strategy to preserve the neurological function in spinal cord hemangioblastomas associated with VHL disease.

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Table 14.2 (continued)

Authors (Year) Location Study Type	Patients (No.)	Treatment	Outcome	Follow up	Findings
Deng X (2014) China Retrospective cohort	N = 92 Male = 59 Female = 33 VHL: 32 (34.8%) Male = n/a Female = n/a	92 patients underwent 102 operations for resection of 116 intraspinal hemangioblastomas. Preoperatively, 13 patients underwent DSA, 15 patients underwent 3D CTA.	Gross-total resection was achieved for 109 tumors (94.0%), and subtotal resection for 7 tumors. Functional outcome improved for 38 patients (41.3%), remained stable for 40 (43.5%), and deteriorated for 14 (15.2%).	Mean, 50 months	Gross-total resection leads to better outcomes. Subtotal resection is a risk factor for poor outcomes. Compared with spinal DSA, 3D CTA is a promising technique because it is noninvasive, takes less time to perform, requires lower X-ray doses and less contrast media, results in fewer complications, and offers high accuracy for delineating the feeding arteries.
Sun H.I (2014) Turkey Retrospective cohort	N = 14 Male = 8 Female = 6 VHL: 0 Male = n/a Female = n/a	14 patients with sporadic spinal hemangioblastoma underwent 15 operations during a span of 23 years.	Symptoms improved after 8 (53.3%) of 15 operations, remained the same after 5 (33.3%), and worsened after 2 (13.3%). Gross total resection was achieved in all cases, and there was 1 recurrence in 15 years.	Mean, 4 years	Sporadic spinal hemangioblastomas occur slightly more often than those associated with VHL disease, are most commonly encountered as solitary lesions, and are most frequently located in the upper spinal cord. Excellent surgical results can be achieved with microsurgery without the use of preoperative or postoperative adjuvant therapies, and the long-term outcome is good with only rare recurrences.

Joaquim AF (2015) USA Retrospective cohort	N = 16 Male = 10 Female = 6 VHL: 7 Male = n/a Female = n/a	16 patients underwent 17 surgeries.	Total resection was achieved in all cases; 4 patients had some functional worsening immediately after surgery but at 6 month follow-up, 1 patient remained functionally worse, 2 improved, and the remainder (81%) remained stable.	Mean, 48 months	The use of neurophysiological monitoring, accompanied with a meticulous surgical technique that avoids disruption of the spinal cord outside the tumor boundaries, can almost work as a guarantee that postoperative deficits will not occur—Surgery generally maintains the patient's preoperative neurological status.
Liu A (2016) USA Retrospective cohort	N = 21 Male = 14 Female = 7 VHL:0 Male = n/a Female = n/a	21 patients with sporadic intramedullary spinal hemangioblastomas underwent 23 surgeries.	Total resection was achieved in all but 1 surgery, and no cases involved intraoperative complications. However, postoperative complications occurred after 5 cases; 12 patients (57%) experienced long-term dysfunction after surgery, and 2 patients experienced recurrence requiring a second surgery.	Mean, 12 months	Total resection can be achieved successfully with surgery and effectively improve neurological function with rare recurrences.

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Table 14.2 (continued)

Authors (Year) Location Study Type	Patients (No.)	Treatment	Outcome	Follow up	Findings
Pan J (2016) USA Retrospective cohort	N = 28 Male = 14 Female = 14 VHL: 14 (50%) Male = n/a Female = n/a	28 patients with 48 tumors were treated using CyberKnife image-guided radiosurgery.	Radiographic follow-up was available for 19 patients with 34 tumors; 32 (94.1%) tumors were radiographically stable or displayed signs of regression. Actuarial control rates at 1, 3, and 5 years were 96.1%, 92.3%, and 92.3%, respectively. Clinical evaluation on follow-up was available for 13 patients with 16 tumors; 13 (81.2%) tumors in 10 patients had symptomatic improvement. No patient developed any complications related to radiosurgery.	Mean, 54.3 months	Stereotactic radiosurgery allows for excellent local control and symptomatic management of spinal hemangioblastomas in both VHL and sporadic lesions with an optimal safety profile. Stereotactic radiosurgery is associated with an optimal local tumor control rate, low risk of adverse events and complications, and can be used to treat spinal cord lesions that pose high risk for resection.
Das JM (2017) India Retrospective cohort	N = 14 Male = 6 Female = 8 VHL: 7 (50%) Male = 3 Female = 4	14 patients underwent 18 surgeries.	8 patients had neurological deterioration in postoperative period (5 recovered); 11 (79%) patients had good functional outcome at 5 years.	Mean, 5 years	Microsurgical removal of spinal hemangioblastoma can result in postoperative neurological deterioration, however, complete microsurgical excision can result in good functional outcomes at 5 years.

Siller S (2017) Germany Retrospective cohort	N = 24 Male = 12 Female = 12 VHL: 10 Male = n/a Female = n/a	24 patients underwent 26 operations for 27 spinal cord hemangioblastomas with intra-operative neurophysiology	Long-term follow-up evaluation revealed a stable or improved McCormick myelopathy grade in 88.2% of the patients, and 88.2% reported a stable or improved overall outcome, according to Odom's criteria. Long-term general performance was excellent with 88.2% having a ECOG performance status grade ≤ 1.	Mean, 7 +/− 4 years	Microsurgical resection with IONM ensures good long-term outcome for patients. Nonpathological IONM findings are associated with a lower risk of new sensorimotor deficits and correlate with a better overall long-term outcome. VHL is a risk factor for a worse long-term prognosis.

CTA computed tomography angiography, *DSA* digital subtraction angiography, *ECOG* Eastern Cooperative Oncology Group, *IONM* intraoperative neurophysiological monitoring, *n/a* not applicable, *TAO* temporary arterial occlusion, *VHL* von Hippel-Landau

Table 14.3 McCormick functional status scale

Grade	Description
I	Neurologically intact, may have minimal dysesthesia, normal gait
II	Mild motor or sensory deficit, patient maintains functional independence
III	Moderate deficit, limitation of function, independent with external aid
IV	Severe motor or sensory deficit, limited function, dependent
V	Paraplegia or quadriplegia, even with flickering movement

disease have been associated with increased tumor recurrence [55]. Sporadic hemangioblastomas have been reported to have a recurrence rate of 6–7% following surgical excision and often occur many years after surgical resection illustrating the need for continued long-term follow-up of these patients [1]. Hemangioblastomas associated with vHL have been classified into three different growth patterns: saltatory, linear, or exponential with tumor growth rates of $4mm^3/y$, $24mm^3/y$, and $79mm^3/y$ respectively [56]. Additionally, hemangioblastomas occurring in the spinal cord and cauda equina grew at slower rates compared with those found elsewhere in the CNS (median $0.3mm^3/y$ and $0mm^3/y$ respectively) and higher growth rates were observed in males compared to females [56].

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Myxopapillary Ependymomas

15

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15.1 Definition

Myxopapillary ependymomas (MPEs) were first defined as a distinct subtype of ependymomas by Kernohan in 1932 [1]. These tumors account for approximately 1–5% of all spinal neoplasms with an incidence of 0.0–0.08 cases per 100,000 persons annually [2, 3]. The incidence in the American population was found to be 1.00 per million person-years [4]. Fifty percent of ependymomas are spinal and—within this group—50% are MPEs [5]. Extramedullary ependymomas arise from the ependyma of the filum terminale located in the area of the conus medullaris and cauda equina. Histologically, the overwhelming majority are myxopapillary [6]. MPE is a slow-growing tumor most frequently found in adults between 30 and 50 years of age [7] and they constitute around 13% of all ependymomas and as many as 90% of all tumors in the conus medullaris [8–10]. MPEs originates from the filum terminale in the area of the conus medullaris and cauda equina [11], and are classified as a WHO Grade I Tumor. The main bulk of the tumor is located in the lumbar canal below the conus medullaris with up to one-third of the tumors extending to thoracic spine and one-fifth of these tumors extending to sacrum [6].

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The recommended treatment for patients with MPE is gross total resection, and patients undergoing subtotal resection usually also undergo radiotherapy [12]. Despite the benign histology and slow-growing nature of most MPE tumors, some MPEs behave in an aggressive manner. Treatment failure of MPE with local recurrence, distant spinal metastasis, and brain metastasis has been reported to occur in one-third of patients [13]. Signs of postoperative aggressive behavior, after either subtotal or gross total resection, are local recurrence and aggressive growth. Another sign of aggressive behavior is secondary seeding (i.e., metastasis) of an MPE to distant cranial and spinal sites or to local spinal sites after surgery [11]. MPEs have been reported to be more aggressive in pediatric patients than in adults with local rates and recurrence of 64% compared with 32% in adults [14]. The focus of our discussion will be on MPEs in adults since the topic of pediatric MPEs has been covered in another chapter of this book (Chap. 16).

15.2 Histopathology and Molecular Biology

Grossly, these tumors are well-encapsulated, reddish to purplish in color, and sausage-shaped [15]. The microscopic morphology of MPE is characterized by a papillary arrangement of cuboidal or elongated tumor cells surrounding a fibrovascular core, which contains both hyalinized blood vessels and a marked abundance of extracellular mucoid matrix [16].

It has been hypothesized that there are intrinsic molecular differences and genetic types of MPE that are currently unrecognized [11]. This could represent a spectrum of different grades of MPE, perhaps with the most aggressive tumors presenting earlier in childhood and the indolent tumors remaining clinically occult due to their slow growth and presenting later in adulthood. Also, one can speculate that in the younger pediatric population, tumor cells of the same type have a higher propensity for division [11]. There are several molecular markers of MPEs. The receptor tyrosine kinase cMET and HOXB13 gene are included in histologic and molecular analysis research of MPE. cMET may have a role in more invasive behavior of MPE since cMET activation in brain malignancy enhances cell proliferation, migration, and invasion and inhibits cell death [11]. The HOXB13 gene has been identified as a molecular signature for MPE [17]. HOXB13 is more specific for MPE while HOXA9 is more specific for ependymoma. HOXB13 was expressed equally in pediatric and adult patients with MPE [17]. MIB-1, a marker for cellular proliferation, has low expression in MPEs due to their inherent benign biological profiles [16]. Epidermal growth factor receptor (EGFR) protein expression has been shown to predict a worse clinical correlate for patients with intracranial MPEs [18] and was found in all recurrent tumors but not in tumors that did not recur [16, 19]. Matrix metalloproteinases (MMPs) are a family of zinc dependent endopeptidases that are capable of degrading extracellular matrix proteins, which may lead to the promotion of metastasis. Aggressive megakaryocyte-erythroid progenitor cells showed overexpression of platelet-derived growth factor receptor A (PDGFRα), MMP2 and MMP14 [16], which may be new diagnostic and therapeutic targets [16]. MPE may

be driven by a Warburg metabolic phenotype [20] with western blot analysis demonstrating increased protein expression of hypoxia-inducible factor 1-alpha (HIF-1α), hexokinase 2 (HK2), pyruvate dehydrogenase kinase 1 (PDK1), and phosphorylation of pyruvate dehydrogenase (PDH)-E1A [20].

15.3 Classification

We have proposed a novel classification system of the MPEs. This classification is based on the location of the tumor and its correlation with extent of resection (Table 15.1). It is important to note that this classification is more an anatomical than surgical one as the biological behavior of the tumor, its aggressiveness, and its recurrence rate depends on multiple factors, which are discussed in this chapter. Figures 15.1, 15.2, 15.3, 15.4 and 15.5 demonstrate various cases of MPEs operated on by the senior author (KIA); Figs. 15.6 and 15.7 demonstrate cases of MPEs operated by primary author. Figure 15.8 shows the schematic diagram of our original classification of MPE.

15.4 Symptoms

MPEs are tumors with long history. Mean time between the first symptom and diagnosis was reported to range from 46 months [21] to 8 years [6]. The clinical presentation of MPEs with regard to patient age and duration of symptoms does not differ significantly from other intradural tumors that occur below the cord in the region of the filum [9]. The most common initial symptom is nonspecific back pain [6, 14, 22, 23]. Back pain, lower limb weakness, and sensory disturbances often occur together

Table 15.1 Classification of myxopapillary ependymomas (MPEs)

Type IA	Only filum terminale is involved by the MPE (rare extramedullary intradural lesion). GTR (gross total resection) easily feasible.
Type IB	Extramedullary MPE involving a lumbar nerve root with filum terminale. GTR more challenging than type I A.
Type II	Intramedullary involvement of conus medullaris and filum terminale. GTR.
Type III	Intramedullary involvement of lower part of spinal cord, conus medullaris and filum terminale (upper lumbar cord enlargement).
Type IVA	Intramedullary involvement of lower part of spinal cord and conus with solid and cystic component. No signs of hydro- or syringomyelia.
Type IVB	Involvement of entire conus and lumbar intumescencia with cystic compartment and signs of hydro- or/and syringomyelia in the upper part of the spinal cord. Slow growing, resection GTR or STR. More aggressive behavior with primary/secondary seeding.
Type VA	Tumor is located outside the lumbar part of the spinal cord but remains intradural (cervical/thoracic spine)
Type VB	Tumor is located outside the spinal canal (sacrococcygeal, mediastinal, intracranial MPE)

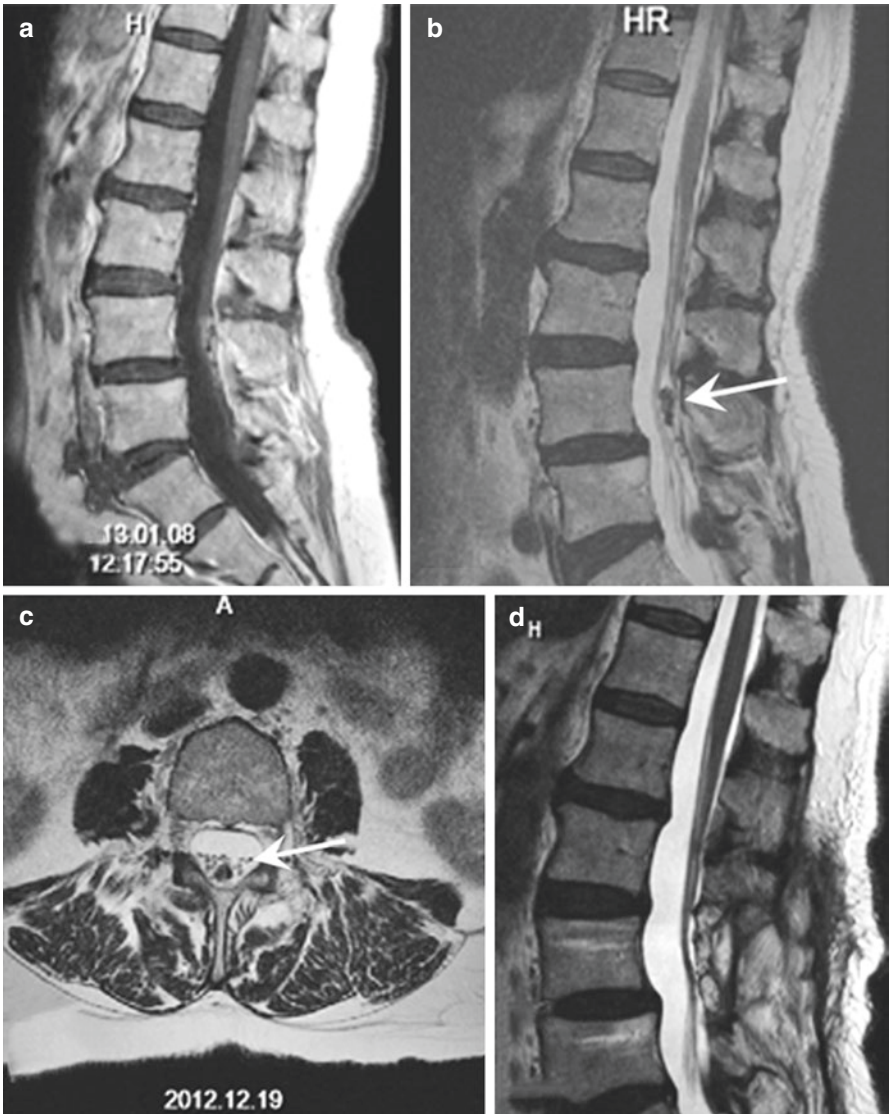

Fig. 15.1 Lumbar spine imaging of a 72-year-old female patient with lower back pain and bilateral leg pain and previous history of cancer. Preoperative MRI of the lumbar spine: (patient operated on by the senior author [KIA]): (**a**) sagittal post-contrast T1-weighted MRI shows intradural-extramedullary tumor (myxopapillary ependymoma) at L4 (arrow) confined to filum terminale without adherence to the nerve roots (Type IA); (**b**) sagittal T2-weighted MRI; and (**c**) axial T2-weighted MRI of the lumbar spine. (**d**) Postoperative sagittal T2-weighted MRI of the lumbar spine demonstrates total resection of the tumor

[14, 24]. Less than 10% of patients consider gait ataxia, sexual problems, or sphincter problems, although up to 50% of patients have bladder dysfunction [9, 10, 21].

Rapid worsening could indicate an intratumoral hemorrhage [21, 25, 26] with rare cases of hydrocephalus due to spinal subarachnoid hemorrhage [21]. Conus

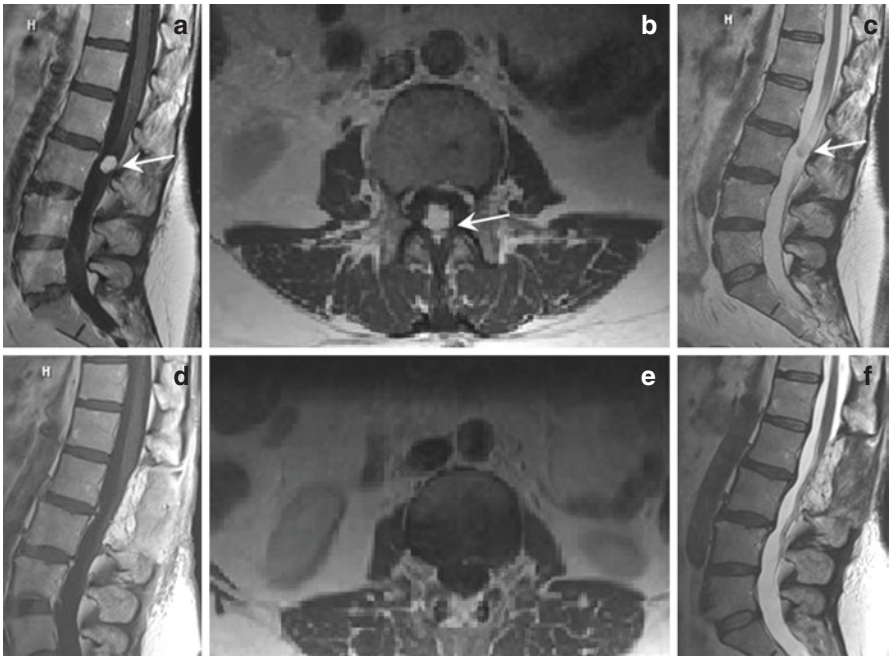

Fig. 15.2 Imaging of a 56-year-old female patient with back pain, numbness and tingling in legs with difficulties voiding. Preoperative MRIs of the lumbar spine (patient operated on by the senior author [KIA]): (**a**) sagittal post-contrast T1-weighted MRI showing encapsulated enhancing tumor at L3 (arrow) without involvement of filum terminale and nerve roots of cauda equine (Type IA); (**b**) axial post-contrast T1-weighted MRI; (**c**) sagittal T2-weighted MRI of the lumbar spine. Postoperative MRIs of the lumbar spine demonstrating complete tumor resection: (**d**) sagittal post-contrast T1-weighted MRI; (**e**) axial post-contrast T1-weighted MRI; (**f**) sagittal T2-weighted MRI. The patient recovered completely and was neurologically intact

medullaris and filum terminale lesions are located at a highly mobile segment of the spine, and the traction forces might cause disruption of blood vessels on the surface of the tumor. Histopathologic factors relate to the presence of numerous small blood vessels and loss of connective tissues in the tumor [25].

15.5 Imaging

On gadolinium-enhanced MRI motor evoked potential (MEPs), like their intramedullary counterparts, enhance brightly with contrast. Enhancement may be homogeneous or patchy due to small intratumoral cysts and hemorrhages [6]. MPEs differ slightly than other ependymomas in that they may appear hyperintense on T1-weighted images as well due to the proteinaceous mucoid matrix [27]. With further improvements in the resolution of MRI, even very small leptomeningeal seeding can be detected [22]. Cysts that expand cranially and caudally from the tumor as well as hydro- and syringomyelia are not uncommon. Unencapsulated tumors are more frequently seen in heterogeneously enhanced tumors on MRI than

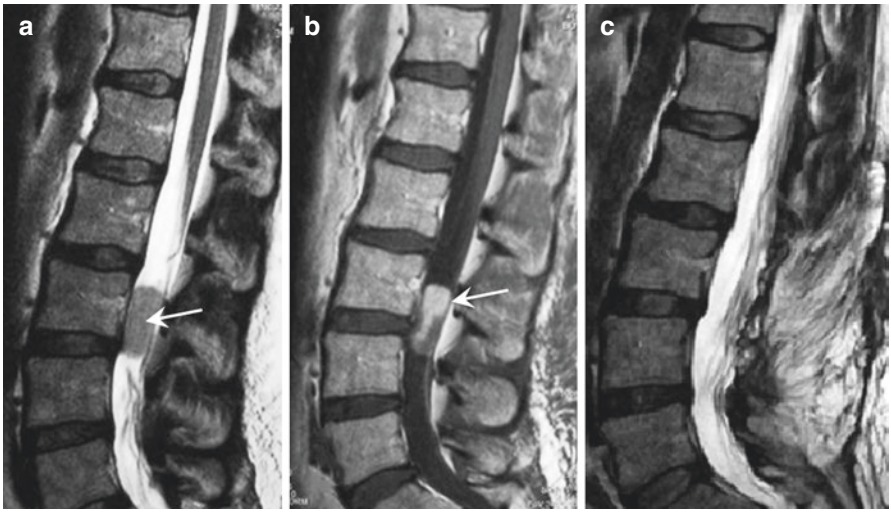

Fig. 15.3 Imaging of a 47-year-old female patient with paraparesis, L2 sensory level, and bowel incontinence (patient operated on by the senior author [KIA]). (**a**) Preoperative sagittal T2-weighted MRI of the lumbar spine demonstrating myxopapillary ependymoma at L3 segment (arrow) Type IB. (**b**) Preoperative sagittal post-contrast T1-weighted MRI of the lumbar spine. Complete resection of the tumor was performed. The patient recovered completely and was neurologically intact. (**c**) Postoperative T2-weighted MRI of the lumbar spine demonstrating complete resection

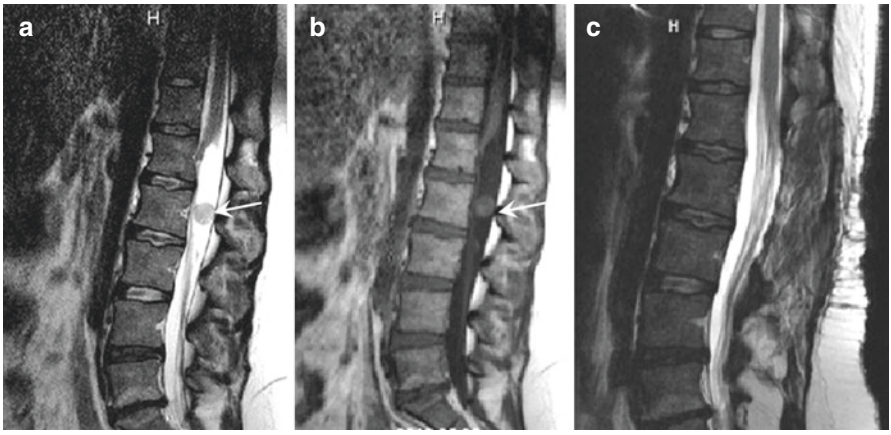

Fig. 15.4 Imaging of a 35-year-old patient with severe low back pain and urinary retention (patient operated on by the senior author [KIA]). (**a**) Preoperative sagittal T2-weighted MRI of the lumbar spine. (**b**) Sagittal post-contrast T1-weighted MRI of the lumbar spine demonstrating MPE at L2 with large cystic component, involvement of conus and lumbar intumescence, and hydromyelia (type IVB). (**c**) Postoperative sagittal T2-weighted MRI of the lumbar spine demonstrating complete resection with cyst drainage and resolved hydromyelia. Urinary retention resolved completely, the patient had no neurological deficits

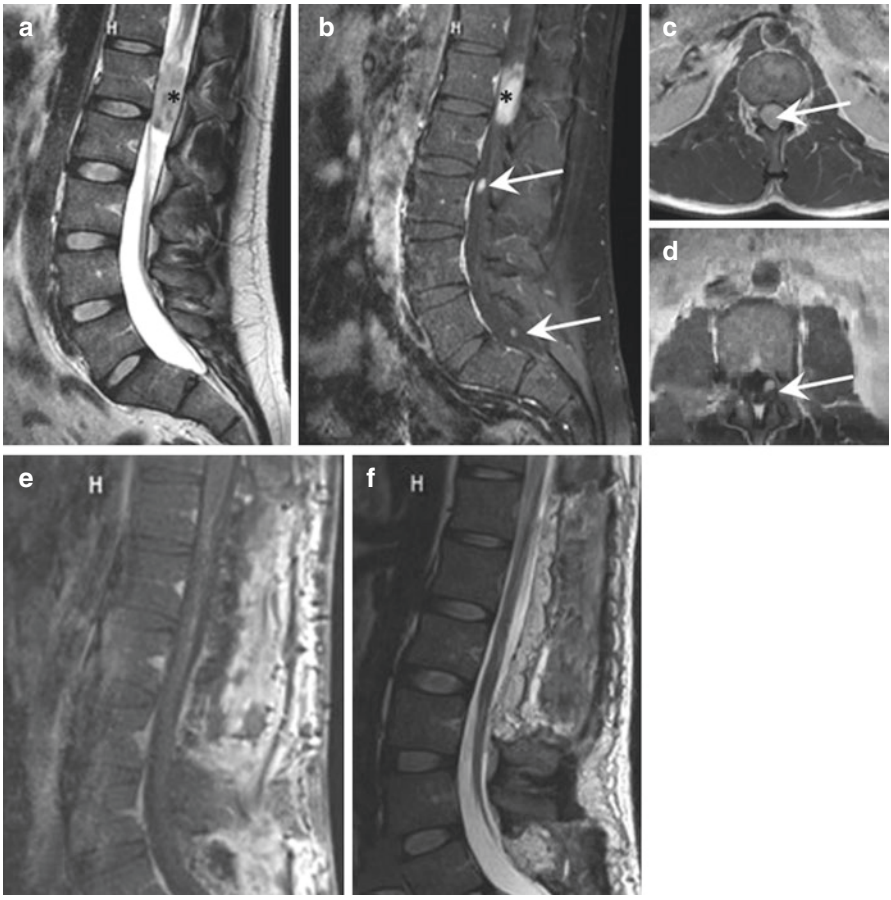

Fig. 15.5 Imaging of a 33-year-old male patient who presented with urinary retention (patient operated on by the senior author [KIA]). (**a**) Preoperative sagittal T2-weighted MRI of the lumbar spine demonstrating large MPE (*) at L1–L2 with involvement of spinal cord, conus medullaris and filum terminale. (**b**) Sagittal post-contrast T1-weighted MRI of the lumbar spine showing 2 further lesions (arrows) at L3 and S1 (type IVB). (**c**) Axial post-contrast T1-weighted image showing tumor at L1. (**d**) Axial post-contrast T1-weighted image shows the tumor at L3. Postoperative MRI demonstrates the total resection of all of the three tumors: (**e**) sagittal T2-weighted MRI and (**f**) sagittal post-contrast T1-weighted MRI. Urinary retention resolved completely. Further screening did not show the presence of secondary seeding

in homogenously enhanced tumors [28]. Computed tomography (CT) scan is useful for demonstrating erosive bone changes that can vary from nonspecific canal widening, to scalloped vertebral bodies, to neural foraminal enlargement, and finally to osseous destruction [29].

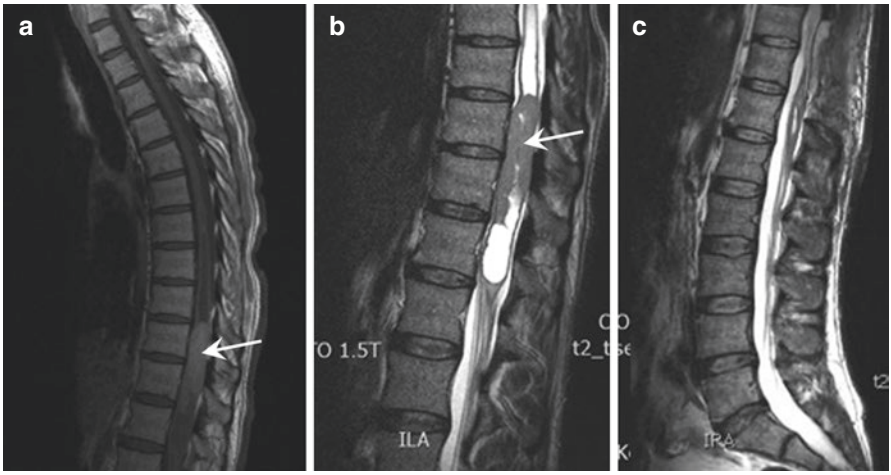

Fig. 15.6 Imaging of a 45-year-old female patient who presented with paraparesis and urinary retention (patient operated on by IO). Preoperative MRI of the spine: (**a**) sagittal post-contrast T1-weighted MRI showing cystic contrast-enhancing tumor (arrow) at T10-L1; (**b**) intratumoral cyst with syringomyelia is best seen in sagittal T2-weighted MRI (Type IV B). (**c**) Postoperative sagittal T2-weighted MRI of the spine showing the complete resection of the tumor with resolution of syringomyelia

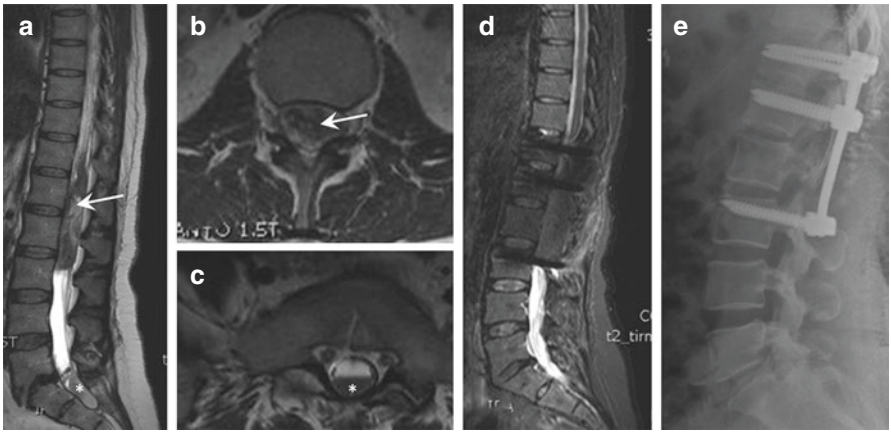

Fig. 15.7 Imaging of a 43-year-old female patient who presented with acute onset of paraparesis and urinary retention (patient operated on by IO). (**a**) Sagittal T2-weighted MRI of the lumbar spine revealing intratumoral hemorrhage at L1–L3 (arrow) with subdural hematoma at S1 (*) (Type IVA). (**b**) Axial T2-weighted MRI of the lumbar spine shows the tumor mass (arrow). (**c**) Axial T2-weighted MRI of the lumbar spine showing subdural hematoma at S1 (*). Complete tumor resection and evacuation of the hematoma were performed. Due to laminectomy over 3 levels, additional spinal stabilization was performed. (**d**) Postoperative sagittal T2-weighted MRI of the lumbar spine following tumor resection and hematoma evacuation showing complete resection without residual hematoma. (**e**) Postoperative sagittal X-ray of the lumbar spine demonstrating T12–L3 stabilization of the thoracolumbar transitional area

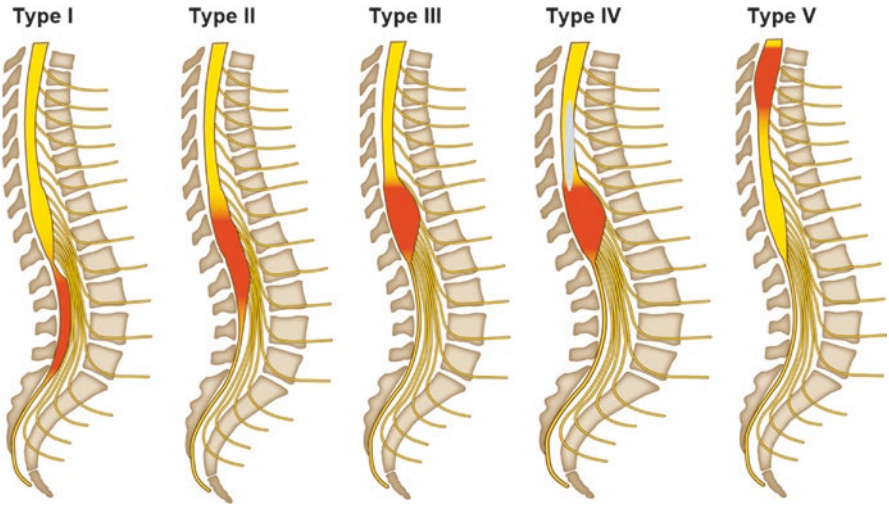

Fig. 15.8 Schematic diagram of the classification of myxopapillary ependymomas (from Omerhodzic, Pojski and Arnautović 2018)

15.6 Rare Locations

Myxopapillary ependymomas can occur in ectopic sites, such as the sacrum and in presacral tissue where ependymal cells may be found. These ectopically located tumors have a worse prognosis and a higher rate of extraneural metastasis. Sacrococcygeal [30–32], intracranial [33], and soft tissue myxopapillary ependymomas have been described, as well as extraneural metastases in the lungs, pleura, liver, and thoracic and abdominal lymph nodes [34]. Case series on extradural ependymomas showed higher local recurrence rate (60% for presacral and 25% for tumors on the dorsal aspect of sacrum) compared with classical MPEs, with a mortality rate of up to 50% in one case of local recurrence [29] and a 100% 5-year mortality if metastases occur. Giant sacral MPEs may require resection, lumbopelvic reconstruction and fusion, followed by radiotherapy [31]. Intradural lumbosacral ependymomas can spread throughout the central nervous system (CNS) but rarely metastasize beyond it, whereas extradural ependymomas seldom disseminate within the CNS but pose a significant risk for systemic metastases [35].

15.7 Surgical Technique

Removal of ependymomas in the lumbar and sacral region may be quite difficult as these tumors are well-vascularized and may not display a capsule, so that they may completely encase nerve roots of the cauda equine [9]. Nerve roots and the spinal cord may be very adherent to—or even infiltrated by—the tumor [36], and surgical

morbidity for these tumors is considerably higher compared with other extramedullary pathologies [37].

Both microsurgical technique and spinal cord monitoring are indispensable to achieve total removal of MPEs and to obtain improvement of neurological recovery [38]. Based on plane of dissection and intraoperative neurophysiological monitoring (IONM), GTR should be always the goal. Tumor resection can be safely achieved, if the tumor is encapsulated. However, as the tumor grows, tumor encapsulation can be lost and adherence to cauda equina can inhibit or make complete resection more difficult and induce new deficits after surgery [39]. Complete resection without capsular violation—the so called marginal en bloc resection—can be curative, and is often simply accomplished by snipping the filum above and below the mass. Nevertheless, this technique can be technically difficult based on tumor size, shape, and anatomical relation to the cauda equina or spinal cord.

The details of the surgical resection of MPE is demonstrated in our surgical videos (Video 15.1). Positioning of the patient needs to fulfill two important goals: first, to provide an optimal working angle, and second, to keep the operative field well above the level of the heart with minimal obstruction of the venous flow, the latter being an important point in keeping the intraoperative bleeding at minimum [40]. (For technical details on prone positioning for resection of spinal cord tumors, refer to Chap. 12, Spinal Cord Astrocytomas.) An alternative to the full prone position described there, some authors recommend the use of the kneeling or so-called "praying to Mecca" position [40].

Arms are properly padded and the head is placed either in straight neutral position or turned to side so that there is an even pressure distribution on the face with the eyelids carefully shut [40]. Intraoperative neurophysiological monitoring—MEPs, somatosensory evoked potential (SSEPs), and free-running electromyography (EMG) are performed routinely for resection of these lesions and it are of vital importance in identifying the filum terminale. Intraoperative fluoroscopy with a C-arm is a good way to determine the cranio-caudal extent of the lesion in the lumbar and cervical region in lateral projections, and in the thoracic spine in anterior-posterior projections.

We routinely harvest fat from the paraumbilical area in the supine position, which will be later utilized to obliterate "dead space" after laminectomy and for CSF leak prevention. After the skin incision, the subcutaneous fat is entered. Diathermia is preferred with meticulous hemostasis throughout the approach, which prevents oozing blood from obstructing the operative field. The exposure is tailored according to the length of the lesion in a cranio-caudal direction. We use hemilaminectomy for smaller lesions and laminectomy for larger lesions (e.g., >3 cm), and where the multilevel decompression is needed. Laminectomy is performed with high-speed diamond drill and Kerrison rongeurs. Laminectomy with three or more segments may be accompanied with spinal fusion following the tumor resection, particularly at the thoracolumbar junction. In other locations, with >three levels involved, laminoplasty is utilized.

The exact extension of the tumor is then demonstrated by ultrasonography before opening the dura. Dura is opened in the midline and tacked to the surrounding

muscle tissue with dural tacking sutures. The arachnoid is opened separately with micro-scissors or a micro knife and delicately freed from the posterior or lateral spinal cord, keeping it intact for closure at the end of surgery. Ligaclips are applied to hold the arachnoid membrane to the dura.

Tumors are usually well-demarcated, grayish, and sausage-like encapsulated structures that displace the cauda equine nerves laterally [41]. The rostral part of the tumor is first mobilized to allow visualization of the attachment of the tumor that arises from filum terminale, which usually has a distinctive white color from a striated pial membrane compared with the yellow tan of the cauda equine nerve roots. Proximal and distal attachment of the filum terminale is then microsurgically dissected off the tumor and isolated for any nerve roots in order to prepare for the resection. Lateral tumor margins are mobilized and freed from any attachments [41].

We recommended transecting the filum terminale first at its proximal end to avoid upward retraction. Prior to coagulation and division of filum terminale, we stimulate it with a probe nerve stimulator to make sure it is not mistaken for a nerve. The key step in the resection of MPE is the transection of filum terminale, which presents the tumor origin. Intraoperative neurophysiological monitoring plays a key role in this surgical step. The modalities that are in standard use are transcranial electrical stimulation and direct root stimulation. Both consist of recorded muscle motor evoked potentials (mMEP) that were evoked by either transcranial electrical stimulation (TES) or by direct stimulation of nerve roots in the surgical exposed area. The bulbocavernosus reflex (BCR) is a third IONM modality to monitor the sacral sensory roots and neural circuitry [42]. Furthermore, free-running electromyography (EMG) monitoring of the lower-limb muscles, external anal sphincter (EAS), and external urethral sphincter (EUS) is routinely performed for monitoring of bladder and anal sphincter function [43]. Direct spinal stimulation has been used to exclude motor function of the surgically identified filum terminale or other tethered structures, whereas TES-mMEP was recorded for monitoring the integrity of sacral motor roots and neural circuitry in the lower spinal cord [42]. Direct nerve root stimulation for identification and mapping of vital nervous tissue is performed by the surgeon. A monopolar and/or a bipolar probe is used applying 200 μs voltage pulses, and when the voltage threshold is over three-times the voltage threshold of a prior stimulated nerve root in the operating field, the structure can be resected [42]. Subsequently a TES-MEP stimulus can be applied in order to reassess the responses of the vital neural tissue after the transection of filum or detethering [42]. The mean electrical threshold for EMG response during stimulation of the filum terminale was 37.1 v (range, 15–100 v) in one series. In comparison, the lowest threshold obtained by direct stimulation of the ventral nerve roots was a mean of 1.46 v (range, 0.1–7 v) [44].

The isolated proximal filum terminale is than coagulated and divided. Gentle traction on a divided filum terminale stump allows for anterior, inferior, and lateral tumor margins to be delivered out of the tumor bed. After transecting the filum, the tumor can be dissected away from the neural structures and completely extirpated. Lifting the proximal end of the filum together with the remaining tumor allows the nerve roots on the ventral side to be mobilized, and additional cotton pledgets can

be placed to keep them separated from the remaining lesion. The cranial pole of the tumor needs to be dissected free in order to follow the ventral tumor side caudally to identify the exact position of the conus. The tumor is gently delivered and rotated from the tumor bed. Attachments of the nerve roots on the tumor surface are carefully isolated and released. Preservation of small sacrococcygeal roots is important to reduce the incidence of postoperative urinary dysfunction [41]. Finally, after completely releasing the tumor from the surrounding nerve tissue, the filum can be transected immediately below the conus to achieve a complete tumor resection (i.e., GTR) [7]. Again, particular care is exercised to avoid violation of the tumor capsule and possible dissemination of tumor cells.

The first step in the resection of an infiltrative MPE is microsurgical debulking of the tumor using micro-scissors and bipolar instrument (mostly without any coagulation). Resection without any violation of the tumor capsule might be difficult in some cases. Capsule rupture has been found in many MPEs extending over three vertebral levels, suggesting that these tumors grow over time and eventually penetrate the capsule [39]. To prevent any subarachnoid spreading of tumor particles during debulking, small cotton patties are positioned around the entire tumor before starting the resection [7]. Fine forceps, micro-dissectors, or sharp dissection with micro-scissors or micro-knife can be used to create a plane between the tumor and the normal spinal cord tissue. Once the tumor mass had been removed inside the capsule, the filum terminale needs to be identified, coagulated, and cut [7].

Following resection, the subarachnoid space is irrigated with warm saline solution. After hemostasis, the pial closure (if applicable) is done with 7-0 Prolene, and arachnoid closure is done by approximating edges with bipolar coagulation. Dural closure is performed with 4-0 Nurolon stitches with application of previously harvested fat graft to prevent CSF leak [45].

15.8 Extent of Resection

Reported extent of resection in surgical series has increased since the introduction of microsurgery. In the literature, the reported incidence was 40–78.9% [7, 10, 21–23, 36, 46, 47]. Table 15.2 provides the literature review of the studies that evaluated patients with spinal MPEs. GTR was achieved in 77.7% of cases in the series by Klekamp, with subtotal resections in the remainder of largely unencapsulated MPEs [7]. There are two possible explanations for the relatively low GTR rates [16]. First, MPEs have a histological feature of myxoid degeneration. The myxoid matrix that accumulates between the tumor cells and blood vessels renders the GTR challenging. Second, the nerve roots of the cauda equine may be embedded in the neoplastic tissue, so the manipulation of the intertwined tumor and nerve tissue may cause irreversible neurological morbidities. Under such circumstances, aggressive removal may not be the preferred option [16]. Some of the complications associated with surgery include postoperative CSF leaks, wound infections, cyst and syrinx formation, declining Franklin grade, tethering of the spinal cord, paraplegia, pulmonary embolism, kyphosis, and scoliosis [60].

Table 15.2 Literature review on main (recent) studies evaluating spinal myxopapillary ependymomas (MPEs)

Authors Year Study Type Institutions (No.) Time Period	Patients (No. and age)	Treatment	Outcome	Follow Up	Findings
Chan et al. [15] 1984 Retrospective study Single institution 1919–1981	N = 7	5 surgery alone 2 surgery plus RT	2 patients were long term survivors (3 and 7 years) 2 patients with STR plus RT survived 1 and 17 years.	3–17 years. follow-up	MPE is not uncommon during childhood but has a good prognosis. All patients with this tumor require prolonged follow-up for tumor recurrence after operation and irradiation.
Sonneland et al. [9] 1985 Retrospective study Single institution 1924–1983	N = 77 Male = 49 Female = 28 Mean, 36.4 (range, 6–82)	All patients underwent surgery	GTR had a recurrence rate of 10%, piecemeal (34%), or STR (41%) had recurrence rates of 19%	GTR resulted in longer survival of 19 years, STR 14 years.	Radiotherapy may be of particular benefit to patients whose tumors are not amenable to intact total removal.
Ross et al. [48] 1993 Retrospective study Single institution	N = 77	6 patients had total resection of encapsulated lesions; GTR, and 4 had STR. 12 received postoperative RT	12 patients are well and disease-free 2 patients have had recurrences after surgery and RT	Mean follow-up of 80 months.	Patients with MPEs should be followed indefinitely because of the potential for late recurrence, even after aggressive therapy.

(continued)

Table 15.2 (continued)

Authors Year Study Type Institutions (No.) Time Period	Patients (No. and age)	Treatment	Outcome	Follow Up	Findings
Celli et al. [10] 1993	N = 28 Male = 17 Female = 11 Median age, 38 (range, 13–64)	20 patients (71%) underwent GTR	8 patients improved, 7 unchanged and 11 deteriorated 7 patients died—5 deaths were related to tumor	Mean follow up of 18 years.	Factors having a positive influence on the prognosis (risk of recurrence) were the following: Clinical history >1 year, confinement of tumor to the filum terminale, and total tumor removal. Postoperative RT had no appreciable effect on outcome. The mode of the tumor growth is cardinal factor in prognosis.
Akyurek et al. [3] 2006	N = 35 Median age, 35 years. (range, 14–63 years.) Male to female ratio was 2.5:1.	21 (60%) patients underwent GTR 13 (37%) underwent STR 1 (3%) underwent biopsy only 22 (63%) also received adjuvant RT.	10-year OS, PFS, and LC rates for the entire group were 97%, 62%, and 72%, respectively Of 11 patients, 5 (45%) who had undergone GTR alone had recurrence Total of 12 (34%) patients had disease recurrence	Median follow-up was 10.7 years.	Long-term patient survival duration for MPE managed with surgery and adjuvant RT is favorable. Regardless of the extent of resection, adjuvant RT appears to significantly reduce the rate of tumor progression. Failures occurred exclusively in the neural axis, mainly at the primary site.
Pica et al. [49] 2009 Retrospective study Multicenter	N = 85 Male==50 Female==35 Mean age, 45.5 years. (range, 14–88)	38 (45%) underwent surgery 47 (55%) received postoperative RT	5-year. PFS was 50.4% for surgery only and 74.8% for surgery plus RT	Median follow-up was 60.0 months. (range, 0.2–316.6)	Age < 36 years, absence of neurologic symptoms at diagnosis, tumor size >or = 25 mm, and postoperative high-dose RT were variables predictive of improved PFS.

Kucia et al. [50] 2011 Retrospective study Single institution 1983–2006	N = 34 Male = 14 Female = 20 Mean age, 45.5 years. (range, 14–88)	27 patients (80%) had GTR alone 7 (20%) had STR plus RT	The overall recurrence rate was 10% (3/34 patients)	N/A	The goal of surgical treatment of MPE is resection to the greatest extent possible with preservation of function. In cases of STR, postoperative RT may improve outcome. If neurological function is maintained at treatment, these indolent lesions allow years of good function.
Al-Habib et al. [51] 2011 Retrospective study Single institution 1972–2005	N = 18 Male = 7 Female:8 (age range, 18–71)	GTR 4 out of 7 cases in which conus was not involved, Only 1 of 10 cases involved conus	No patients with GTR developed recurrence All patients survived at long-term follow-up.	Median postoperative follow-up was 56 months.	MRI is very sensitive (100%) and moderately specific (67%) in detecting direct anatomical contact between conus and MPE tumors.
Agbahiwe et al. [52] 2013 Retrospective study Single institution 1984–2010	N = 16 Mean age, 16.8 (range, 12–21)	All patients received surgery (GTR or STR) 50% followed with RT	LC at 5 and 10 years. was 62.5% and 30%, respectively for surgery alone vs. 100% for surgery and adjuvant RT	Median follow-up of 7.2 years. (range, 0.75–26.4 years.)	50% of the patients receiving surgery alone had local failure.
Tsai et al. [53] 2014 Retrospective study Single institution 1968–2007	N = 51 Mean age, 35 years. (range, 8–63)	22 patients (39%) had surgery alone, 30 (59%) had surgery plus RT, 1 (2%)had RT only	10-year OS, PFS, and LC were 93%, 63%, and 67%, respectively 19 patients (37%) had recurrence, mostly local (79%)	Median follow-up of 11 years. (range, 0.2–37 years.)	Postoperative radiotherapy after resection of MPE was associated with improved PFS and LC.

(continued)

Table 15.2 (continued)

Authors Year Study Type Institutions (No.) Time Period	Patients (No. and age)	Treatment	Outcome	Follow Up	Findings
Kukreja et al. [54, 55] 2015 Systematic review Multicenter	N = 337	N/A	Patients in GTR group had better PFS and OS. Patients in older age group (>35 years.) had better PFS	N/A	Overall, PFS did not improve if RT was combined with surgery compared with surgery alone; however, the adjuvant RT benefitted patients aged ≤35 years.
Weber et al. [13] 2015 Retrospective study 11 institution	N = 183 Male = 108 Female = 75 (range, 19–51)	97 patients (53.0%) underwent surgery without RT 86 (47.0%) were treated with surgery and/or RT	Treatment failure in approximately 1/3 of patients.	Median follow-up was 83.9 months.	Recurrence pattern was mainly local. Younger patients and those not treated initially with adjuvant RT or not undergoing GTR were significantly more likely to present with tumor recurrence/progression.
Abdulaziz et al. [56] 2015 Retrospective review 2 institutions 1990–2013	N = 58 Male = 31 Female = 27 Mean age, 40.8 years. (range, 7–68)	27 patients En block resection (46.5%), GTR 20 (34.5%), STR 11 (18.9%)	12 patients (20%) underwent adjuvant RT following either STR or GTR Overall recurrence rate was 13.8% (N = 8), 5-year PFS was 81%.	Median follow-up was 51.5 months. (range, 12–243 months)	A strong correlation between capsular violation and recurrence was found following removal of MPE. Adjuvant radiotherapy in cases of capsular violation showed a trend toward improved PFS.
Khalatbari et al. [57] 2016 Retrospective study Single institution 2003–2010	Overall: 22 M:14 F:8 (range, 11–66)	22 patients underwent surgeries (14 adults, 8 children)	N/A	N/A	En bloc resection or piecemeal resection with radiotherapy were associated with satisfactory outcome without recurrence.

Chen et al. [16] 2016	N = 27 Male = 13 Female = 14 Median age, 32 (range,7–57)	GTR achieved in 18 patients (66.7%) STR achieved in 9 (33.3%)	MPE recurrence rate was 4 in 27 (14.8%) with a median time of 26.5 months. (range, 17–83 months.) Patients who received GTR had a lower recurrence rate (11.1% vs. 22.2%), although not statistically different	Mean follow-up period was 49.8 months. (range, 13–122 months.)	Extent of resection and age are major factors related to tumor recurrence. PDGFRα, MMP2 and MMP14 may be new diagnostic and therapeutic targets, and EGFR may be a potential predictor of improved prognosis for MPE.
Bagley et al. [14] 2009	N = 52 Male = 34 Female = 18 Mean age, 31.8 years.	44 patients underwent surgery (40 adults, 12 children)	Pediatric patients had higher rates of LC and dissemination (64% vs. 32%) Median time to disease recurrence was 88 months. For the entire group OS after 11.5 years follow-up was 94%	Mean follow-up time was 6.1 years. (range, 0.6–33 years.)	Excellent outcomes may be obtained, however, with the use of aggressive surgical techniques. No clear benefit for adjunctive chemotherapy, and radiation therapy was demonstrated
Klekamp et al. [7] 2015	N = 42 Male = 25 Female = 17 Mean age, 38 ± 14 years. (range, 11–73 years.)	34 four patients underwent 36 operations for 39 tumors 27 operations were performed to treat de novo tumors and the remainder were undertaken on recurrent tumors	GTR achieved in 28 operations (77.7%) and STRs in the remainder RT was employed after 6 operations on unencapsulated tumors, with 5 of these also demonstrating subarachnoid seeding	Mean follow-up 10 years. (127 ± 100 months.)	Despite their delicate location and often enormous size, surgical morbidity in experienced hands is low with good chances for postoperative clinical improvements and very low recurrence rates after GTR for encapsulated tumors. The role of postoperative radiotherapy remains controversial. RT may be considered after incomplete resections of unencapsulated tumors and/or for patients with subarachnoid dissemination.

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Table 15.2 (continued)

Authors Year Study Type Institutions (No.) Time Period	Patients (No. and age)	Treatment	Outcome	Follow Up	Findings
Chao et al. [58] 2011	N = 37 Male = 15 Female = 22 Median age, 33 years.	25 (67.6%) GTR 9 RT	16 patients (43.2%) were found to have a recurrence with a median time to recurrence of 7.7 years Mean survival time was 12 years.	N/A	Radiotherapy improved time-to-progression following first relapse, not up front. Less aggressive resection to maintain functionality and delaying RT at the time of recurrence is a reasonable approach. This may maximize patient quality of life by delaying any sequelae from aggressive surgery or side effects from radiation.
Kraetzig et al. [22] 2018	N = 19 Male = 9 Female = 10 Median age, 32 years. (range, 9–58)	78.9% GTR, with adjuvant RT in 20%. Of the 21.2% who underwent STR, 75% underwent postoperative RT	Tumor progression in 26.3%. Distant metastases were found in 57.9%, 36.4% of which were present at initial diagnosis. Following metastatic tumor diagnosis, 72.7% did not show progression or symptoms. OS 100% with excellent neurological outcome in 78.9% of cases	Median follow-up, 36 months. (range, 12–240)	For distant metastases of myxopapillary ependymoma without clinical manifestation, close clinical and MRI follow-up represents a sufficient strategy because most of the metastases remain asymptomatic and do not show progression over time. Additional resection or irradiation as salvage therapy would be recommended if metastases become symptomatic.

Sakai et al. [28] 2009	N = 20	GTR achieved in 14 Piecemeal GTR achieved in 3 STR achieved in 3	Neurologic deterioration after surgery was seen in 5 patients, all of which were unencapsulated tumors GTR in 2 patients STR in 3 patients Recovery of postoperative bladder dysfunction remained unchanged in 2 patients. There were no tumor recurrence and progression of the remaining tumors.	Follow-up period ranged from 2–12 years. (median, 72.9 months.)	In the unencapsulated ependymomas, tumor separation and manipulation of the surrounding neural tissue caused neurologic injury. The heterogeneously enhanced ependymoma not only should be evaluated and treated meticulously, but surgeons should also not stick to total removal in infiltrated and adhering tumors as subtotally resected tumors with postoperative radiotherapy have not always recurred.
Nakamura et al. [39] 2009	N = 25 Male = 5 Female = 3 Mean age, 33 years. (range, 14–58)	15 patients total resection + RT (6 en bloc, 9 piecemeal) 1 total resection without 4 STR + neuroaxis RT 6 partial resection after local radiation alone	In 1 case of total resection without RT, local recurrence occurred 2 years. after surgery 6 patients with partial resection after RT died of CSF dissemination 2 patients with STR + neuroaxis RT 2 developed recurrence	The mean postoperative follow-up period was 10.4 years.	Surgical margin obtained at the initial surgery and the extent and amount of postoperative radiation are crucial factors determining the prognosis. CSF dissemination can occur once tumor capsule is violated, before or during surgery. Therefore, early diagnosis is essential, and a therapeutic strategy including radiotherapy, on the assumption that this tumor is malignant, should be established.

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Table 15.2 (continued)

Authors Year Study Type Institutions (No.) Time Period	Patients (No. and age)	Treatment	Outcome	Follow Up	Findings
Balasubramaniam et al. [24] 2016	N = 44 M:35 F:9 Mean age, 30.95 ± 12.78	Total excision in 89%	In majority of patients at follow-up, back pain and motor weakness improved, Sphincter problems improved in only 25% Recurrence occurred in 2 patients	22.23 ± 11.32 months. Follow-up	Long term prognosis is excellent with respect to recurrence and functional outcome in cases with complete tumor excision.
Wang et al. [59] 2014	N = 19 Male = 11 Female = 8 Median age, 33 (range, 14–72)	9 patients had GTR 10 patients had STR. 5 patients with STR also received RT.	Higher tumor recurrence is associated with a lower LC rate and vice versa. All 9 GTR patients had no recurrence, with a 100% LC rate STR followed by RT group had a significantly higher LC rate than the STR alone group	142 months. Follow up	GTR of the tumor or STR followed by radiotherapy are more likely to avoid tumor recurrence than STR alone.

EGFR epidermal growth factor receptor, *GTR* gross total resection, *LC* local control, *MMP* matrix metalloproteinase, *OS* overall survival, *PDGFRα* platelet-derived growth factor receptor, *PFS* progression free survival, *RT* radiotherapy, *STR* subtotal resection

15.9 Recurrence

Recurrence in adults usually happens at the site of primary resection, whereas in the pediatric population, recurrence in the form of disseminated disease is more common [11]. Extent of resection and age are found to be major factors related to tumor recurrence [16]. Therefore, GTR is recommended whenever possible, unless neurological dysfunction following GTR is predicted. Younger patients demonstrate a shortened recurrence time [16]. Long history and infiltration of nerve roots are further independent factors for a tumor recurrence [36].

A strong correlation between capsular violation and recurrence was found following removal of MPE [56]. One of the first series on MPEs reported a recurrence rate of 10% after complete resections, 34% after piecemeal removals, and 41% after partial removals [9]. The overall recurrence rates in series of 34 MPEs from Klekamp were 6.6%, 19.0%, and 37.0% after 1 year, 10 years, and 20 years, respectively [7]. For non-encapsulated MPEs, the corresponding rates were 15.6%, 32.5%, and 66.2% after 1 year, 10 years, and 20 years, respectively, with significantly lower rates of 9.1% after 10 and 20 years for encapsulated tumors [7].

The overall recurrence rate was shown to be 15.5% in patients treated by GTR and 32.6% in patients treated by STR, irrespective of whether they underwent adjuvant therapy ($p < 0.001$) and with higher rates in younger patients [60]. Another study, however, showed opposite results (i.e., that the use of radiotherapy as salvage therapy after initial recurrence significantly correlated with longer times to a second recurrence—9.6 years for those who received RT vs. 1.1 years for those who did not) [58].

Late recurrence can occur decades after the surgery with latest clinical recurrence described after 42 years [61]. In the event of recurrence, however, spinal MPEs continue to have a favorable prognosis [14]. Treatment of recurrent MPEs without evidence of seeding includes reoperation, whereas in cases of local or distant metastases or for refractory cases (i.e., second and third recurrence), surgical resection with postoperative radiotherapy and chemotherapy should be considered. It has been recommended to perform radiotherapy of the craniospinal axis following incomplete resection in order to prevent seeding and recurrence [39]. While some studies demonstrated no benefit in recurrence-free survival for patients treated with adjuvant radiotherapy after surgery [58], others found that adjuvant radiotherapy was associated with better outcomes for both patients who underwent GTR and those who underwent STR [3, 49, 62].

15.10 Primary (Metastatic) and Secondary (Post–Surgical) Seeding

"Seeding," "metastasis," and "tumor dissemination" are terms used interchangeably and present a known phenomenon that describes many tumors of the CNS [63]. Despite MPEs being classified as WHO I Grade tumors, recurrence after both partial and gross total resection is well documented.

Primary MPE seeding is well recognized in pediatric patients but under recognized in adults despite the fact that MPEs are far more common in the adult population [11, 64]. There are only few case reports of primary metastases into multiple cerebrospinal locations before resection of MPE [11, 65]. Two recent studies have shown that the proportion of patients presenting with metastases at initial diagnosis ranges between 36.4% in patient cohorts with dominantly adult patients, and 50% in pediatric cohorts [22, 66].

Secondary seeding (metastasis) of lumbosacral MPEs describe seeding after surgery and has been described in detail with reports as early as the 1950s [67–69]. Secondary seeding is not uncommon and occurs in patients undergoing subtotal resection. When MPE metastasizes, it tends to spread rostrally in the CNS [70], mostly affecting the thoracic and cervical spine, followed by intracranial seeding [22]. In cases of dissemination or metastasizing disease, histological characteristics of benignity are commonly preserved in MPEs [69]. The extent of the initial surgical resection was significantly associated with dissemination and patients with residual tumor were more likely to develop disseminated disease, whereas violation of the capsule during surgery may lead to CSF seeding and dissemination [71]. There are extremely rare cases of double MPEs that could not be directly considered as dissemination, since both tumors were in the site of classical origin of MPE [72].

In pediatric patients with primary seeding, GTR is followed by radiation, adjuvant chemotherapy, or both. Because these are subarachnoid metastases, focal radiation targets the lumbar theca and radiation is directed up to mid-thoracic levels or even applied to the entire craniospinal axis [60]. Chemotherapy is reserved for patients with tumors that are refractory to radiotherapy and is generally considered less effective [12]. In adults with primary seeding and after a GTR, however, the issue of adjuvant therapy is not established, probably because primary seeding of MPE is not a recognized phenomenon [11]. Only follow-up with craniospinal MRI studies after gross GTR—or "prophylactic" postoperative irradiation and chemotherapy after GTR or STR—may be considered [12].

Recent study showed that up to one-third of all patients with MPE have distant metastases at the time of diagnosis, whereas around 73% did not show progression or symptoms during the follow-up of 3 years [22]. For distant metastases of MPEs without clinical manifestation, some authors prefer close clinical examination; MRI follow-up represents a sufficient strategy because most metastases remain asymptomatic and do not show progression over time. Additional resection or irradiation as salvage therapy would be recommended if metastases become symptomatic [22].

15.11 Adjuvant Treatment

Radiotherapy of the brain and whole spine may be recommended when a piecemeal resection is performed due to the rupture of the tumor capsule during surgery in order to prevent the local recurrence and CSF dissemination [39]. Usually, adjuvant high-dose radiotherapy (≥50.4 Gy) will be administered to patients undergoing subtotal resection or biopsy [13].

In 2006, Akyurek et al. [3] observed a significant decrease in the rate of tumor progression with adjuvant radiotherapy regardless of the extent of resection. Further studies showed that 5-year PFS was improved in patients receiving surgery plus radiotherapy (74.8%) compared with PFS in patients who received surgery alone (50.4%) [49]. Radiotherapy increases 10-year PFS from <40–70% in patients who received radiotherapy [13]. Radiotherapy dose-response relationship with PFS was also demonstrated in research that focused on pediatric MPE patients [54], which suggested that stereotactic radiosurgery with adjuvant radiotherapy provided an improved prognosis in disease control than with GTR alone [73] with significant improvement in the 5-year local control rate in patients who were treated with radiation doses higher than 50 Gy than those who received lesser doses [62].

However, the role of adjuvant radiotherapy remains controversial. One meta-analysis found that radiotherapy did not result in significant improvements in treatment with GTR alone compared with GTR plus radiotherapy, or in treatment with stereotactic radiotherapy alone compared with stereotactic radiotherapy or radiotherapy [60].

Chemotherapy has been suggested as a potential treatment to prevent recurrence, but its efficacy has not been established in MPEs. There are single case reports that describe the benefit of use of temozolomide concomitant with radiotherapy following multiple surgeries of recurrent MPEs with disseminated metastases [74]. Imatinib as second-line chemotherapy and the multi-kinase inhibitor sorafenib as third-line chemotherapy for metastatic MPEs have been reported [75].

15.12 Outcomes

We differentiate between the surgical (neurological) outcome and survival of patients with MPEs. In one recent analysis, the Surveillance, Epidemiology, and End Results (SEER) database, which includes over 700 cases of MPEs, identified surgical resection, radiotherapy (adverse prognostic factor of overall survival, likely due to selection bias), age < 30 years, and Caucasian race (decreased OS on multivariate analysis) as significant prognostic factors [4]. Despite their delicate location and often enormous size, surgical morbidity in experienced hands is low with good chances for postoperative clinical improvements and very low recurrence rates after GTR for encapsulated tumors [7]. Long-term outcome depends on the amount of resection and the presence of a tumor capsule [7], whereas larger tumors are found to perforate the capsule due to delayed diagnosis [39]. Preoperative functional status and the extent of removal were the significant prognostic factors influencing postoperative outcome [46]. Outcome is better for patients presenting predominantly with pain rather than neurological deficits [6]. Presence of urinary difficulties at the time of diagnosis is a relatively poor prognostic sign [76]. Permanent surgical morbidity is seen in 8–15% of patients [7, 23].

The estimated 10-years overall survival has been reported to be 92.4% [13] with 10-year PFS of 61.2% [13]. Age (<36 vs. ≥36 years), treatment modality (surgery alone vs. surgery and radiotherapy), and extent of surgery are prognostic factors for

local control and PFS [13]. However, treatment failure—including local failure, distant spinal relapse, and brain failure—has been reported to occur in up to one-third of patients [13]. The observed pattern of failure is mainly local, but up to one-fifth of patients presents with a concomitant spinal or brain component [49].

Risk of treatment failure decreases with GTR [9, 13]. According to most studies, GTR is strongly associated with PFS, while other studies suggest that GTR must be combined with high-dose radiotherapy in order to increase PFS [49]. Factors having a positive influence on the prognosis (risk of recurrence) are clinical history >1 year, confinement of tumor to the filum terminale, and total tumor removal [10]. Postoperative radiotherapy tends to prolong the recurrence-free interval for patients with unencapsulated tumors [7].

15.13 Follow-Up

If a complete resection of MPE is performed, the patient should be followed conservatively; however, if the capsule was violated or there was a STR, craniospinal irradiation may be performed to prevent CSF dissemination [39]. Neurosurgeons should be aware of the possibility of primary seeding and drop metastasis of an MPE, and they should also consider complete craniospinal imaging as part of both the preoperative work-up and postoperative follow-up and surveillance [11]. Diagnostic lumbar puncture at the time of diagnosis and before resection—or at a time of recurrence—to assess dissemination should be considered [11]. Long term or even lifelong MRI follow-up for these patients could be considered [11].

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Pediatric Spinal Cord Tumors: Diagnosis and Management

16

Jaafar Basma, Jimmy Ming-Jung Chuang, and Frederick A. Boop

16.1 Introduction

Intramedullary spinal cord tumors (IMSCTs) are a rare entity. They account for only 4–6% of all central nervous systems (CNS) tumors [1]. In the United States, only around 150 cases of pediatric IMSCTs are newly diagnosed each year [2]. Pediatric IMSCTs comprise around 35% of all intraspinal neoplasms, whereas this ratio drops to 20% in adults [3]. Primary glial tumors—such as astrocytomas, ependymomas, and gangliogliomas—account for more than 80% of Pediatric IMSCTs, most of which have a low histological grade [4, 5]. High grade tumors comprise about 10% of pediatric IMSCT [6]. Other pathologies include developmental tumors, such as lipomas, teratomas, dermoids, and epidermoid cysts [7, 8].

Most pediatric IMSCTs progress slowly. The pattern of clinical presentation varies according to the anatomical site. They can be focal, or may involve the holocord from the cervicomedullary junction to the conus medullaris. At least 50% occur in the cervical and cervicothoracic region and usually span an average of 5.4 vertebral

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levels when diagnosed [4]. Most have a cystic component at the rostral and/or caudal aspect of the solid tumor, and intratumoral cysts can occur within the solid portion as well. Extramedullary or extradural tumors rarely extend over many levels and usually do not have a cystic component [9].

Surgery is indicated for any newly diagnosed intramedullary tumor in a child. If the pathology is focal and benign, the aims of the surgery are to obtain a histological diagnosis and remove as much tumor as possible to prevent neurological decline. Advances in neuroimaging, microsurgical technique, surgical equipment, and intraoperative neurophysiology have encouraged a more aggressive resection with safer functional preservation [2, 10, 11]. Although current retrospective series support aggressive resection with improvement in long-term survival and quality of life, late recurrences do occur despite adequate surgical resection. If the lesion is high grade and infiltrative, only a biopsy is generally warranted. Adjuvant therapy, including chemotherapy and radiation, although of limited efficacy, still has some role. The tumor pathology, tumor location, and the possibility of achieving a gross total resection determine whether adjuvant therapy is needed.

16.2 Epidemiology

The incidence of pediatric intramedullary spinal cord tumor is less than 1 per 100,000 with a slight predominance in boys [6]. Pediatric IMSCTs are found throughout the neuraxis, most commonly in the cervical and cervicothoracic regions. In adults, the incidence of intradural—but mostly extramedullary—tumors is increased and the lumbar location is more preponderant [11]. Astrocytomas are the most common IMSCTs in the pediatric population [10, 11]. In children younger than 10 years old, around 90% of IMSCTs are astrocytomas (and are also more frequently benign). This percentage declines to around 60% in the adolescent years with an increase in percentage of ependymomas. In adults, intramedullary ependymomas become the majority of IMSCTs [12]. Spinal hemangioblastomas are rare and they can be associated with von Hippel-Lindau (VHL) disease [13]. Table 16.1 shows the different characteristics of the two most common pediatric IMSCTs (ependymomas and astrocytomas). Table 16.2 compares the features of pediatric and adult IMSCTs.

Neurofibromatosis type 1 (NF1) and neurofibromatosis type 2 (NF2) are both associated with tumors of the CNS [14]. Patients with NF1 are more likely to have astrocytomas as IMSCT. NF2 is more commonly associated with schwannomas and meningiomas, but there is also an association with intramedullary ependymomas [15, 16]. Around 70% of intramedullary ependymomas that did not meet the neurofibromatosis criteria have NF2 gene mutation [17]. Besides NF1, pediatric intramedullary spinal cord astrocytomas can be clustered with inherited syndromes, such as Li-Fraumeni syndrome, Turcot's syndrome, tuberous sclerosis complex (TSC), and Maffucci Ollier disease [18, 19].

Table 16.1 Characteristics of pediatric intramedullary astrocytomas and ependymomas

	Astrocytoma	Ependymoma
Incidence	Younger children	Older children
Location in cord	Eccentric	Central
Level	Cervicothoracic	Cervical spine and filum terminale
MRI findings	Ill-defined borders Heterogeneous enhancement	Better defined borders Symmetric enhancement Hemosiderin deposit sign
Association with neurofibromatosis	Neurofibromatosis type I	Neurofibromatosis type II
Grading	10% are malignant	Most are benign
Tumor/cord interface	Usually poor plane	Usually clear plane
Neurological function after surgery	Less improvement	Better improvement
Evidence-based treatment	Resection (class IIB) and radiation (class IIa); chemotherapy is class IIb	Resection (class I) and radiation (class IIa); chemotherapy is class IIb
Prognosis	Worse	Better

Table 16.2 Characteristics of adult and pediatric IMSCT

	Adult IMSCT	Pediatric IMSCT
Incidence	Around 850–1700 cases/year	Around 150 cases/year
Ratio of all spinal tumors	<20%	35%
Most common pathology	Ependymoma	Astrocytoma
Location	Most in cervicothoracic region, but increased in lumbar	Most in cervicothoracic region
Long term prognosis	Better	Worse

16.3 Clinical Presentation

Most pediatric IMSCTs are benign and slowly progressive. Clinical diagnosis is difficult due to their insidious clinical presentation. The median duration of symptoms for pediatric IMSCTs from the initial complaint to the time of surgery is 9.2 (range, 1.6–27) months. Malignant tumors usually progress rapidly and insidiously. The pattern of clinical presentation varies according to the anatomical site. Local pain is the most common early presenting symptom. Other symptoms include motor disturbances, dysesthesias, torticollis, kyphoscoliosis, and (rarely) sphincter dysfunction [20, 21].

While extramedullary tumors tend to be associated with radicular pain, dysesthetic pain is more common in IMSCTs due to alteration in peritumoral edema [22, 23]. Young children are often unable to express their complaints clearly; for example, they often speak of abdominal pain and "mis-localize" their symptoms.

Some children may complain of disproportional symptoms following a trivial injury. But this pain is not relieved with rest and may be nocturnal, even awakening them from sleep. In children, progressively worsening back pain should be taken seriously, especially when it occurs during the night and causes sleeplessness.

Children may present with motor deficits, such as clumsiness, weakness, and frequent falls. In infants, this may manifest as motor regression after having learned how to walk. When the tumor occurs in the cervical region, nuchal pain and torticollis are common early symptoms. Sensory complaints are not common and are usually limited to one upper extremity. A discrete sensory level may be noted in the late course of the disease [10]. Progressive spinal deformity, such as kyphoscoliosis and limb length deformities are also common. Thirty-six percent of children with IMSCTs have preoperative spinal deformity [24]. This deformity could progress particularly after the tumor resection, most likely resulting from a combination of neuromuscular dysfunction, laminectomy, and radiation therapy [2]. Patients should be followed up throughout childhood and adolescence for development or aggravation of spinal deformity.

Hydrocephalus in IMSCTs is not rare and can occasionally be fulminating in its presentation. Rifkinson-Mann et al. reported 25 patients (14.6%) with hydrocephalus in a single institution series of 171 patients with IMSCT [25]. Symptoms and signs include headaches and papilledema. The incidence of hydrocephalus occurs in greater frequency in the adult population and with malignant pathology [25, 26].

There is often a lag between the onset of pediatric IMSCT symptoms and diagnosis. Only a high degree of suspicion, a detailed clinical history, and a targeted neurological examination lead to more accurate and timely diagnosis.

16.4 Magnetic Resonance Imaging

Magnetic resonance imaging (MRI) is the most important imaging tool for the diagnosis of IMSCTs. T1-weighted imaging may reveal the extent and content of neoplasia and the state of the arachnoid space. T2-weighted imaging better delineates the edema and any cystic components. Gadolinium contrast enhancement reveals the tumor's vascularity and homogeneity (Fig. 16.1). Differences in the patterns of enhancement can suggest certain pathologies over others. In general, ependymomas capture the contrast medium more readily than astrocytomas (Table 16.1). Although a precise differential diagnosis is not possible from imaging characteristics alone, different lesions tend to have different radiological features.

Ependymomas are usually centrally located in the spinal cord with symmetrical contrast enhancement and sharply defined borders, whereas astrocytomas are usually eccentric, with heterogeneous contrast enhancement and ill-defined borders. Intramedullary ependymomas can show a "Cap sign" in which areas of low signal density appear on the tumor borders due to hemosiderin deposition.

Non-neoplastic intramedullary lesions should be considered also in a differential diagnosis, such as demyelinating lesions or vascular malformations. These can sometimes show gadolinium enhancement, but generally, the spinal cord is not expanded and its diameter is not enlarged.

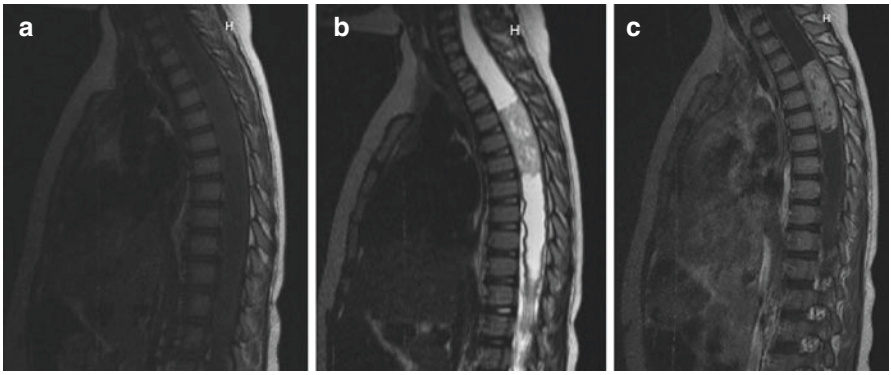

Fig. 16.1 A 3-year-old female presented with progressive weakness, back pain, and torticollis. Sagittal T1 (**a**), T2 (**b**), and Gadolinium-enhanced T1 (**c**) magnetic resonance images were performed. These demonstrate a T4–6 enhancing intramedullary spinal cord tumor with associated holocord syringomyelia. A T3–7 laminoplasty was performed with a dorsal median myelotomy to resect the tumor. The final pathological analysis was consistent with Grade I pilocytic astrocytoma

16.5 Histopathology and Genetic Biology

16.5.1 Astrocytoma

Histopathology. Astrocytomas are the most common type of pediatric IMSCT [9]. Tumor cells arise from glial cell precursors that infiltrate the spinal cord These tumors can be divided in subtypes following the new grading scale established by the World Health Organization (WHO) in 2016: Grade I (pilocytic astrocytoma and subependymal giant cell astrocytoma), Grade II (diffuse astrocytoma, pleomorphic xanthoastrocytoma, gemistocytic astrocytoma), Grade III (anaplastic astrocytoma) and Grade IV (glioblastoma multiforme and gliosarcoma) [27]. The most common astrocytoma subtype in pediatric IMSCT is the pilocytic astrocytoma. They occur more commonly in the thoracic region and can involve the holocord. Pilocytic astrocytomas may be associated with large tumoral cysts (Fig. 16.1), or with leptomeningeal metastases.

Classic histology includes bipolar tumor cells, eosinophilic Rosenthal fibers, and granular bodies that alternate with microcystic areas comprising loosely arranged astrocyte-like cells. However, pilocytic astrocytomas can show a wide morphologic spectrum with areas resembling oligodendrogliomas or high-grade gliomas, which can make a definitive diagnosis challenging.

Genetic Biology. Genetic studies of intramedullary astrocytoma are limited owing to the rarity of their incidence. Genetic analysis of pilocytic astrocytomas has found numerous genetic aberrations, but no specific tumor suppressor genes or oncogenes have been identified. However, genetic research of intracranial astrocytomas has paved the way to discerning candidate genes in IMSCT. The most frequent aberrations detected in cytogenetic and array-based analyses involved trisomy of chromosome 5 and chromosome 7 or gains of 7q [28, 29]. Pfister et al. reported

30 of 66 low-grade astrocytomas (45%) with copy number gain at chromosome band 7q34 spanning the BRAF locus [30]. This led to the conclusion that there may be a gain of BRAF, with subsequent BRAF overexpression in MAPK pathway activation in low-grade astrocytomas [31]. Jones et al. described a tandem duplication at 7q34 in 66% of pilocytic astrocytomas, which is not observed in series of high grade astrocytomas. This aberration results in an in-frame fusion gene incorporating the kinase domain of the BRAF oncogene [32]. In addition, the canonical Val600Glu BRAF mutation has been found in a variety of low grade astrocytomas [33]. Beyond BRAF, Horbinski et al. reported a deletion of the tumor-suppressor gene cyclin-dependent kinase inhibitor 2A (CDKN2A, also known as p16) as the most common mutation in pilocytic astrocytomas [34]. This study also found loss of heterozygosity at 9p21, which encompasses CDKN2A, or at 10q23, which includes the phosphatase and tensin homologue gene in 31.6% and 50% of pilocytic astrocytomas. The frequency and specificity underline its potential as a therapeutic target and as a diagnostic marker.

Pilocytic astrocytomas and high-grade intramedullary astrocytomas have also been reported to be associated with familial NF1 [14, 16]. Patients with NF1 have a mutation in the neurofibromin gene (17q11.2). Loss of heterozygosity of the NF1 gene was observed in 92% of pilocytic astrocytomas with NF1 compared with only 4% of those without NF1 [35].

16.5.2 High Grade Astrocytoma

Data on intramedullary high-grade gliomas suggest that they are rare, occurring in only 10% of cases [36, 37]. Patients present with rapid clinical decline, and sometimes with signs and symptoms of metastatic disease. On imaging, it is difficult to differentiate a malignant astrocytoma from a low-grade tumor, except for the high rate of leptomeningeal spread at presentation. It is recommended that full preoperative neuraxis MRI be performed in children in whom a rapidly progressive clinical course suggests a malignant lesion. This will likely have a high positive yield and provide valuable information prior to surgical intervention.

The prognosis for high-grade astrocytomas is extremely poor with most patients dying from progressive disease in less than 6 months [37]. The majority of these patients will develop leptomeningeal metastases at recurrence and get an unsatisfactory response to adjuvant radiotherapy and chemotherapy [36]. There is no evidence to support aggressive resection in the management of malignant IMSCTs. No correlation has been proven between extent of resection and survival [36, 37]. A frozen-section analysis is recommended in order to determine whether the tumor is malignant. Consequently, resection of a high-grade astrocytoma is usually conservative, with the aim to perform a palliative decompression with myelotomy and cyst drainage.

Approximately 68% of intracranial astrocytomas demonstrate mutations in isocitrate dehydrogenase 1 (IDH1) and IDH2 genes. However, the rate of IDH mutations in spinal astrocytomas is not fully known. Pollack et al. reported a low

IDH mutation frequency in pediatric spinal cord astrocytomas [38]. Govindan et al. reported six spinal glioblastoma, of which five were immunoreactive for tumor suppressor protein 53 (TP53) [39]. Recent studies also reported the importance of the H3.3 variant in glioblastomas, which implicated abnormal deoxyribonucleic acid (DNA) methylation in the generation of intracranial and spinal high-grade gliomas [40, 41].

16.5.3 Ependymoma

Histopathology. Ependymomas are the second most common type of pediatric IMSCT and the most common IMSCT in adults [10, 11]. Tumor cells are thought to arise from ependymal cells of the central canal, but recent evidence suggests that they have similar histopathology to radial glial stem cell undergoing malignant transformation [42, 43]. Based on specific histological findings, ependymal neoplasms are classified according to the 2016 World Health Organization grading system. Grade I includes subependymoma and myxopapillary ependymoma. Grade II encompasses ependymomas, papillary ependymomas, clear cell ependymomas and tanycytic ependymomas, while anaplastic ependymomas are of grade III. Grade II intramedullary ependymomas are often found in the cervical and thoracic spinal cord [44]. Most intramedullary ependymomas are slow growing and display a benign pathology.

On classic histological examination, ependymomas are highly cellular tumors, irrespective of their grade. Grade II ependymomas are usually well circumscribed and do not infiltrate adjacent spinal cord tissue. Microscopic findings include pseudorosettes and perivascular clustering.

Myxopapillary ependymomas are less common in the pediatric population and tend to be more aggressive and prone to distant subarachnoid dissemination [45]. They account for up to 50% of intramedullary spinal cord ependymomas, especially in adults, and typically arise from the filum terminale. Myxopapillary ependymomas are characterized by cuboidal or elongated tumor cells, which are arranged in a papillary pattern around the stromal cores. Abundant mucin can accumulate between myxopapillary ependymoma cells and vessels. Adjuvant radiation therapy improves local disease control after surgery, and craniospinal radiation may be required for any intracranial or intraspinal dissemination [46].

Genetic Biology. Adult and pediatric ependymomas seem to represent different clinical entities. Recent evidence suggests that they arise from distinct stem cell precursors [42, 43]. In addition, emerging evidence also suggests that intramedullary ependymomas are genetically distinct from intracranial ependymomas [47, 48]. Witt et al. studied two non-overlapping databases of grossly histologically similar ependymoma tissues and applied non-negative matrix factorization [49]. They identified three distinct groups of tumors on the basis of their location: supratentorial ependymomas, posterior fossa ependymomas, and a group of posterior fossa ependymomas with spine ependymomas. The spinal ependymomas—clustered with a distinct subgroup of posterior fossa ependymomas—demonstrated whole-chromosome anomalies.

Applying ribonucleic acid (RNA) expression analysis, Korshunov et al. reported high expression levels of HOXB5 (17q21.3), PLA2G (1p35), ITIH2 (10p15), and CDKN2A (9q21) genes in spinal ependymomas [47]. Homozygous deletions, loss of heterozygosity, and mutations in the NF2 gene have been found in both sporadic and NF2-associated spinal ependymomas [48]. Monosomy and alteration of 22q, where NF2 gene is located, are observed in 30% and 40% of intramedullary ependymoma [50].) In one study, 71% of patients with intramedullary ependymomas without meeting the criteria for neurofibromatosis were shown to possess mutation in the NF2 gene [17].

16.5.4 Hemangioblastoma

Intramedullary hemangioblastomas are rare and benign tumors that can occur sporadically or as a manifestation of VHL disease. They account for 3% of all IMSCTs and are the third most frequent IMSCT. Their tumor cells are thought to arise from a mesenchymal origin within the vascular system of the spinal cord. Tumors tend to occur in the dorsal aspect of the cord, which causes progressive sensory or proprioceptive deficits. Due to their high vascularity, there is higher risk of tumor hemorrhage, leading to a clinical presentation with acute symptoms.

Around 30% of patients with intramedullary hemangioblastomas also have VHL disease [51]. VHL disease has an autosomal dominant inheritance pattern and is caused by loss of the tumor suppressor gene located at 3p25-26 [52]. VHL gene mutation stimulates the growth of new blood vessels with an increased level of vascular endothelial growth factor (VEGF) [53]. Lesions associated with VHL include CNS hemangioblastomas, pancreatic cysts, pheochromocytomas, retinal angiomas, renal cysts, and epididymal cystadenomas [54].

16.5.5 Gangliogliomas and Miscellaneous Spinal Cord Tumors

Intramedullary gangliogliomas are very rare. They account for only 1% of pediatric IMSCTs [55]. The mean age of patients with intramedullary gangliogliomas is 12 years, ranging from 8.5 to 31 years. Ganglioglioma cells are from both neuronal (ganglion cells) and glial origins. They are usually slow-growing and benign. Although their pathology may vary between WHO Grades I to III, the majority is Grade I, depending on the relative differentiation of the neuronal and glial elements [56]. The most common location for gangliogliomas to arise in the spinal cord is the cervical region with possible extension from the medulla [57]. Intramedullary gangliogliomas span an average length of eight vertebral bodies, whereas intramedullary astrocytomas or ependymomas span an average length of four vertebral bodies. Intramedullary gangliogliomas may even affect the entire spinal cord in 15% of cases [57].

Histologically, gangliogliomas are composed of large clustered neurons and neoplastic glial cells. Eosinophilic granular bodies and Rosenthal fibers are common.

The neurons are immunopositive for synaptophysin, neurofilament protein, neuron-specific enolase, and chromogranin A [58].

Inclusion tumors, metastases, lymphomas, melanomas, and neurocytomas account for most of the remainder of IMSCTs. Around 4% of intramedullary lesions are not neoplastic lesions. Lipomas are the most common developmental lesion and account for 1% of all intramedullary spinal cord masses [59].

16.6 Treatment Rationale

Although most pediatric intramedullary spinal cord tumors have a benign pathology, most will progress and ultimately lead to progressive neurological deficits [11, 60]. Despite the progress of adjuvant treatments (i.e., chemotherapy and radiation therapy) in other fields of oncology, their success in controlling most pediatric IMSCT remains poor. Surgery continues to be the mainstay of treatment, with a goal to achieve gross total resection whenever possible. Complete surgical resection was shown to confer a higher rate of overall and progression-free survival [61–63]. Disease control with repeat surgeries for recurrent residual tumors may be an alternative to the employment of expensive and ineffective long-term adjuvant therapies. Outcome depends on tumor pathology (low grade vs. high grade), patient's age (younger patients have a better recovery), preoperative neurological function, and surgical extent of resection.

16.7 Surgery

The goal of surgery for pediatric IMSCT is gross total resection with optimal preservation of neurological function. Several factors influence the surgical success, including tumor infiltration (it is difficult to achieve a gross total resection of infiltrating astrocytomas), tumor pathology (ependymomas have a better defined margin with the surrounding spinal cord compared with astrocytomas), tumor grade (high grade astrocytomas carry a greater risk of recurrence), preoperative neurological status (patients with preoperative deficits are less likely to improve after surgery), and tumor size [60, 64, 65].

16.7.1 Extra–Medullary Stage

In our center, the patient is usually positioned prone with the knees and hips flexed. Depending on the patient's age, small gel bolsters or chest rolls made with towels and sheets are used. Pressure points are well padded, especially in the pediatric population, including ankles, knees, hips, iliac crests, wrists, elbows, ribs, and clavicles. We use a 3-point Mayfield head holder (Mayfield Medical Services, Bethalto, IL) for the cervical and upper thoracic spine tumors. While most surgeons prefer to place the patient in a reverse-Trendelenburg position to maximize venous drainage,

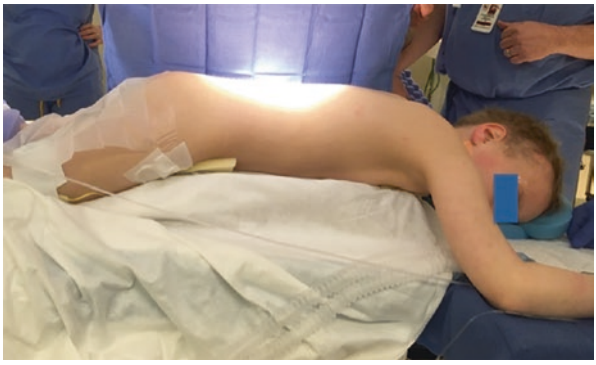

Fig. 16.2 A 9-year-old patient with a metastatic anaplastic ependymoma presented with recurrent progressive disease in his lumbar spine. To avoid emptying his ventricles of CSF, we placed the patient in a slight Trendelenburg position to avoid excessive drainage of cerebrospinal fluid

special attention should be made to younger patients, especially those with concern for cerebrospinal fluid (CSF) outflow obstruction, hydrocephalus [25], and ventricular shunts. In patients with shunts, intradural procedures (including spinal surgeries) can result in shunt malfunction [66]. In these instances, we recommend using a slight Trendelenburg position to avoid excessive drainage of CSF and an abrupt change of CSF pressure differential with the intracranial cavity (Fig. 16.2).

The X-ray fluoroscopy C-arm machine is used to localize the tumor level. Full longitudinal exposure is necessary with the incision extending rostrally and caudally to the tumor. Following a midline incision, a subperiosteal dissection is performed to expose the laminae. Careful technique is needed in the pediatric population with gentle palpation of the bony landmarks to avoid plunging into the dural sac. Using a curette, the superior border of the superior lamina and the inferior border of the inferior lamina are dissected off the dura; laminectomies are started with a Kerrison rongeur. The footplate of a high-speed drill, usually with a B-5 drill bit, can then be inserted to complete the laminotomy over the entire area of exposure. The bone is preserved to perform a replacement laminoplasty after the dura is closed. Intraoperative ultrasonography can be useful in visualizing the tumor and ensuring that the exposure includes its rostral and caudal poles. The dura is opened with a 15 or 11 blade knife, and the arachnoid is divided using a blunt nerve hook. The dural leaflets are retracted along with the arachnoid using 6-0 Prolene sutures. To keep the surgical field dry, long strips of cottonoids are placed in the epidural space.

16.7.2 Intramedullary Stage

Surgical access to the tumor. Access to the tumor should be made with the shortest, most direct, and safest route. In certain cases, the lesion expands the dorsal aspect of the cord and becomes visible through the pia. In these instances, a direct transpial approach can be used, as no significant parenchymal dissection is needed to reach the tumor bed. The tumor can then be followed rostrally and caudally by splaying the pial tissue overlying it. If the tumor is not visible, the surgeon should study the preoperative images and plan for the least disruptive transparenchymal

corridor to expose the tumor. The posterior median sulcus approach—or dorsal median myelotomy—is most commonly used for pediatric spinal cord tumors (mostly ependymomas and astrocytomas). Alternatively, a dorsal root entry zone approach through the dorsal lateral sulcus or a lateral approach can be employed, if the tumor is more laterally oriented (smaller hemangioblastomas and vascular malformations) (Fig. 16.3) [67–69].

During the posterior median sulcus approach, it is mandatory to identify the midline before the myelotomy is carried out. The posterior median sulcus is frequently visualized under the posterior spinal vein, which needs to be dissected and mobilized (Figs. 16.3 and 16.4a). Smaller exiting veins can be carefully cauterized and divided, but the larger posterior spinal vein should be preserved when possible. Alternatively, the midline can be identified as the midpoint between the posterolateral sulci or between the posterior spinal arteries (Fig. 16.3) [68]. After the myelotomy, the posterior sulcal central veins, which course vertically on either side of midline, are also helpful in orienting the surgeon, especially during tumor resection adjacent to edematous parenchyma (Fig. 16.4c). After the initial myelotomy, the opening is extended rostrally and caudally by splaying the medullary tissue with the bipolar forceps (6B). Care must be taken to preserve the posterior arterial sulcal branches supplying the dorsal columns to avoid significant postoperative sensory syndromes.

Smaller tumors located laterally in the spinal cord and deep below the pial surface can be accessed through a posterolateral sulcus or dorsal root entry zone approach [67–69]. The posterolateral sulcus is identified between the posterior spinal artery and the dorsal nerve root. A myelotomy at the level of the dorsal root entry zone leads to the posterolateral tract of Lissauer and eventually to the substantia gelatinosa at the dorsal and medial aspect of the dorsal horn of the gray matter. A further lateral myelotomy can also be performed midway between the ventral and dorsal nerve roots. To achieve this lateral approach, the facet joint and the pedicle have to be drilled and the dentate ligament cut to mobilize the spinal cord. The lateral myelotomy opens a plane between the dorsal and ventral spinocerebellar tracts anterior to the lateral corticospinal tract (Fig. 16.3) [67].

Identification of the tumor-parenchyma plane and tumor debulking. Although this step is critical to achieving gross total resection with minimal injury to normal surrounding tissue, the interface between the tumor and spinal cord may be difficult to appreciate. In cases of infiltrative astrocytomas or high-grade and recurrent tumors, such a plane may not exist. Preoperative tractography can help differentiate tumors that are infiltrative from those that displace the white matter tracts. The surgeon should take advantage of every possible cue, including tumor texture, color, vascularity, behavior under suction and ultrasonic aspirator, vascular and peritumoral edema, gliosis, and hemosiderin deposits. Dissection should be performed on the side of the tumor at the interface to minimize collateral injury to normal spinal cord. Micro-coagulation of the tumor surface can shrink the tumor away from the spinal cord, which is particularly helpful in hemangioblastomas [70, 71]. Feeding arteries should be carefully identified, coagulated, and cut. En passage perforators need to be preserved, especially at the ventral aspect of the tumor where

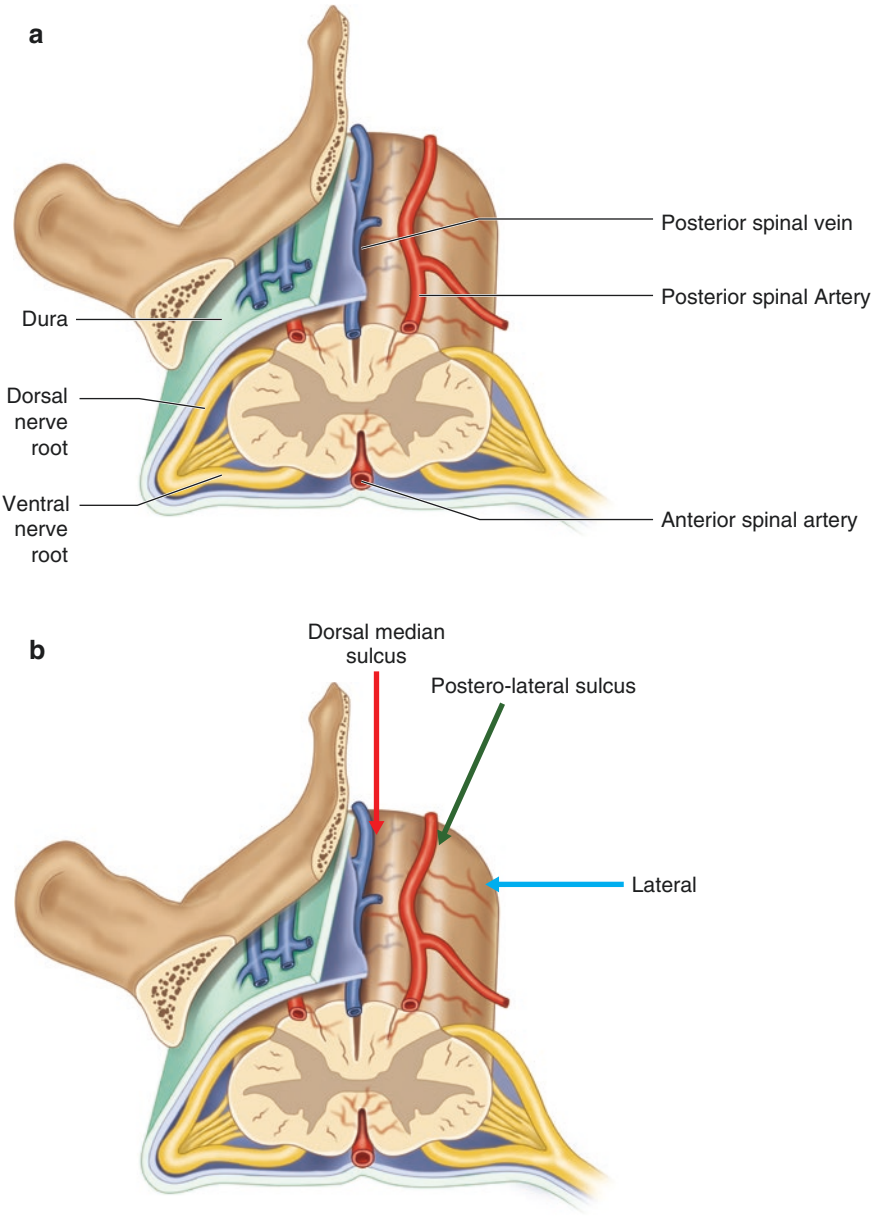

Fig. 16.3 Illustration of the surgical anatomy of the spinal cord. (**a**) The arachnoid covering the spinal cord is thickened at midline, forming the midline septum. The posterior spinal vein travels along the dorsal median sulcus. In difficult cases, midline can also be estimated at the median between the two posterior spinal arteries. The posterolateral sulcus is between the posterior spinal artery and the dorsal nerve root. It includes the dorsal root entry zone and overlies the posterolateral tract of Lissauer, leading to the dorsal horn of the gray matter. The anterior spinal artery courses in the anterior median fissure where it sends major perforators to the spinal cord. (**b**) Approaches to lesions located deep to the pial surface of the spinal cord include the dorsal median sulcus approach, the posterolateral sulcus approach (dorsal root entry zone) and the lateral approach (midway between the dorsal and ventral nerve roots)

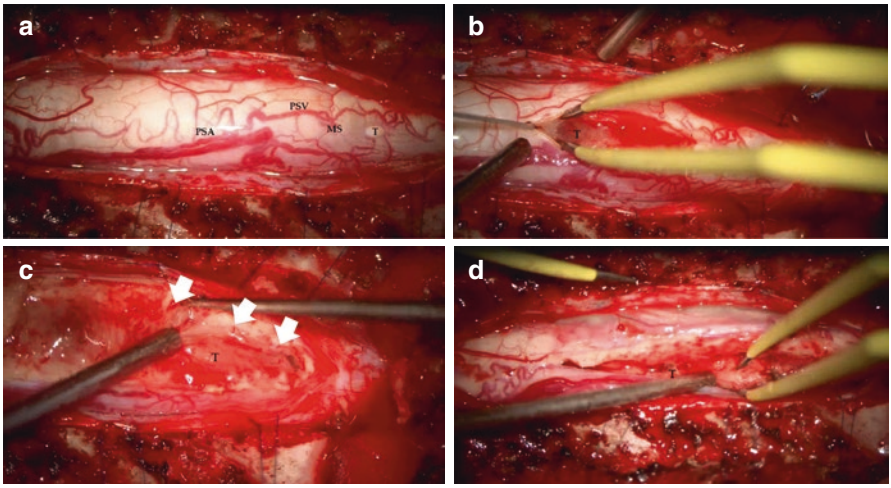

Fig. 16.4 Intraoperative microscopic photographs showing the microsurgical resection of an intramedullary spinal cord astrocytoma. (**a**) The tumor (T) is visible through the pia at the rostral pole of the exposure. The posterior spinal vein (PSV) runs over the median sulcus (MS), while the posterior spinal artery (PSA) is lateral to it. (**b**) Sharp dissection to the tumor by splaying the median sulcus. (**c**) The vertically oriented sulcal vessels (arrows) are helpful landmarks to identify the median plane and the dorsal edge of the tumor. (**d**) The ventral limit of the tumor is carefully dissected with lower power electro-coagulation to avoid injury to the anterior spinal perforators, and using feedback from intraoperative monitoring

there is an abundance of branches from the anterior spinal artery (Figs. 16.4d and 16.5). Tumor resection can be done en bloc if the tumor is small in size and has a well-circumscribed plane around it (e.g., ependymomas). However, excessive traction of normal parenchyma should be averted. Tumor debulking with a suction device or an ultrasonic aspirator is often necessary for a safer resection in larger and more infiltrative tumors. Debulking should be performed in a longitudinal fashion slowly progressing one layer at a time with frequent inspection of tumor-cord interface and coagulation of small tumor feeders.

Adapting the surgical technique to the pathology. Early recognition of tumor pathology helps guide the necessary surgical technique. Careful inspection of tumor characteristics and—most importantly—sending a sample for early pathological analysis of a frozen section can change the course of surgery. If the tumor shows obvious signs of high-grade pathology and invasiveness (i.e., necrosis, frequent mitoses, microvascular proliferation, necrosis and hemorrhage), then either treatment or aggressive resection should not be attempted as it will not have any influence on the overall survival. In these instances, the spinal cord is decompressed by performing a myelotomy and removing any cystic components of the tumor.

Ependymomas usually have a cleavage plane with the surrounding spinal cord. The tumor can be dissected off the normal parenchyma by following its capsule and coagulating the small feeding vessels that course into it. Ependymomas also tend to be central and frequently have cysts or syrinxes at their poles, which can be helpful

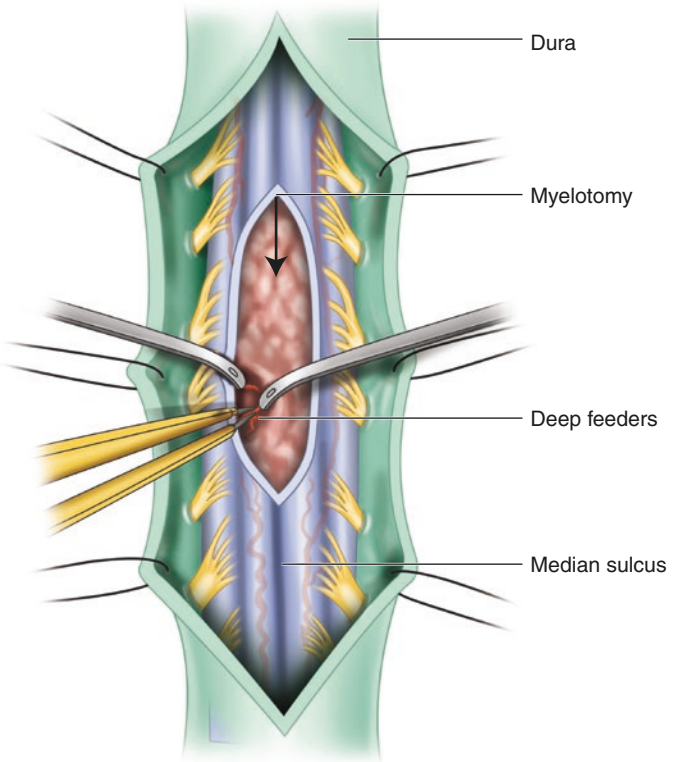

Fig. 16.5 Illustration of a microsurgical resection of an intramedullary tumor through a midline myelotomy. Sufficient exposure at the poles of the tumor must be achieved. In tumors with a well-defined capsular plane (most commonly seen in ependymomas), once the interface with normal parenchyma is identified, the deep feeders are coagulated and circumferential dissection is performed around the tumor

in defining the tumoral margins both rostrally and caudally. If deemed safe, gross total resection should be attempted due to its direct impact on the long-term progression-free survival [72, 73].

Astrocytomas on the other hand have a tendency to be excentric and infiltrative, which makes it more difficult to identify the tumor/parenchyma plane and achieve gross total resection. The strategy for these tumors is to debulk them from inside until the tissue becomes difficult to differentiate from normal tissue. The tumor is resected one plane in depth at a time to avoid breaching through the surrounding parenchyma. If evoked potentials become abnormal, then it is likely that normal tissue is being encountered [9, 63].

In cases of hemangioblastomas, the small feeding arteries can be visualized, coagulated, and divided around the tumor capsule. The main draining veins, most commonly lying on the dorsal aspect of the tumor, should be preserved until most arterial feeders are coagulated. The tumor can be shrunken away from the

surrounding parenchyma by using direct electrocoagulation, and placing small cottonoid strips at the tumor/gliosis interface. Gelfoam (Pfizer, New York, NY) soaked in thrombin may be utilized to control the bleeding that originates from the tumor capsule [70, 71, 74]. It has been shown that preoperative spinal angiography and embolization may be used as an adjunct prior to surgery. Some series suggest that spinal angiography and embolization helped determine the location and the nature of the tumor and anatomy of the feeding artery and vascular supply [75].

Closure. After complete hemostasis and irrigation, the arachnoid can be closed with either interrupted 6.0 polydioxanone sutures (PDS) (Ethicon, Somerville, NJ). We prefer to close the dura with Gor-Tex sutures (Gore Medical, Putzbrunn, Germany) as they procure a stronger watertight closure. Fibrin glue and Surgicel (Ethicon, Somerville, NJ) can be applied to the suture line. The laminae are placed back in their native position and reattached to the neighboring spine with 2.0 silk sutures and small titanium plates and screws. Although laminoplasty was not shown to decrease the risk of spinal deformity, it does significantly limits the occurrence of postoperative cerebrospinal fluid leak [76].

16.7.3 Special Surgical Equipment

Microsurgical resection of spinal cord tumors requires special micro-instruments to achieve a safer and more effective surgery. Finer micro-dissectors and small controlled suction devices are very helpful to dissect the plane around the tumor and avoid collateral injury to the spinal cord. Small bipolar forceps with fine tips should be employed usually with lower power-settings to avoid spread of thermal heat to normal parenchyma [74]. Epstein first described the use of the ultrasonic aspirator in pediatric spinal cord tumors [77]. This device combines the mechanisms of suction, high frequency vibration and cavitation. Interestingly, tumors have weaker cellular connections than normal vessels and nerves, and are usually more readily fragmented by the acoustic energy of the ultrasonic aspirator than normal tissue [78].

Nd:YAG laser scalpels were also reported for the resection of intradural tumors [79]. Unlike non-contact laser beam devices, laser scalpels have their energy concentrated to a sapphire tip, which only transmits heat to the tissue in direct contact with the scalpel. The laser scalpel can be used as a micro-instrument, and can achieve a relatively bloodless myelotomy [80]. Laser scalpels are believed to transmit less thermal energy to normal surrounding parenchyma than the ultrasonic aspirator, and do not result in electrical artifact during simultaneous recording of motor evoked potentials (MEPs).

The operative microscope should be checked and must allow for optimal illumination, magnification, and focus. Indocyanine green technology is a helpful adjunct to visualize and analyze the vascular anatomy [68]. Its use may be valuable in cases in which it is difficult to estimate the location of the posterior median sulcus, or in hemangioblastomas in which vascular configuration cannot be determined with certainty [70]. Intraoperative ultrasound is a serviceable tool to explore the extent of the tumor exposure, and in showing the cystic and solid components of the tumor.

In our experience, we were also able to use intraoperative MRI in pediatric patients with cervical and upper thoracic intradural tumors. Proper patient positioning and a safe setup are crucial for such endeavor.

16.7.4 Intraoperative Monitoring

Neurologic electro-physiologic monitoring has become a standard procedure during spinal cord surgery in most centers. Since the tumor is frequently embedded in spinal cord parenchyma, neurosurgical maneuvers can easily result in collateral injury. This may be due to stretching, retraction, coagulation, vascular manipulation, and mechanical abrasions to the normal medullary tissue. Intraoperative monitoring provides crucial feedback in the anesthetized patient, alerting the surgeon to change the operative strategy when necessary. Different modalities are available, but their timing in detecting injuries and their interpretation are very user-dependent.

Somatosensory evoked potentials (SSEPs) detect the interruption of sensory inputs (dorsal columns). Because they provide an average of multiple signals, they tend to become abnormal later, after the injury occurs. Transcranial MEPs are designed to track signal transmission in the motor pathways in a more real time fashion. *Myogenic* MEPs are recorded from needle electrodes placed in extremity muscles (tibialis anterior, gastrocnemius). If the patient has a preoperative weakness with a muscular power of 2/5 or less, myogenic MEPs may be difficult to obtain. *Spinal* MEPs are recorded from electrodes placed in the epidural space caudally and rostrally to the tumor, and can detect activity in large corticospinal axons. Unlike the myogenic response, which is all or none, their amplitude correlates with the number of stimulated axons. Spinal electrodes also register D-waves, which—if preserved along with a drop in MEPs—may indicate a rather reversible deficit [81, 82].

Neurophysiological changes should always be taken seriously and interpreted appropriately. A change from polyphasic to biphasic myogenic waveforms indicates an injury to the motor circuitry. A decrease of 50% in MEPs usually predicts a significant, and possibly a permanent deficit. A drop of MEPs associated with maintained D-waves usually anticipates a recoverable injury [83]. Anesthetic agents may interfere with electrophysiological recording; paralytics, halogenated anesthetics and boluses should be therefore avoided. A clear and regular communication with the recording technician and anesthesiologist is mandatory [82].

16.7.5 Postoperative Complications

Transient clinical deterioration after surgery is common. This may be related to collateral injury to the spinal cord due to surgical manipulation or vascular injury. After a dorsal midline myelotomy, patients may develop a transient dorsal column dysfunction. The thoracic spinal cord has watershed vascularity and is particularly vulnerable to ischemia. Shunt malfunction may occur after intradural tumor resection.

Syringomyelia may worsen after surgery and cause progressive neuropathic pain. It is believed that a tumor-associated syrinx is generally secondary to the tumor and *complete* resection eventually results in the dissipation of the syrinx. It is usually not necessary to drain the cyst during surgery; however, a close imaging follow-up is advised as a subgroup of patients with refractory syringomyelia may require a cysto-subarachnoid shunt.

Deformity is another risk after large exposures for spinal intramedullary tumors, especially in younger patients with ligamentous laxity, muscular weakness, and who may already have some degree of associated scoliosis or syringomyelia [62, 64]. The risk is also level dependent (less in the cervical region) and increases with multiple surgeries, exposure of the thoracolumbar junction, and radiation [84]. Although laminoplasty was advocated to decrease the theoretical risk of deformity, this has not been shown to be statistically significant in several published clinical series [76]. Follow-up with serial imaging is necessary, especially in high-risk patients, to detect early deformity and address it with appropriate fusion if needed. Deformity correction should include techniques with instrumentation that still allow MRI surveillance for recurrent tumor or late syrinx formation.

16.8 Adjuvant Therapy

16.8.1 Radiation Therapy

Currently, radiation is mainly indicated for high-grade lesions and tumors not amenable to gross total resection. Radiation of the entire neuraxis is advised in the management of malignant astrocytomas [85]. Adjuvant radiation therapy after subtotal resection of lower-grade ependymomas and astrocytomas is debatable [65]. While some centers advocate for postoperative radiation, others prefer an expectant strategy with consideration for repeat surgery if the tumor recurs [86]. Experts argue that radiation offers a controversial benefit at the cost of spinal deformity or delayed secondary neoplastic disease.

The recommended radiation dose is 5000–5500 cGY (less for younger children) delivered in fractions of 180–200 cGY [85]. Larger fields of radiation, and even craniospinal radiation, are indicated for high-grade, metastatic, or multifocal tumors. Unlike benign myxopapillary ependymomas in adults, pediatric ependymomas located in the cauda equina are more aggressive and prone for dissemination. They thus require a complete workup, adjuvant radiotherapy and often a larger field of radiation [46].

16.8.2 Chemotherapy

Although current regimens extrapolate data related to the treatment of intracranial and adult spinal ependymomas and astrocytomas, no substantial benefit has been documented in the pediatric population. Platinum-based and nitrosourea-based

treatments can be considered to delay adjuvant radiation. Etoposide has a questionable benefit for recurrent ependymomas [51]. Targeted therapies may offer more valuable options in the future to treat tumors with specific genetic mutations.

16.9 Disease Control

Resecting more than 95% of low-grade tumors results in significant improvement of both overall and progression-free survival [63]. Although this is easier to accomplish in the better-demarcated ependymomas, the natural history of residual low-grade astrocytomas remains slow. Even with gross total resection, spinal cord tumors can still recur in a delayed fashion [11, 60]. In cases of residual and recurrent therapies, adjuvant therapies offer minimal benefit with potential side effects and a higher financial burden. We recommend a close clinical and imaging follow-up of these patients after surgery, and a consideration for re-operation in cases of documented decline. In the senior author's experience, repeat surgery is a cheaper and more effective mean to achieve long-term disease control. Patients can "live with their disease" with optimal preservation of function for the longest period of time possible.

16.10 Conclusion

Pediatric IMSCT remain a challenge to the neurosurgeon, pediatrician, and pediatric oncologist. Surgery prevails as the first-line treatment for most of these tumors. The surgeon should be familiar with the most advanced microsurgical techniques, operative devices, and intraoperative monitoring technology to perform the widest and safest resection with optimal functional preservation. Treatment, from specific surgical strategies to adjuvant therapy and long-term management plans, should be adapted to the pathology and to the individual patient.

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Spinal Cord Ependymomas

17

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17.1 Introduction

Spinal cord tumors constitute 5–10% of all primary central nervous system (CNS) malignancies [1]. There are generally three broad categories of spinal tumor lesions: (1) extradural, (2) intradural-extramedullary (i.e., outside of the spinal cord), and (3) intradural-intramedullary (i.e., within the spinal cord). Approximately 40% of all primary spinal cord tumors are intradural intramedullary. In this category of intramedullary tumors of the spine, ependymomas comprise 60% in adults and 30% in children [1]. Ependymomas are the most common intramedullary spinal cord tumors in the adult population representing half of all intramedullary tumors [1].

17.2 Epidemiology

Each year in the United States, 1000–2000 adults are diagnosed with spinal or intracranial ependymoma [2]. There are approximately 230 new cases of spinal cord ependymoma seen yearly in the United States [1]. Although spinal ependymomas may occur at any age, they most frequently present in adults 20–40 years of age [1]. Men and women are affected equally.

In the adult population, 75% of ependymomas occur in the spinal canal comprising 50–60% of all intramedullary spinal cord tumors [1]. Intramedullary ependymomas represent about 34.5% of all CNS ependymomas [3, 4].

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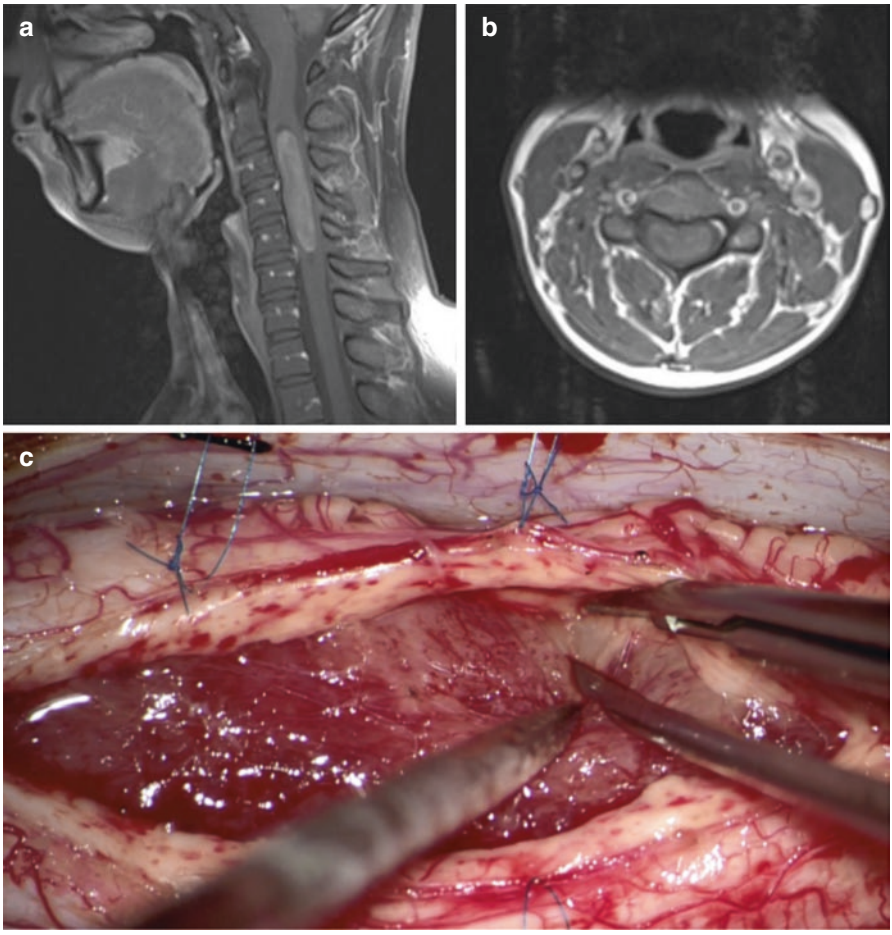

Fig. 17.1 Cervical spinal cord ependymoma. (**a**, **b**) T1-weighted MRI images with gadolinium suggested a cervical spinal cord ependymoma. (**c**) A midline myelotomy was performed. The tumor had a clear interface separating it from the spinal cord providing for a gross total resection

Spinal cord ependymomas (SCEs) arise in the cervical region more than 65% of the time (Fig. 17.1) [1, 5, 6]. More than 90% of spinal cord ependymomas are "benign," meaning WHO Grade 1 and 2. About 50% of SECs span 3 or more vertebral levels [1, 7–9].

17.3 Presentation

Patients with spinal cord ependymomas typically experience nonspecific symptoms that progress over years prior to making the diagnosis. There are rare circumstances of intratumoral hemorrhage that results in acute neurologic deterioration. Common

symptoms that patients may encounter include back pain, sensory loss, paresthesias, weakness, spasticity, and gait disturbance. Intramedullary spinal tumors in the cervical region can present with upper and/or lower extremity deficits if they affect the corticospinal tract and dorsal columns, respectively [2]. In contrast, patients with lumbar region myxopapillary ependymomas may present with incontinence and radicular back and leg pain (Fig. 17.2). Asymmetric weakness and numbness can result if the tumor gets large enough to exert significant mass effect.

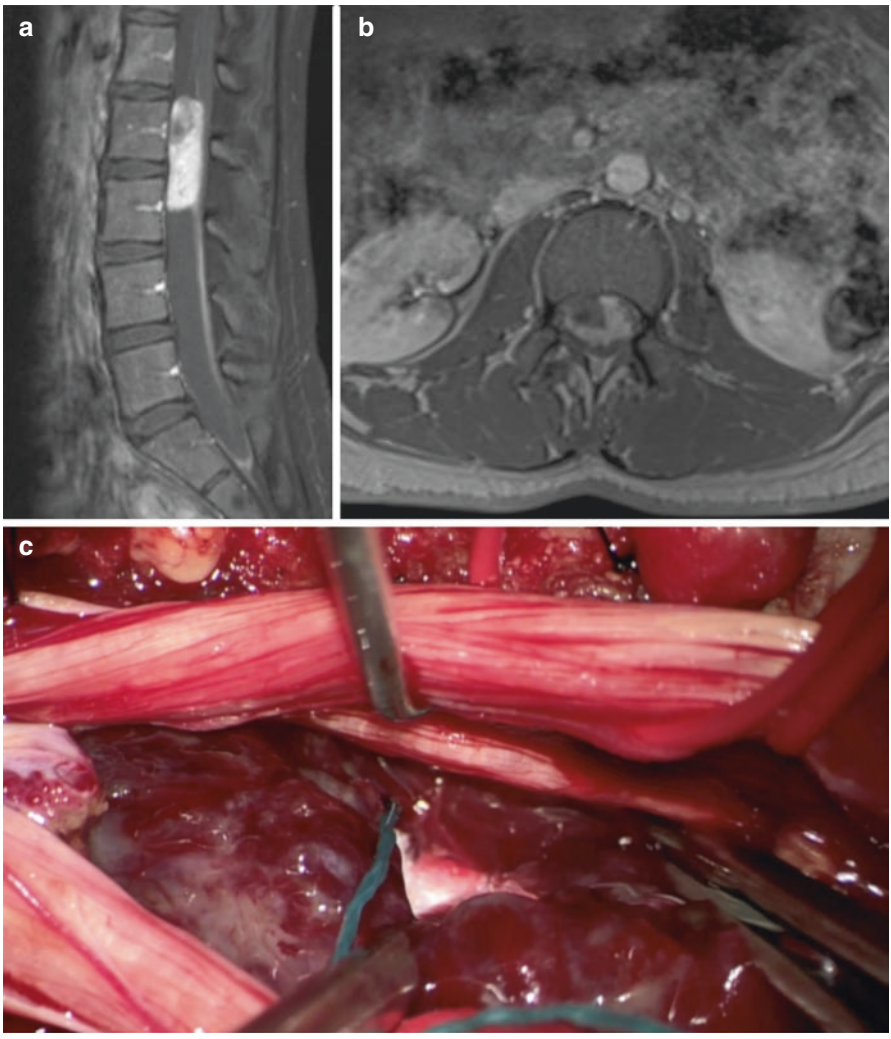

Fig. 17.2 Myxopapillary ependymoma of the lumbar region in a 52-year-old man who presented with worsening urinary incontinence and numbness in the legs. (**a**, **b**) T1-weighted MRI images with gadolinium suggested a myxopapillary ependymoma. (**c**) The tumor was debulked with preservation of the nerve roots

17.4 Pathology

Ependymomas arise from the ependymal cells of the ventricles of the brain, cortical rests, and the central canal of the spinal cord that have undergone cancerous transformation [10]. Two distinct types of spinal ependymomas occur. The myxopapillary type comprises half of all spinal cord ependymomas. It originates from the filum terminale and occur at the conus medullaris (Fig. 17.2) [11]. The other histologic subtype of ependymoma is the classic cellular ependymomas found within the spinal cord. The cellular ependymoma type accounts for 50% of all spinal ependymomas. They are often located in the cervical or thoracic spinal cord.

Greater than 90% of spinal cord ependymomas have a benign pathology. They are slow growing and tend to compress adjacent spinal cord parenchyma rather than infiltrate it, unlike astrocytomas. Although they do not infiltrate the spinal cord, these tumors are not always encapsulated. However, there is oftentimes a clear interface between the tumor and the spinal cord.

On gross pathologic examination, ependymomas oftentimes have a smooth reddish-gray glistening surface that is clearly distinct from the surrounding spinal cord. Blood vessels can be seen crossing the surface of these tumors, which does not occur in astrocytomas.

The World Health Organization (WHO) classification divides ependymomas into different subtypes. Myxopapillary ependymoma (MPE)and subependymoma are WHO Grade 1 and thus the least aggressive in histologic appearance. WHO Grade 2 lesions include classic, cellular, clear cell, papillary, and tanycytic subtypes of ependymoma, which all have similar biologic behavior and lack anaplastic features. Anaplastic ependymoma is WHO Grade 3 and the most aggressive in behavior [12–14]. Ependymoblastomas (WHO Grade 4) should not be confused as a subtype of ependymoma. They are a different type of tumor, classified under embryonal primitive neuroectodermal tumors [1].

WHO Grade 1 tumors include subependymomas and myxopapillary ependymomas. Subependymomas very rarely occur in the spinal cord. Their distinguishing feature is their tendency towards a more peripheral location whereas other subtypes typically are located more centrally within the spinal cord. On microscopy, subependymomas exhibit microcystic spaces and grouped cells on a dense fibrillary background. In contrast, myxopapillary ependymomas histologically exhibit loosely structured cells with intervening pools of mucin. They oftentimes have markedly hyalinized blood vessels.

Classic ependymoma (WHO Grade 2) is the most common spinal cord ependymoma and comprises 55–75% of lesions within the spinal cord [15]. They are typically intramedullary and oftentimes cystic 58% of the time [16]. Histologic features that are characteristic of ependymomas include pseudorosettes, which occur in 80% of patients [17]. Pseudorosettes consist of perivascular cuffs of cells with processes oriented towards the central vessel. “True” or “ependymal” rosettes are seen in approximately 10% of patients with spinal ependymomas [15]. True rosettes are more specific to ependymomas and consist of cells arranged with processes oriented towards a central lumen. Spinal ependymomas typically do not invade into adjacent

tissue, and the margins of tumor are usually well-defined on gross and microscopic examination.

As mentioned, in addition to the classic ependymoma, there are several other subtypes of WHO Grade 2 ependymoma including: (1) cellular, (2) clear cell, (3) papillary, and (4) tanycytic. Cellular ependymoma is characterized by hypercellularity and a high nuclear-to-cytoplasm ratio. There are few rosettes and they lack the mitosis, cellular pleomorphism, and the microvascular proliferation associated with WHO Grade 3 lesions. Clear cell ependymoma is rare and has perinuclear halos and pseudorosettes. Papillary ependymoma subtype exhibits an arrangement of neoplastic cells around a fibrovascular core. Tancytic subtype is the least common WHO Grade 2 subtype. On staining there are cells with long processes similar to pilocytic astrocytomas.

WHO Grade 3 lesions, such as anaplastic ependymoma, are the rarest of the ependymoma subtypes. They are characterized histologically by a high mitotic rate, nuclear pleomorphism, and endothelial proliferation. Furthermore, they tend to infiltrate surrounding neural tissue, unlike Grade 2 ependymomas. This makes gross total resection much less likely [18].

17.5 Molecular Genetics

SCEs frequently exhibit a loss of chromosome 22q, but no specific tumor suppressor genes in this region appear to be consistently altered [19]. Patients with Neurofibromatosis can sometimes exhibit spinal cord ependymomas. Although the merlin (NF2) gene is found in chromosome 22q, it has not been found to be involved in the pathogenesis of spinal cord ependymoma [19, 20]. MPEs exhibit the greatest number or genetic abnormalities of all the subtypes of ependymomas. Chromosome 7 is commonly affected in MPEs [21]. MDM2 gene, which functions to regulate p53-mediated cell growth, is commonly found to be amplified and overexpressed in SCEs [22]. Although alterations in p53 was not common, p53 expression appears to be higher in Grades 2 and 3 ependymomas compared with Grade 1 subependymomas although the data were not able to show a statistical significance [23].

17.6 Diagnosis

Contrast enhanced magnetic resonance imaging (MRI) of both the brain and entire spine is the key study in the evaluation of a patient with suspected ependymoma. MRI demonstrates focal expansion of the spinal cord by the intramedullary tumor. Normal caliber diameter of the spinal cord should suggest other non-neoplastic etiologies such as a demyelinating disease. With SCEs, there is slight hypo-intensity on T1-weighted imaging and hyper-intensity on T2-weighted images. Contrast MRI will demonstrate heterogeneous enhancement [24, 25]. Spinal cord ependymomas can also be accompanied by syrinx, hemorrhage, or cystic degeneration. In fact, about 60% of spinal cord ependymomas have an associated intramedullary syrinx rostral and/or caudal to the tumor [26].

Myxopapillary ependymomas are distinguished by their location around the conus medullaris. On MRI, they appear heterogenous on both T1 and T2 sequences with isointense cellular components and hyperintense areas of mucin and hemorrhage.

Anaplastic ependymomas appear hypo-intense on T1 and isointense or hyperintense on T2. They have variable contrast enhancement. These tumors can be difficult to distinguish from infiltrative astrocytomas given the similar infiltrative pattern of both pathologies. Given their malignant nature, it is essential to screen the entire neuroaxis on MRI.

Computer tomography (CT) has little utility in the diagnostic workup of these spinal cord tumors. CT can capture the occasional calcifications that occur in ependymomas. CT and CT myelography are an alternative only when MRI is unattainable in a patient. Positron emission tomography (PET) is occasionally used and will portray ependymomas as hypometabolic due to their slow cell growth and low cellular density [27].

Cerebrospinal fluid (CSF) cytology is a useful test if there is suspicion of CSF seeding of the tumor. CSF seeding has been reported to occur in 3–12% of intracranial ependymomas and is most frequent in anaplastic ependymomas [1, 12, 28]. This is most helpful with anaplastic ependymomas after surgery or tumors in which there is a subtotal resection [29]. Positive test results for ependymoma cells in the sampled CSF will influence the radiation doses for the craniospinal axis.

17.7 Treatment Options

17.7.1 Surgical Treatment

Surgical resection of the tumor is the optimal treatment for spinal ependymomas with well-defined margins if surgical resection can be performed safely [3, 30–32]. When these tumors can be removed completely with gross total resection, treatment outcome and prognosis are excellent and there is a low risk for recurrence [33, 34]. The rate of gross total resection of ependymomas ranges between 84 and 93% of cases. Such high rates are largely because these tumors are rarely infiltrative and most often have a distinct border [16]. Extent of resection of spinal cord ependymomas is affected by size of tumor and its location, the presence of a capsule or syrinx, and the histology [35–37].

There are several retrospective studies assessing surgical resection of spinal cord ependymomas that suggest a correlation between the extent of resection and progression-free survival (PFS) [37–41]. However, because spinal cord ependymomas are so rare, there is insufficient data to demonstrate a definitive relationship with progression-free survival and overall survival (OS) in these patients [2].

Although patients with Grade 2 ependymomas who have gross total resection had a significantly lower recurrence rate than patients who had a subtotal resection, not all patients benefit from gross total resection of spinal ependymoma. In patients with myxopapillary ependymoma (WHO Grade 1), the recurrence rate does not

differ between those who had gross total resection versus subtotal resection [36]. For grade 3 anaplastic ependymomas the recurrence rate appears to be lower in patients who underwent a gross total resection versus subtotal resection but the sample size studied was too small to demonstrate a statistically significant difference [36].

Microsurgical resection alone can achieve long-term tumor control or even cure while also preserving neurologic function [31, 42]. As mentioned, although ependymomas are not always encapsulated, there is still oftentimes an identifiable interface between tumor and spinal cord as these tumors typically do not invade into the spinal cord parenchyma. Determining the plane between the tumor and the spinal cord is the most critical step of the surgery. Tumors with distinct capsules or tumor-parenchyma interfaces are associated with fewer neurologic deficits post-operatively. This is probably because they are easier to separate from normal tissue and thus less likely to result in compromise of neural structures [35, 43]. In spinal cord ependymomas a midline myelotomy will often need to be performed, extending the entire cranial-caudal axis of the tumor to expose this tumor-parenchyma interface. Presence of a syrinx may facilitate surgical resection and increase the chances of a gross total resection.

In regards to predicting postoperative functional outcomes, the preoperative functional neurologic status is the most important and significant predictor [33, 34, 44]. Thus, for patients who already have long-standing neurologic deterioration, there is little chance of significant neurologic improvement even with excellent surgical resection [7, 8]. Furthermore, the morbidity from surgery can be increased in patients who already have profound preoperative neurologic deficits.

Post-operative neurologic deficits after resection of a spinal cord ependymoma are common despite meticulous efforts to not disrupt normal tissue. The risk can be predicted by the patient's pre-operative neurologic function [35, 37]. Patients with intact or good neurologic function are less likely to experience post-operative neurologic symptoms compared to patients with deficits pre-operatively. Furthermore, they are also more likely to improve when symptoms appear [35].

After a midline myelotomy to access an intramedullary ependymoma, it is not uncommon to experience somatosensory deficits from disturbance of some of the tracts in the posterior columns [6, 7]. This may also result from traction of the posterior column tract or from microtrauma resulting in transient edema, Furthermore, vascular insult be also lead to neurologic deficits. For example, patients with SCEs in the thoracic region are more likely to develop neurologic deficits after resection because of the limited blood supply in this region of the spinal cord and the narrow spinal canal [41]. Most patients generally experience resolution of their somatosensory deficits within a few months [8]. Some use neuromonitoring to potentially decrease post-operative morbidity. Motor-evoked potentials may detect injury to motor tracts and possibly prevent further damage intra-operatively [41]. Somatosensory-evoked potentials, on the other hand, have not proven to affect or predict functional outcomes [41]. Given that this is such a rare pathology, there have been no large randomized trials to determine whether intra-operative monitoring significantly improves outcomes from surgery [2].

Myxopapillary ependymomas typically appears around the conus medullaris usually involving both the filum terminale as well as cauda equina. Although these tumors lack malignant histological features, they have a higher recurrence rate than WHO Grade 2 ependymomas of the spinal cord [38]. Part of the reason that myxopapillary ependymomas have a lower gross total resection rate may be from efforts to spare the nerve roots of the cauda equine [38]. Recurrence rates for myxopapillary ependymomas range from 15–33% of operations. However, mortality rates remain low with an 85–100% overall survival at 5 years [45]. Due to their location near the conus medullaris, myxopapillary ependymomas exhibit the highest rate of post-operative bowel and bladder incontinence [35, 46]. Thus, since the there is a dearth of evidence to suggest a benefit of gross total resection in MPE, the surgeon needs to consider whether maximal resection is worth the risk of possible post-operative neurologic injury. Some speculate that preservation of the tumor capsule in MPEs may be vital in preventing recurrence [47, 48].

Subsequent treatment after surgery depends largely on the extent of residual disease, which can be assessed with MRI. In instances of significant residual disease, reoperation should be considered since full surgical resection significantly improves the survival of these patients [49].

17.7.2 Radiation Therapy

In patients who have residual disease but are not surgical candidates for reoperation, limited-field radiotherapy is administered. The majority of tumor recurrences are local, often at the site of the original tumor [12, 28, 30]. Therefore, if gross total resection is not attainable due to anatomy or tumor location, adjuvant radiotherapy should be given, as some studies suggest that adjuvant radiation therapy can decrease the rate of progression [50]. The standard regimen is a cumulative dose of 54 Gy of fractionated external beam therapy. This has been demonstrated to improve local tumor control [51]. There is controversy surrounding the use craniospinal irradiation in patients with local disease and no metastases. If there is disseminated disease, then craniospinal radiation should be considered.

Stereotactic radiosurgery can be considered in patients with co-morbidities that contraindicate surgery or for untreatable lesions. The advantage of stereotactic radiosurgery is that it may reduce tumor burden while limiting radiation exposure and treatment-related complications [52]. Although the use of radiation as an adjuvant is still controversial, further studies are warranted to assess whether adjuvant radiation therapy may be helpful for the prevention of local recurrence [51].

There are other radiation therapies with promise. Amsbaugh et al. reported 100% PFS and a 20-month OS in patients with spinal cord ependymomas that were treated with proton beam therapy [53]. Like stereotactic radiosurgery, proton beam therapy uses less radiation and may have similar benefits.

17.7.3 Chemotherapy

There is no clear role for chemotherapy for spinal cord ependymomas. There are a few studies that suggest that chemotherapy may be used as a salvage therapy for tumor recurrence if both surgical resection and radiation fail [2]. There is only one prospective study studying chemotherapy for spinal cord ependymomas, which was done by Chamberlain et al. on oral etoposide on ten patients with recurrent, low-grade spinal cord ependymoma [54, 55]. All ten patients in the study had spinal ependymomas that recurred after surgery and radiotherapy, of which four had also failed prior chemotherapy. After treatment with etoposide adjuvant chemotherapy, three patients had progression, two patients had a partial response and five patients had disease stabilization. The median PFS was 15 months ranging from 2.5 to 45 months. The median overall survival was 17.5 months with range 3–45 months. The drug was well tolerated by the cohort in this phase I trial.

17.8 Conclusion

Ependymomas are a rare type of tumor that occurs both in the brain and spine. In regards to spinal cord ependymomas, they can either occur intramedullary within the spinal cord or at the filum terminal as the myxopapillary subtype. Because of the less aggressive and non-infiltrative nature of most spinal cord ependymomas, they are very amenable to surgical resection. Although there are fewer data on adjuvant treatments, radiation is also a powerful tool in the treatment of patients with possible disseminated disease or subtotal resection.

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Malignant Intramedullary Spinal Cord Tumors

18

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18.1 Introduction

Compared to their intracranial counterparts, spinal cord tumors are quite rare, accounting for less than 10% of all central nervous system (CNS) lesions. Intramedullary spinal cord tumors (IMSCTs) comprise 20–30% of all spinal cord tumors in adults and 4–10% of all tumors of the spinal cord in children [1]. The most frequently encountered IMSCTs are gliomas. In adults, the most common pathology is ependymoma followed by astrocytoma, comprising 60% and 30% of intramedullary spinal cord tumors, respectively [1]. Children demonstrate the opposite incidence of pathology with astrocytomas being the most common (60%) followed by ependymoma

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(30%), while embryonal tumors, such as primary neuroectodermal tumors as described by the prior World Health Organization (WHO) classification, represent 4% [2]. There has also been observed a pattern based on the age of the child. Children younger than 2 years of age will more commonly have neuroblastomas, teratomas, or dermoid tumors [2]. Children ages 2–5 years present with astrocytomas, gangliogliomas, and epidermoid tumors. Children 6–10 year of age have a mix of tumor types. Astrocytomas predominate in children >10 years of age [2]. Astrocytomas comprise approximately 90% of all intramedullary tumors in patients >10 years of age and about 60% of adolescent intramedullary neoplasms. By around 30 years of age, ependymomas become slightly more common than astrocytomas and predominate in the middle decades of life. After the sixth decade of life, astrocytomas and ependymomas are encountered with fairly equal frequency. Other IMSCTs include gangliogliomas, lipomas, subependymomas, hemangioblastomas, dermoids, teratomas, central neurocytomas, oligodendrogliomas, and in extremely rare cases, intramedullary metastases. There is a slight predilection for such lesions in males [3]. A propensity for the development of spinal cord astrocytomas exists in children with neurofibromatosis type 1 (NF1). There is an additional propensity for the development of spinal cord ependymomas in children with neurofibromatosis 2 (NF2). In this chapter we are focusing on the most common malignant spinal cord tumors, astrocytomas and ependymomas, their differential diagnosis, diagnostic features, management and disease course.

Malignant spinal cord tumors are only reported in a small proportion of all spinal cord tumors. The incidence of malignant spinal cord tumors in adults has been reported as 0.22–0.24 per 100,000 person-years. However, most epidemiological reports incorporate data for meningiomas, schwannomas, and neurofibromas as well as IMSCTs; therefore, the true incidence is difficult to determine [1].

Malignant transformation of a low-grade glioma has been reported in approximately half of recurrent glial tumors in adults. The risk of malignant transformation increases with higher initial pathologic grade, incomplete resection, age greater than 45 years, and previous radiation [4]. As opposed to the adult population, malignant transformation of low-grade gliomas in pediatric patients is very rare. Case series have provided few examples; however, most patients had either received radiation or chemotherapy prior to progression, which may confound true pathologic progression [5]. The specific molecular markers responsible for the differences between adult and child tumor histology may result from the tumor's evolution in a developed versus still-developing nervous system [6].

Molecular markers associated with gliomas, such as isocitrate dehydrogenase (IDH) 1 and 2 gene mutations, have long discussed in relation to intracranial gliomas, yet for spinal cord tumors, the data are still fairly scarce [7, 8]. BRAF mutations are also been extensively studied especially for brain tumors, BRAF can be activated either by mutation or by fusion with another gene. The most common mutational variant is BRAF-V600E, which results in constitutive BRAF activation and is seen in 50–60% of pleomorphic xanthoastrocytomas, <10% of pilocytic astrocytomas (particularly extra-cerebellar pilocytic astrocytoma), 20–75% of gangliogliomas, and 50% of anaplastic gangliogliomas [9]. BRAF-V600E is also seen in the majority of subependymal giant cell astrocytomas [10]. Pilocytic astrocytomas have activation of BRAF via duplication of the BRAF locus at 7q34 because of an in-frame fusion

between the KIAA1549 and BRAF genes in 80% of tumors [11–14]. Spinal cord astrocytomas were shown to have similar characteristics in relation to BRAF mutation; these findings hold promise not only for diagnostic value but also for treatment options with the utility of BRAF-MEK inhibitors [15]. Further segregation of these tumors by the histone mutation H3F3A K27 M, which is known to be expressed in midline brain and brain stem tumors as well as in high-grade gliomas, also seem to have similar features as intracranial lesions with the more high-grade tumors harboring the mutation and predicting a less favorable outcome [15]. This mutation is important in order to guide the aggressiveness and extent of surgical resection with assistance of neurophysiological intraoperative monitoring of the sensory and motor pathways. This approach helps limit postoperative neurologic deficits, given the predicted natural history as defined by *H3F3A* K27 M mutation status [16].

The new findings of genetic alterations and molecular subtyping help adjust management and treatment options for patients, adults, and pediatrics suffering from intramedullary spinal cord tumors. The combination of the new era of molecular biology in neuro-oncology with the advances in neuromonitoring and surgical techniques hold a promise for a better future for these patients.

18.2 Clinical Presentation

A thorough history and physical examination should be performed to establish a clear sense of the behavior and the clinical consequence of a spinal tumor. IMSCTs most commonly arise in the cervical and thoracic spine, resulting in associated clinical symptoms. Thoracic, lumbosacral, conus, and filum lesions are rarer.

The duration and quality of clinical symptoms is highly variable with IMSCTs. Typically, IMSCTs exhibit indolent growth, which corresponds to their underlying slow and progressive clinical symptomatology. Therefore, it is not surprising that delays in diagnosis are fairly common. Pain is the most frequent presenting symptom often with axial back or neck pain and occasionally, radicular pain due to nerve root impingement. Nocturnal pain related to the diurnal variation of endogenous steroid production can also be present. In children, the general presence of back pain (and especially nocturnal pain) should raise concern with clinicians as this is an uncommon condition of youth. Symptoms evolve from pain to motor weakness, gait disturbance, torticollis, and kyphoscoliosis [2]. Motor deficits can be perceived initially as clumsiness if the child is delayed in milestones, such as walking, or presents with frequent falls. Previously reported average duration of symptoms until diagnosis of spinal cord tumors is between 8.1 and 17 months [17, 18]. The expansile nature of IMSCTs can affect any of the traversing spinal cord tracts and structures in their vicinity. For example, weakness may occur due to corticospinal tract or lower motor neuron involvement. Sensory impairment, including numbness or paresthesia, may occur due to dorsal horn and spinothalamic tract impairment, although children are less likely to notice and complain of these sensory disturbances. Long tract impairment may result in gait ataxia and limb stiffness. Additionally, late-occurring findings can include bowel and bladder dysfunction, which usually indicates a more advanced disease state. Sphincter dysfunction is rarely reported [3]. Both the

McCormick classification scale and Karnofsky performance scale are useful in defining the preoperative functional status of a patient [19]. While motor paresis and sensory impairment are possible on examination, long tract signs on clinical evaluation include a positive Hoffman or Babinski sign as well as hyperreflexia. Scoliosis is another possible presenting sign and may ultimately lead to the diagnosis of an IMSCT; this phenomenon likely occurs as a result of impaired innervation to the paraspinal musculature. Up to one-third of children may present with scoliosis as the initial finding [20]. Any child or adolescent that develop progressive scoliosis should be thoroughly examined and send for magnetic resonance imaging (MRI) in order to rule-out spine tumor. Given the variety of possible presenting signs and symptoms of IMSCTs in the pediatric population, it is critical that all practitioners involved in a child's care maintain vigilance in determining a valid etiology for a child who presents with specific or nonspecific neurological complaints, or with objective findings on physical examination. Even unexplainable abdominal pain or newly diagnosed hydrocephalus of unclear etiology can be the result of an IMSCT. Therefore, a low threshold for diagnostic imaging should be utilized in these patients [17, 21]. In general, these malignant tumors have a much shorter duration to presentation compared with low-grade or benign tumors.

18.3 Diagnostic Imaging

The diagnostic modality of choice for IMSCTs is MRI. There is no strong indication to obtain X-ray, or computed tomography (CT) imaging of the spine. Any new rapidly progressing or atypical scoliosis in pediatric population diagnosed by either X-ray or CT should be further investigate via MRI in order to assess the existence of spinal tumor. Intramedullary spinal cord tumors appear as expansile lesions within the spinal cord. Different IMSCTs have variable locations within the spinal cord: astrocytomas tend to be more eccentric, involving the white matter of the spinal cord, while ependymomas tend to rise from the central canal.

Astrocytomas are either isointense or hypointense on T1-weighted MRI, and hyperintense or isointense on T2-weighted imaging. Contrast enhancement is variable and is most often described as a heterogeneous enhancement (Figs. 18.1 and 18.2). Up to 30% of astrocytomas do not enhance. In some cases, tumor-associated cysts may be present within or immediately rostral or caudal to the lesion, and the presence of syringomyelia is also possible. T2-weighted signal change in the surrounding spinal cord indicates edema associated with the tumor. Astrocytomas are occasionally exophytic with a portion of the tumor extending into the intradural extramedullary compartment. As mentioned, astrocytomas typically have poorly defined margins that may be apparent on imaging studies. Peritumoral edema is present in approximately 40% of cases. Intratumoral cysts are present in about 20% of cases, and peritumoral cysts are present in 15% of cases. Unlike ependymomas, hemorrhage is also uncommon (Fig. 18.3) [22].

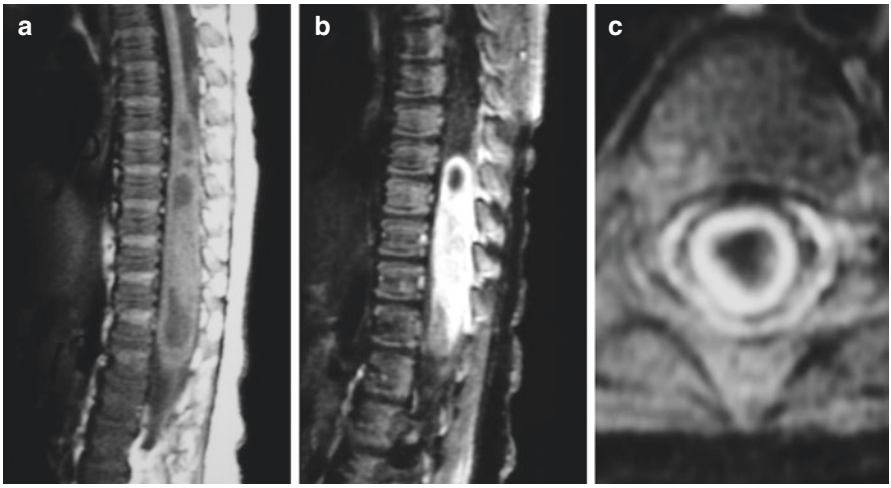

Fig. 18.1 Thoracic anaplastic astrocytoma. MRI of the thoracic cord showing sagittal (**a**, **b**) and axial (**c**) views of relatively heterogeneous enhanced tumor with areas of ring enhancing tumor. Enhancement tends to be patchy in many cases

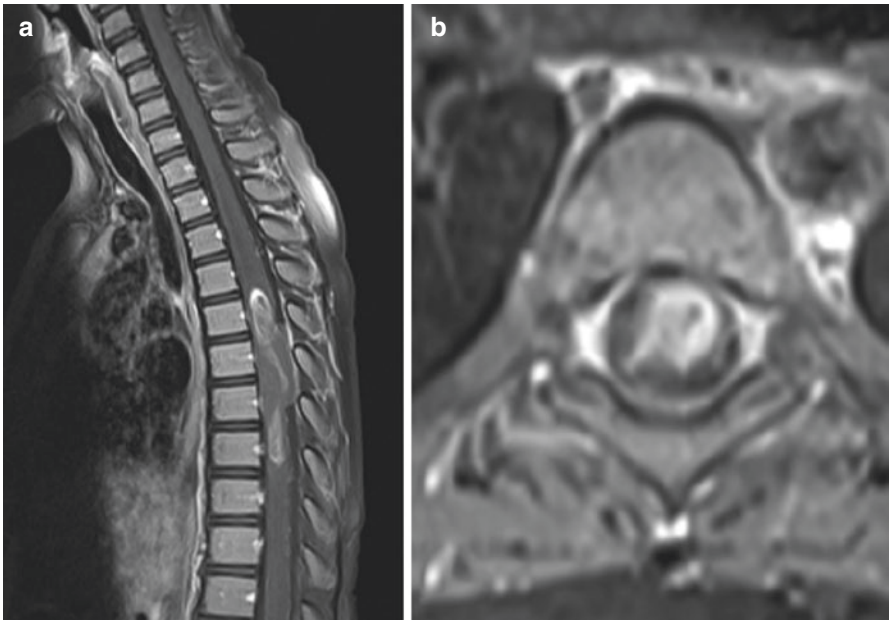

Fig. 18.2 Spinal cord glioblastoma. Sagittal (**a**) and axial (**b**) of views thoracic MRI showing spinal cord glioblastoma with non-homogenous enhancement, swelling of the cord and adjacent syrinx

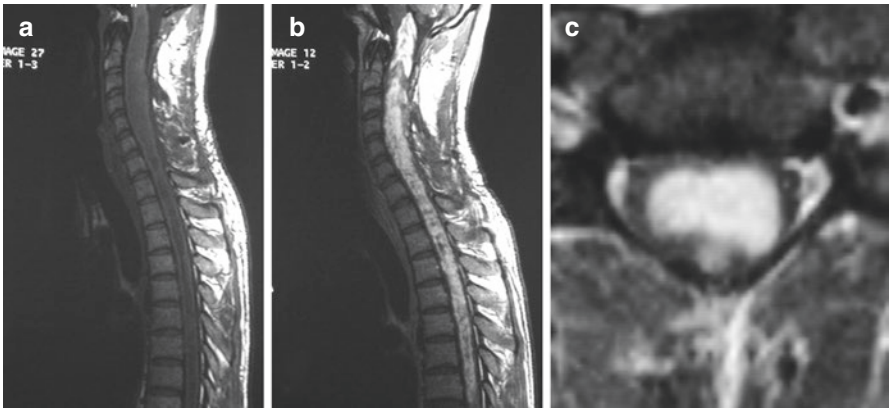

Fig. 18.3 Holocord anaplastic astrocytoma. Cervicothoracic holocord tumor as seen in sagittal (**a, b**) and axial T1 (**c**) before and after injection of gadolinium

Ependymomas are well-circumscribed, elongated, and cylindrical mass lesions that cause symmetric central expansion of the cord. There is usually a well-defined margin between the tumor and the surrounding cord. Typically, ependymomas are isointense to hypointense on T1, and variably hyperintense on T2. Hemorrhage and hemosiderin are common and are seen as heterogeneity of signal on MRI. Cysts are a typical finding in ependymomas with previous reports suggesting that 50% of spinal ependymomas have an associated cyst [23, 24]. Three distinct types of cysts have been identified: intra-tumoral cysts, rostral or caudal cysts, and reactive dilation of the central canal (i.e., syringomyelia) [24]. An intra-tumoral cyst is thought to arise due to degeneration, necrosis, and liquefaction within the neoplasm and contains a mixture of elements, such as protein, old hemorrhage, and necrotic tumor tissue [23, 25]. This inhomogeneous composition leads to variable signal characteristics on MRI and not always the expected isointensity to hypointensity on T1-weighted images and hyperintensity on T2-weighted images. Rostral and caudal cysts tend to appear less enhanced compared with the intra-tumoral cysts, and have been shown to contain hemorrhagic or xanthochromic fluid, but not tumor cells [19, 23]. In approximately 20% of cases, the "cap sign"—a rim of low signal along the border of the neoplasm—can be identified. This sign is a result of a rim of extreme hypointensity due to hemosiderin at the poles of the tumor on T2-weighted images (Fig. 18.4) [25]. Ependymomas typically enhance homogeneously with contrast.

Ependymomas and astrocytomas account for more than 90% of spinal cord tumors, and their treatment paradigm is different (in ependymomas, aim for gross total resection [GTR] with no further adjuvant therapy, whereas in astrocytomas GTR is rare and adjuvant therapy is usually needed). Hence, it is most helpful to distinguish between these two entities before surgery when possible. Some of the imaging features differentiating astrocytomas from ependymomas are their location within the spinal cord (astrocytomas are eccentric while ependymomas are more central), the presence of hemorrhage (which is more common in ependymomas), hemosiderin staining (which is more common for ependymomas), contrast

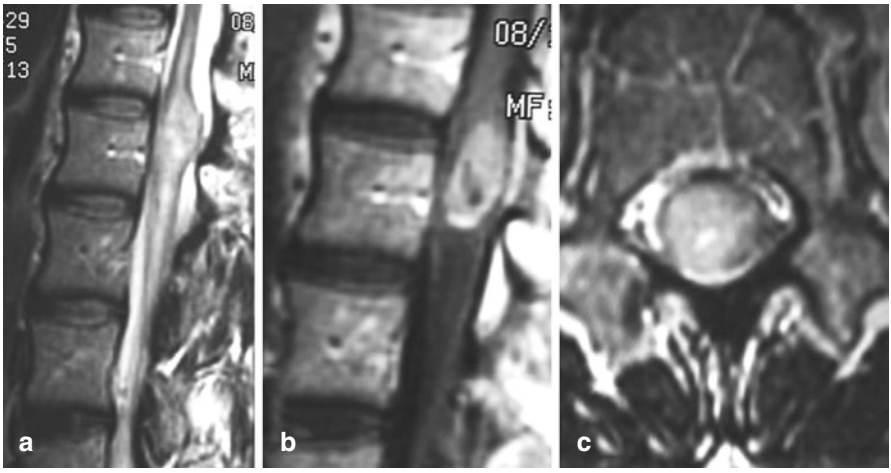

Fig. 18.4 Anaplastic ependymoma. Sagittal (**a, b**) and axial (**c**) MRI of the thoracic spine showing relatively centralize lesion with strong enhancement and adjacent syrinx

enhancement (ependymomas demonstrate homogeneous enhancement, while astrocytomas are patchy), and the presence of cysts (which are more common for ependymomas) [23, 26]. Besides these features, ependymomas have traditionally been known to have a clearer margin than astrocytoma due to their tendency to displace rather than infiltrate adjacent neural tissue [27–29]. Yet others did not find this difference to be significant [30].

In recent years there is a growing interest in the use of advance imaging techniques for the evaluation and management of spinal cord tumors. MRI parameters like regions of interest (ROI) can be placed at specific columns, and the apparent diffusion coefficient (ADC), fractional anisotropy (FA), axial diffusivity (AD), and radial diffusivity (RD) values can be obtained for quantitative analysis. All of these features—as well the new utilization of DTI (diffusion tensor imaging) and DTT (diffusion tensor tractography)—lead to better understanding of spinal cord tumors and promote the evolution of the treatment paradigm [31]. The association among quantitative changes of FA and ADC within the lesions (which usually decrease in FA values and increase in ADC values as a result of changes in water content that result in reduced restriction of water motion within the lesion) of the CNS may be complex; although multiple publications suggest this association, others failed to show significant correlation, hence further study is needed [31, 32].

18.4 Pathology, Histology, Genetics and Molecular Subtyping

As mentioned previously, the most common types of intramedullary spinal cord tumors are astrocytomas and ependymomas. Spinal cord astrocytomas represent a heterogeneous group with respect to histology, gross features, and natural history.

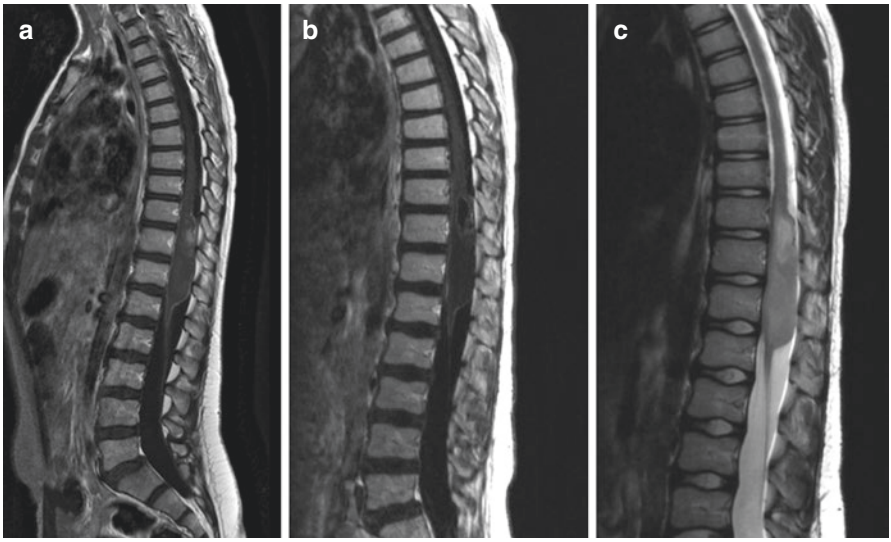

Fig. 18.5 Glioblastoma of the spinal cord. Different sagittal views of thoraco-lumbar glioblastoma, showing non-homogenous enhancement (**a**), with signs for Intratumoral necrotic areas (**b**), and hyperintense signal on T2 (**c**)

WHO Grade I and Grade II astrocytomas are known as pilocytic astrocytomas and diffuse astrocytomas, respectively. Malignant astrocytomas (WHO grade III and IV), such as anaplastic astrocytomas and glioblastoma, account for about 10–20% of intramedullary astrocytomas (Fig. 18.5). These lesions are characterized by a rapidly progressive clinical course, a high incidence of cerebrospinal fluid (CSF) tumor dissemination, and poor survival regardless of intervention [33]. Importantly, leptomeningeal spread is more frequent in spinal glioblastoma than intracranial tumors. CSF dissemination does not necessarily limit overall survival. The development of hydrocephalus, however, does limit survival. Pediatric glioblastoma differs from adult glioblastoma in tumor features, such as molecular biology and genetic features.

Spinal astrocytomas commonly display infiltrative features without a clear surrounding plane that separates them from normal neural structures, making total resection challenging. Hence, the goals of surgery in infiltrative astrocytoma are to obtain a tissue diagnosis, reduce tumor volume, and preserve neurological function. The most common subtype of intramedullary astrocytic tumors is diffuse astrocytomas, classified as WHO Grade II, while malignant astrocytomas are less common and account for 20% and 10% of intramedullary astrocytic tumor cases in adults and children, respectively [34].

Several genetic and molecular variables have been associated with the development of astrocytomas including p53 mutation, proliferative activity (Ki-67), 1p/19q chromosome loss, and epidermal growth factor receptor (EGFR) amplification [35]. The new era of molecular subtype analysis has broadened our understanding of

CNS tumors. Further studies to evaluate associations between specific markers and progression-free survival, neurologic outcome, and overall mortality are currently being conducted. Few publications showed several well-established genetic alterations in spinal diffuse gliomas, such as p53, p16, ATRX, and PTEN mutations. These are well recognized mutations in intracranial gliomas. However, spinal diffuse gliomas have yet to be associated with IDH1/IDH2 mutations, even in low grade gliomas [36]. Intracranial gliomas rarely exhibit the combined absence of IDH mutations, p53 mutations, and 1p19q co-deletion. In contrast, spinal diffuse gliomas commonly exhibit p53 mutation without IDH1/2 mutation [34]. Interestingly, the mutation of IDH1 is also rare in other midline structures, like the brainstem and thalamus [37]. In the pediatric population, platelet-derived growth factor receptor (PDGFR), loss of heterozygosity on 19q and 22q, and p53 have overexpression in intramedullary high grade gliomas. The deoxyribonucleic acid (DNA) methylation of glioblastoma has led to the increased use of temozolomide as a chemotherapeutic form of treatment; however, the prognostic importance of this tumor marker remains unclear [38].

When analyzing the few data we have about spinal cord astrocytomas, the *BRAF-KIAA1549* translocation was the most common finding for Grade I astrocytomas. In addition, these WHO grade I astrocytomas had mutations for *NF2*, *NTRK1*, *NTRK3*, *PDGFRA*, and *TP53* [15]. WHO grade II astrocytomas had alterations in the MAPK-ERK or PI3K pathways, including *BRAF-KIAA1549* translocation and *BRAF* amplification. WHO Grade III and VI high grade gliomas had a mutation in histone H3F3A K27M, which was noted to be in more than 80% of malignant spinal cord gliomas [15]. This mutation is more prominent in the pediatric population and is characterized by point mutations within the chromatin modifiers H3 that are usually associated with poor clinical outcome regardless of the WHO subtyping [39, 40].

Ependymomas arise from the ependymal cells lining the central canal. In the past, four subtypes of ependymomas were identified: cellular, papillary, clear cell, and tanycytic. With the revision of the WHO guidelines in 2016, it was decided to delete the cellular subtype [33]. Ependymomas of the spinal cord are typically WHO Grade II. Subependymomas (WHO Grade I) and anaplastic ependymomas (WHO Grade III) can also be found, while myxopapillary ependymomas (WHO Grade I) are generally considered separate as they commonly occur in the lumbar cistern and affect the conus medullaris and filum terminale. Ependymomas are typically well circumscribed; therefore, GTR easier to achieved.

The classification of ependymomas is subdivided to papillary, clear cell, and tanycytic subtype. Ependymoma with *RELA* fusion type is a new subtype. This variant accounts for the majority of supratentorial tumors in children. Anaplastic ependymoma is still the highest grade available carrying the worst prognosis. Yet in recent years, there is a growing understanding that ependymomas of the spinal cord, in an infratentorial location, and in a supratentorial location—although called ependymomas—are actually different tumors with different biological behavior [41, 42]. Genetic difference can be a possible reason of this discrepancy. Spinal ependymoma is associated with NF2 and loss of expression of Merlin (the protein encoded

by the NF2 gene), whereas intracranial ependymoma is associated with EPB41L3 and HIC1 [43]. Myxopapillary ependymomas may be considered molecularly different from intracranial ependymomas, as well as other spinal ependymomas, and are considered as a different entity and also categorized as WHO Grade I. Previous studies showed high expression of some genes, including NEFL, HOXB5, PLA2G5, and ITIH2 [33, 43, 44]. Better understanding of the genetics and biological behavior of spinal cord ependymomas will promote our management paradigm and care for the patient.

18.5 The Association of Malignant Spinal Cord Tumors and Hydrocephalus

The association between spinal cord tumors and the development of hydrocephalus is a well-known entity (Figs. 18.6 and 18.7). About 1% of patients with spinal cord tumors have various degrees of hydrocephalus at initial presentation [45]. Although astrocytomas and ependymomas are the spinal tumors more frequently associated with hydrocephalus, almost any kind of spinal lesion can present with signs of raised intracranial pressure.

There were several attempts to explain this correlation, but the true mechanism has yet to be found. Previous explanations include protein transudation from certain tumors that lead to inflammatory response in the basal leptomeninges. Neoplastic

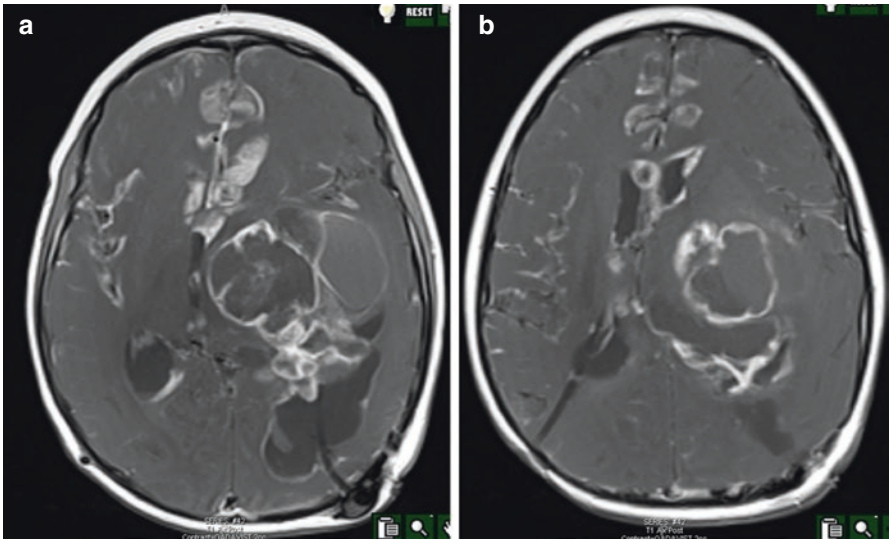

Fig. 18.6 Disseminated Glioblastoma. Axial T1 after gadolinium injection, showing multifocal extensive disease that eventually lead to development of hydrocephalus and need for active draining of the cysts (**a**) and ventricular system (**b**). The extensive disease disseminated to the rest of the CNS

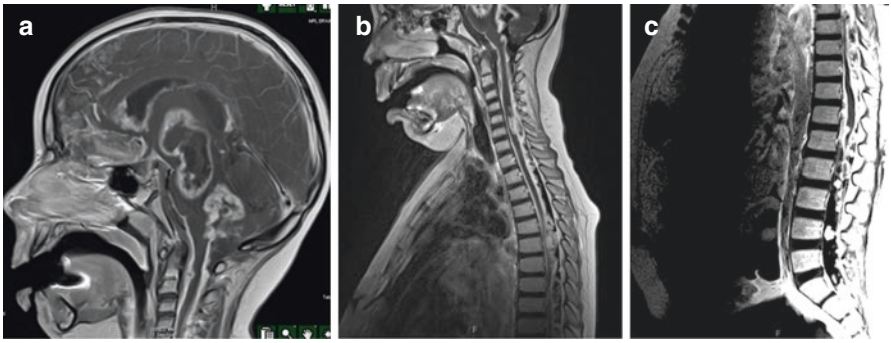

Fig. 18.7 Disseminated Glioblastoma. Different MRI T1 after gadolinium injection in sagittal cuts of brain (**a**), cervical and upper thoracic spinal cord (**b**), and thoraco-lumbar area (**c**)

meningeal infiltration with metastatic arachnoiditis is another possible explanation (Fig. 18.7) [46, 47]. The pathophysiology of this phenomenon can be related to several potential factors, such as increased CSF viscosity, although animal models showed that increased CSF viscosity due to a higher protein content is unlikely to consistently raise the intracranial pressure and/or ventricular enlargement [48]. Increased CSF content of fibrinogen either from chronic inflammation, breach of the blood-brain barrier or as a result of tumor related bleeding is another possible explanation. Hydrodynamic theory suggests that hydrocephalus in patients with benign intraspinal tumors could be caused by a reduction in the spinal compliance secondary to tumoral obstruction of the spinal subarachnoid space. This obstruction reduces total CSF compliance and hence raises the total resistance for flow [49, 50]. Oher possible pathophysiological explanations are occlusion of the CSF pathways around the obex, and neoplastic arachnoiditis, as mentioned before [45].

Development of signs of raised intracranial pressure should raise the suspicion for this phenomenon and need to be addressed in an urgent fashion in patients with a known spinal lesion, or during the presentation of a patient with signs of active hydrocephalus, and signs and symptoms suggesting other neurological deficits that cannot be explain by hydrocephalus.

18.6 Surgical Intervention

The first successful resection of an intradural spinal cord tumor was documented by Victor Horsley in 1887. Resection of an intramedullary tumor was performed in Austria by Anton von Eiselsberg in 1907 [20]. The first description, of an intramedullary tumor resection, however, did not appear until 1911 by Charles Elsberg, describing a 2-stage strategy for removal [20]. The first stage of the operation involved a myelotomy, followed by a return to the operating room in approximately 1 week for the second stage of the surgery to remove the spinal cord tumor that had extruded from the myelotomy site [20]. For a time thereafter, neurosurgeons then

advocated for radical resection of intramedullary spinal cord tumors. However, significant postoperative neurologic morbidity became evident after a more aggressive approach, and neurosurgeons tailored their treatment to favor more conservative biopsy, dural grafting, and radiation therapy. In the modern age, microscopic technique, advanced imaging, and intraoperative neurophysiology monitoring have allowed neurosurgeons to move toward complete resection of intramedullary spinal cord tumors with improved long-term survival and acceptable morbidity [20]. Like their intracranial counterparts, the recommendation for the extent of surgery is "maximum safe resection".

In some cases of clinically silent, incidentally found lesions, such as those discovered following trauma, serial monitoring and watchful waiting may be appropriate. However, for symptomatic or progressively enlarging lesions suspicious for IMSCTs, surgical intervention is the mainstay of treatment. The goals of surgery are to obtain a diagnosis and to decompress the spinal cord by performing a maximal tumor cytoreduction without causing new and permanent neurological deficits. Several groups have reported their experience with surgical resection of low grade IMSCTs [12, 40, 51–53]. In experienced hands, GTR can be achieved in a significant fraction of IMSCTs. Spinal ependymomas typically demonstrate clear surrounding cleavage planes that facilitate tumor extirpation in its entirety. On the other hand, given the infiltrative biology of astrocytomas, tumor margins are often blurred with normal neural structures, making total removal more challenging. The use of intraoperative monitoring is helpful in aiding the surgeon to perform a maximal safe resection.

For spinal cord high grade gliomas (anaplastic astrocytoma and glioblastoma), many previous studies, advocated limited resection of high-grade gliomas because of their infiltrative nature, lack of distinct cleavage planes, and overall poor prognosis regardless of therapeutic intervention. Yet, most of these publications failed to separate anaplastic astrocytoma from glioblastoma. Recent publications suggested that radical resection have much better results for anaplastic astrocytoma [54].

For pediatric spinal cord astrocytomas, patients who had surgery fared better than those who had no surgical procedure or biopsy only [55]. Surgery improves outcome when controlling for tumor size, grade, and extension. Surgical intervention was shown to be the mainstay of treatment for improving survival and should be performed early for spinal cord astrocytomas [55]. For spinal cord glioblastomas and anaplastic astrocytomas, these intramedullary spinal cord tumors were historically treated with biopsy, possible duraplasty, and radiation therapy [55, 56]. However, more aggressive treatments, including cordectomies and GTR, have recently been examined. Several studies have found improved mortality in patients with GTR of primary malignant spinal cord tumors [1, 54, 57, 58]. Yet, others found that GTR did not benefit this group of patients [59–61]. Neurological function can be preserved with aggressive resection of malignant intramedullary spinal astrocytomas, yet motor decline may be observed postoperatively when surgeons attempt GTR of this biologically infiltrative tumor. As mentioned before, radical resection was shown to benefit more patients suffering from anaplastic astrocytomas than glioblastoma [54]. Radical resection for glioblastoma did not show significant difference from the historical treatment paradigm of biopsy and adjuvant therapy [54].

Today, markers (such as H3 K27M) may be more influential than histology alone. Since even adjuvant therapy failed to show significant benefit, radical safe resection for these cases is still the mainstay of spinal cord malignant astrocytomas. As such, the potential morbidity associated with GTR compared with that of more conservative treatment options must be carefully considered when selecting the most appropriate management option for malignant spinal cord tumors.

18.7 Surgical Technique

Surgical intervention for IMSCTs is typically performed with the head in 3-point fixation since the most common locations for such lesions are the cervical and cervicothoracic spine. Intraoperative neurophysiological monitoring is critical in providing the surgeon with real-time feedback regarding the functionality of longitudinal spinal cord tracts. This typically consists of SSEPs, MEPs, and epidural D-wave potentials, which are indicative of functioning corticospinal tract units below the level of resection. The mean arterial pressure is kept above 70 mmHg at all times with the aid of vasopressors, if required to provide adequate perfusion and prevent ischemic injury to the cord. In the pediatric population this cutoff of mean arterial pressure is derived mainly from the child's age and blood pressure before surgery. The patient is positioned prone on gel roles that support all bony elements in order to prevent pressure sores from positioning during the surgical procedure. Arms are usually positioned along the body for cervical and upper thoracic lesions, and above the head (i.e., in a "superman" position) for mid thoracic to lumbar lesions. Shoulders should be positioned to avoid pressure at the brachial plexus in order to prevent injury to the nerves.

Neurophysiological monitoring should play an important role in surgery and the amount of tumor resection. Monitoring has shown to be predictive of functional motor outcome for intrinsic spinal cord tumor surgery [20]. Intraoperative MEPs allow direct monitoring of corticospinal tracts. Motor potentials are evoked with transcranial stimulation of the motor cortex. The MEPs are elicited with a short high-frequency train of electrical stimuli. The responses are recorded with needle electrodes from limb muscles. The motor potentials are interpreted as on or off—their presence indicates intact motor control and their absence marks temporary loss of motor function. A single electrical impulse results in the activation of fast-conducting axons, which is recorded by an epidural electrode placed caudal to the tumor. This recorded potential is the D-wave and is a relative measure of the number of functioning fast conducting corticospinal fibers. When MEPs are evaluated together, myogenic or limb potentials and motor potentials are evoked with transcranial stimulation of the motor cortex. The myogenic MEP exhibits either a present or absent (all-or-none) response, whereas the epidural D-wave amplitude monitoring provides valuable real-time feedback regarding the number of functional corticospinal tract units below the level of the lesion. The graded potential serves as a threshold form when a neurological deficit can be expected; when interpreted in combination with MEPs, graded potential determines whether a deficit is

likely to be transient or permanent [62, 63]. Commonly, the D-wave threshold of 50% reduction in amplitude is interpreted as a threshold at which tumor resection should cease, since any further loss of MEP will result in a potentially permanent deficit. As long as the D-wave amplitude remains above 50%, the patient is likely to awaken with a temporary motor deficit that is likely to improve [20].

At the start of surgery, a midline skin incision and standard subperiosteal dissection is performed to expose the laminae of interest. Laminectomies, or an osteoplastic laminoplasty, can be performed to provide exposure of the thecal sac. Care should be taken not to disrupt the facet joints, which can lead to iatrogenic instability of the spinal column and future deformity. The bony exposure should extend above and below the lesion to allow adequate room for tumor resection without significant spinal cord retraction or manipulation. Use of an osteoplastic laminoplasty, which allows for re-affixation of the posterior bony elements following tumor removal, has been shown to have some positive effect on decreasing the incidence of post-operative spinal deformity requiring fusion in pediatric patients. In addition, a trend towards a decreased rate of CSF leak has also been observed across age groups [64, 65]. Following removal of the laminae, intraoperative ultrasound can provide further transdural tumor localization. The bony opening needs to be large enough to expose the solid component of the tumor. The rostral and caudal cysts do not need to be fully exposed [20]. Epidural electrodes are subsequently placed for D-wave monitoring.

A midline durotomy is performed with placement of tenting sutures. If at this point there are changes to either MEPs or SSEPs, tension should be release in order to explore the possibility that there was too much tension on the cord itself. Surrounding epidural cottonoids help to absorb blood from the epidural space and prevent blood entry into the intradural space. Once the dura is opened above and below the tumor margins, it is important to survey the spinal cord and make note of irregularities, such as rotation, focal prominence, bulging, or discoloration near the cord surface. Use of an operating microscope is essential for IMSCT resection. It is important to consider tumor laterality, if any, when considering the location in which to perform the myelotomy. Special attention should be paid to surface veins that dive inwards within the dorsal median sulcus and the dorsolateral sulcus, which can help orient the surgeon in cases of cord rotation and irregularity. The dorsal median sulcus is the most common chosen entry point to the spinal cord, but the dorsolateral sulcus should be used in cases in which the dorsolateral sulcus allows for a shorter path to the tumor.

Once the myelotomy is performed, retraction may cause diminished SSEPs due to dorsal column manipulation. The myelotomy should extend a sufficient length to have access to the tumor poles. Yet, there is no need to extend the myelotomy all the way above the poles, which can lead to unnecessary resection of viable neural tissue. The myelotomy should be large enough to give enough access to the tumor without using excessive retraction that can lead to cord injury. The tumor typically lies several millimeters below the cord surface. Once the tumor substance is encountered, it may be useful to first obtain a few small specimens with small tumor forceps for frozen section pathological examination to ensure a high likelihood of

obtaining a definitive diagnosis. Following this, the remainder of the resection can be performed. Intramedullary tumors have differences in appearance, such as texture and color, which help differentiate the tumor type. Astrocytomas or gangliogliomas have a gray-yellow appearance. A true plane between tumor and normal spinal cord does not exist in these tumor types, and therefore the surgeon should not attempt to define a tumor-spinal cord interface since additional manipulation can be harmful to the surrounding spinal cord. Ependymomas are typically a red-gray color. These tumors are well demarcated from surrounding spinal tissue and a safe interface can be found for dissection [20].

In both cases it is advisable not to try and first dissect the tumor from the normal spinal cord, but rather to decompress its interior and then try to dissect the tumor from normal cord (which is more amenable in ependymomas than astrocytomas or gangliogliomas). Yet in some cases in which tumor size allows, some authors advocate en bloc resection for ependymoma [66]. Use of bipolar cautery should be limited as thermal injury can harm surrounding normal neural structures, resulting in loss of function heralded by changes in neurophysiological monitoring. Effective resection can be achieved with gentle tumor manipulation and dissection from surrounding structures. Retraction should be dynamic (i.e., changing) throughout the surgery in such a way that the area under active surgical manipulation is retracted but other areas are relieved from retraction in order to regain cord blood supply. The presence of a syrinx is less common in children with IMSCTs than in adults with similar lesions, although resectability may be enhanced given the fluid filled space that, when decompressed, creates increased room for tumor manipulation [67]. Gentle suction and dissection can be effective in removing the tumor, but an ultrasonic aspirating device or contact laser probe may be required with firmer lesions for cytoreductive debulking. The Cavitron ultrasonic aspirator (CUSA) uses high frequency sound waves to fragment and then suction tumor tissue from its tip. Micro tips allow for tumor removal with minimal manipulation of adjacent spinal cord [53]. The Nd:YAG contact laser system (SLT, Montgomeryville, PA) has a hand piece and various contact probes, which. Can be used to perform myelotomy and dissect the glial-tumor interface [57].

Once tumor resection is completed, meticulous hemostasis should be achieved with a variety of hemostatic agents and, if needed, low-intensity bipolar cautery. The dura should be closed in a watertight fashion to decrease the likelihood of postoperative CSF leak. Use of a fibrin sealant may add additional protective effect following dural closure. We recommend waiting to remove the epidural D-wave electrodes until after the dural closure is complete. If utilized, the laminoplasty should be re-affixed with mini-plates with special care taken to avoid epidural compression of the thecal sac, hence we prefer to fix the bone in a way that leave an excessive epidural space that prevent any bony compression on the cord after surgery. The muscular fascia is closed in a watertight fashion and a layered superficial closure is preferred.

In some cases, GTR can be achieved, but in other instances it is not feasible without causing significant neurological deficit. Therefore, surgeon judgment is critical in determining when tumor resection should cease regardless of whether remnant tumor is present.

18.8 Surgical Outcome

The location, type, and size of the tumor can affect surgical outcome. An extensive tumor extending over multiple segments requires a more extensive myelotomy, which can disrupt the dorsal column tracts. Due to the low incidence of other IMSCTs, reports of clinical outcomes are scarce. In general, a radical resection for any IMSCT has been correlated with long-term survival [20, 68]. To date, studies assessing the effects of GTR on progression-free survival have yielded mixed results, and further clarification is needed with larger patient samples with more extended follow up [59, 69]. The use of intraoperative neuromonitoring allows the surgeon to be more aggressive; however, acute but transient postoperative decline is not unusual. Up to one-third of patients will experience worsening of their neurologic status during their post-operative hospital course. Yet, approximately 25–41% of patients with worse status will at least revert to their preoperative status within 6 months of surgery [60, 70]. A good outcome following surgery is dependent on the preoperative functional status of the patient, the general tumor burden, the presence of surgical plane between the tumor and the normal structures, and the final pathology. The mean time from primary resection to recurrence is on average 3 months [71], yet neurological improvement can be seen even 1 year after surgery. Progression-free survival is associated with the extent of resection as do long-term survival at 10 years and 20 years [71].

Different factors affect survival for malignant spinal cord tumors. For malignant spinal cord astrocytomas (both anaplastic astrocytoma and glioblastoma), some of the available data mix both histology types and these publications are yet to incorporate the recent understanding of molecular subtyping that emerged in recent years (e.g., H3 K27M). In most publications, age, location in the spinal cord, gender, and extent of resection affect outcome. Altogether, anaplastic astrocytomas are associated with increased survival with histology, adult patients, male patients, and patients undergoing radical resection [72]. For pediatric patients, better rates of survival are associated with young patient age at time of diagnosis, and shorter lag-time for surgery [55].

The resection of intramedullary high grade astrocytomas presents unique challenges. A higher morbidity is associated with radical resection of astrocytomas in some reports. Clinical recurrence rates of partially excised astrocytomas has been found to be up to 50% of cases in 5 years [73]. Overall, GTR is possible for low-grade and high-grade astrocytomas in 41–55% and 9–17% of cases, respectively [59, 70, 74]. In the pediatric population despite aggressive treatment of intramedullary astrocytomas, these tumors continue to carry a poor prognosis. High-grade astrocytomas (anaplastic astrocytoma and glioblastoma) are associated with an especially poor outcome, with a median survival of around 6 months, while patients with far more common low-grade tumors may live longer than 6 years [55]. Patients with glioblastoma have a higher mortality compared with patients with anaplastic astrocytoma. The literature describes survival rates varying from 6 to 72 months for patients with anaplastic astrocytoma and 6–10 months for patients with

glioblastoma [72]. In the past, several publications advocated minimal surgical intervention and promoted biopsy and radiation therapy; yet as mentioned before, recent studies suggested that extent of resection is a significant predictor of survival rate, especially for anaplastic astrocytoma [75].

For spinal cord ependymomas, survival and progression-free survival were described in previous publications, yet most of them included myxopapillary ependymomas (WHO Grade I) as part of the analysis. The biology and tumor behavior for WHO I ependymomas are completely different, and hence can significantly influence the results regarding survival parameters. The factors associated with survival for spinal cord ependymomas are histological grade, extent of resection, and proliferation index (Ki-67). Low Ki-67 was shown to predict better progression-free survival as well as low WHO grade [76]. GTR was shown in several publications to significantly improve survival for spinal cord ependymomas. The resection of ependymomas poses a different challenge for the surgeon since recurrence rates of ependymomas is dependent mainly upon the extent of tumor resection [77]. Recent reports have cited a GTR rate of around 90–93% for ependymomas [70]. Histology and extent of resection are considered to be the most important prognostic factors for the post-surgical outcomes of spinal cord ependymomas [78]. Different publications cited higher recurrence rates after STR (up to 40%) when compared to GTR (up to 20%) [79]. Better extent of resection of spinal cord ependymomas correlates with better survival, with 90% 10-year survival after GTR and only 80% 10-year survival after subtotal resection [76, 80]. Factors like size of the tumor (in some publications >10 cm) and location (thoracic is worse than cervical and lumbar) are risk factors for failure to achieve GTR in spinal cord ependymomas [66, 81, 82].

Postoperative progressive spinal deformity has been reported in 16–100% of IMSCT resection cases [83]. The pathology may be due to neuromuscular dysfunction of paravertebral muscle denervation and lack of support to the vertebral column. The pathology may also be due to a loss of the posterior tension band after laminectomies, which can cause biomechanical instability and difficulty maintaining sagittal alignment, especially after a multi-level laminectomy and particularly in skeletally immature children [83]. Contributing factors for post-IMSCT resection spinal deformity are young age (in some series less than 13-years-old and in some less than 7-years-old), pre-operative kyphoscoliosis deformity, greater than 2-level laminectomy, post-operative radiation, involvement of the cervicothoracic junction, and presence of a syrinx [20, 83–85].

Laminectomy versus laminoplasty has been investigated as a contributing factor to postoperative deformity; however, outcomes have been mixed. Instrumented fusion at the time of the index operation is not recommended—even with the above risk factors—due to the need for serial imaging to evaluate for tumor recurrence and the impedance of the metal artifact. Currently, close follow-up with serial imaging is recommended, including imaging and at more frequent intervals for at-risk patients to evaluate for post-operative deformity; even with the diagnosis of post-operative deformity, management with external bracing may be sufficient in some cases [85].

18.9 Adjuvant Therapy

Aggressive surgical intervention for IMSCTs has yielded excellent outcomes with minimal mortality and excellent quality of life among children [86]. Morbidity in the form of new neurological deficits is often temporary, and a post-operative decrease in more than one functional grade is rare [87]. While microsurgery may allow for GTR, microscopic cellular infiltration warrants continued monitoring over time. These cellular remnants may not progress even over significant periods of time. Hence, patients who recovered from spinal cord surgery for resection of IMSCT need to stay under follow-up for many years post-surgery (sometimes indefinitely). If relapses or recurrences occur, repeat surgery or chemotherapy should be considered with increased urgency in a symptomatic patient. Radiation therapy may play a beneficial role for patients with lesions that are not surgically amenable, patients do not tolerate chemotherapy, or patients with rapidly progressing malignant lesions. Radiotherapy and chemotherapy are reserved for tumor recurrence, high grade tumors, infiltrative tumors, or when surgical resection is contraindicated [88]. Some groups have reported their experiences with an approach involving surgery for biopsy or partial resection, followed by radiation therapy in cases of incomplete resection [89, 90]. One series reported that the use of radiation improved progression-free survival in low and high-grade astrocytomas after complete or subtotal resection or after recurrence [91]. For pediatric glioblastoma patients, a recently published article showed that radiotherapy as adjuvant for GTR yield higher survival rates than after subtotal resection [38]. Radiation therapy with 40 Gy to the entire spinal axis (other studies advocate higher doses in extreme cases) increased patient survival from 4.5 to 22.7 months as shown in previous publications [51, 69, 92]. Yet other studies only found a statistical trend, not a significant relationship between radiation and survival outcomes in these patients [72]. Survival benefit in patients undergoing radiation versus no radiation has been found to be 15 months versus 5 months. This trend is especially remarkable in adult patients if plotted and analyzed separately from the pediatric subgroup [72]. One of major problems in studies comparing patient groups that do and do not receive radiotherapy for malignant spinal cord tumor is that the non-radiotherapy group is usually very small in most publications. Comparisons between radiation-treated patients and non-radiation-treated patients are, therefore, not statistically significant. We know there is a biological difference between pediatric and adult malignant spinal cord gliomas when considering all available data, and yet radiation therapy is still recommended for both age groups.

Radiotherapy has been used for years—especially after subtotal resection—in intramedullary ependymomas or astrocytomas with conventional fractionation and doses of 45–50 Gy. It has been limited by the risks of radiation myelopathy, and gastrointestinal or fertility compromise, and with mixed effects on tumor control [93]. While adjuvant radiation in ependymomas is often used after subtotal resection, the role of radiation after GTR is debatable [73, 94]. The effectiveness of radiation therapy for spinal cord ependymomas was questioned in several publications that did not show clear a significant effect of radiotherapy on progression or

recurrence. Some publications even showed a negative effect of radiotherapy on survival after subtotal resection [80, 94, 95]. Controversy also arises with the use of radiation therapy in children with IMSCTs as possible toxicity includes growth retardation, secondary malignancy development, radiation-induced myelopathy, vasculopathy, impaired spine growth, changes to the normal parenchyma, and spinal deformity requiring fusion (particularly if further intervention is required). Radiation can create real difficulty in two ways: first, radiation necrosis or changes are hard to differentiate from tumor progression; and second, after radiation the tissue tends to scar in a way that makes second-look surgery or surgery for suspected relapse dangerous and challenging. A 25% risk of secondary tumors is also associated with radiation therapy, especially in children [88]. In recent years there has been a growing interest on using radiosurgery as a treatment modality. Several authors published excellent results, and a recent systematic literature review on stereotactic radiosurgery for intramedullary spinal cord tumors concluded that the technique is safe and effective in selected cases [96–98]. The risk of spinal cord toxicity and radiation myelopathy had to be discussed with the patient with up to 25% treatment-related toxicity on adjacent organs [99]. For all these reasons, radiation therapy is reserved as a last resort in the treatment IMSCTs, especially in the pediatric population. The preferred treatment paradigm (especially for ependymoma) is repeat resection when possible and use of radiation therapy only when resection is not possible.

Chemotherapy in the treatment of IMSCTs has traditionally been utilized only when resection and adjuvant radiotherapy were contraindicated or unsuccessful [88]. Options are more limited due to the blood-spinal cord barrier and the inability of large molecules to penetrate and provide therapeutic effect while limiting systemic toxicity. Additionally, CSF pulsations diffuse the effect of the chemotherapy even further limiting the dose potency. Chemotherapy treatment paradigms for spinal cord ependymomas and mainly astrocytomas are derived mainly from data related to intracranial treatment of the same group of tumors. Yet in recent years with the growing understanding of molecular subtyping, we know that spinal ependymomas are not similar to supratentorial ependymomas, and the same is true for spinal cord high-grade gliomas. Chemotherapies for intramedullary astrocytomas most commonly include alkylating agents (e.g., temozolomide) and vascular endothelial growth factor (VEGF) inhibitors (e.g., bevacizumab), which are used in the same treatment paradigm as intracranial anaplastic astrocytoma and glioblastoma [100]. Since the randomized trials by Stupp et al. demonstrating the beneficial effect of combined temozolomide and radiotherapy [101], adjuvant temozolomide has become the standard of care for patients with glioblastoma and may have a role as an adjuvant therapy in spinal glioblastoma as well [102–104]. The dosage is usually determined by the intracranial protocol for 6 weeks of treatment. The additional use of bevacizumab to temozolomide was used in a rodent model and suggested an increased efficacy of temozolomide for intramedullary spinal cord gliomas [105]. Salvage therapy with bevacizumab in recurrent spinal cord glioblastoma following failed temozolomide treatment has been described in a small cohort resulting in stable or partial response in 5 out of 6 patients [100, 106].

The role of chemotherapy for IMSCTs in children is not clear-cut as no randomized controlled trial has been performed evaluating its efficacy in this particular population of patients. Various chemotherapeutic and radiation therapy options have been utilized for spinal cord glioblastoma in an attempt to achieve a small increase in survival in this dire patient population [52]. Studies have demonstrated possible therapeutic value for temozolomide, a DNA-alkylating agent. Temozolomide is currently part of the standard of care for intracranial astrocytomas and its use has subsequently been translated to IMSCTs. The search for chemotherapeutic agents for pediatric patients with glioblastoma has not yielded compelling results [107–110]. As mentioned above, concomitant temozolomide and radiotherapy and adjuvant temozolomide have been shown to confer some benefit to adult patients with spinal cord Glioblastoma [101], yet such results have not been replicated in children [111], which can be explained by recent findings that spinal cord glioblastomas differ between pediatric and adult patients (like in the case of supratentorial glioblastomas), although they share the same name. One of the differences shown in previous studies that described overexpression of O(6)-methylguanine-DNA methyltransferase (MGMT), which was adversely associated with survival [101, 111]. MGMT-independent pathways of resistance to temozolomide have also been identified [112]. In a recent study, Cohen et al. treated 90 children with high-grade gliomas with concomitant chemo-radiotherapy with temozolomide followed by adjuvant temozolomide. Outcomes were compared to a previous published study from the cohort of the Children's Cancer Group study (CCG-945) and shown to be similar [111]. The additive value of bevacizumab for high-grade gliomas in adults was shown to be less significant for pediatric high-grade spinal cord gliomas. Same is true for the use of irinotecan, which was shown to achieve a significant response in high-grade adult gliomas, but failed to show the same significant response in children [113–115]. Although results are less promising, the current paradigm still suggests using surgery with adjuvant multimodal therapy of chemotherapeutic agents for pediatric spinal cord glioblastoma with the use of radiation therapy either right away or with failure of initial treatment [116]. For pediatric spinal cord anaplastic astrocytoma, there are fewer data, hence some surgeons will advocate strict follow up with GTR while some will advocate the use of adjuvant therapy immediately regardless of the extent of resection.

Overall, the treatment approach to growing or symptomatic IMSCTs should be microsurgery with maximal safe tumor resection. If a satisfactory resection is achieved, interval monitoring can be applied in certain cases; although for malignant astrocytomas, adjuvant treatment is warranted in most cases as an adjuvant treatment. In less aggressive tumors, small post-operative tumor remnants can be carefully observed with serial imaging. With large recurrences, repeat surgery may be needed, and for inoperable cases, adjuvant therapy (preferably with chemotherapy as a first-line intervention) is appropriate. For malignant astrocytomas, post-surgical adjuvant therapy is usually warranted, taking into account the infiltrative nature of the tumor. On the other hand, for high-grade ependymomas, consider surgery and repeat surgery before using adjuvant therapy. For ependymomas if GTR achieved, there is no need for adjuvant oncological therapy.

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Intradural-Extramedullary and Intramedullary Spinal Metastases

19

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19.1 Introduction

Intradural metastatic disease to the spinal cord is an uncommon phenomenon, and accounts for up to 6% of all spinal metastases [1]. Intramedullary spinal cord tumors are even more uncommon, affecting approximately 2% of all cancer patients [2]. The more common location for intradural spinal metastases is to the vertebral body, causing extradural compression, which is beyond the scope of this chapter. Regardless, the management of spinal metastases can be complex and must take into account the patient's complaints, overall clinical status (i.e., tumor burden and Karnofsky status), radiographic findings, and life expectancy. The acuity and intensity of the interventions are largely determined by the severity of the neurologic deficit.

Current management strategies employ a multi-disciplinary approach, which promotes a more rigorous treatment protocol to optimize patient outcomes. A multitude of rigorous clinical studies have been published to address metastatic spinal disease in general, from which treatment models have been generated [3–6]. This chapter provides a comprehensive review of management strategies and offers recommendations in the treatment of intradural spinal metastases.

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19.2 Epidemiology

Improved survival from cancer has increased the prevalence of spinal metastases, and is estimated to be present in up to 40% in patients with cancer [7]. About 300,000 patients have bony metastases with upwards of 60% having a spinal lesion [7–9]. In this regard, the spine is the most common site for bony metastases [7]. The incidence of spinal metastases is estimated to be 10% [10], and an additional 10% will eventually develop spinal cord compression [7].

Over 95% of all spinal metastases are extradural within the vertebral body, and more than 50% of cases have more than 1 level of involvement [1]. Less common are the metastases to the intradural-extramedullary and intramedullary areas, accounting for only 5–6% and 0.5–2%, respectively [1, 2]. The most common primary source of spinal metastases is lung (31%), followed by breast (24%), other (13%), gastrointestinal tract (9%), prostate (8%), lymphoma (6%), melanoma (4%), and kidney (1%). The infrequency of intradural and intramedullary lesions have resulted in difficulties with delineating the true epidemiology—a few studies have identified the most common source as lung, but they can also originate from the breast, prostate, or renal cells, or from lymphoma and melanoma [8, 11]. Depending on the primary lesion, either osteoblast or osteoclast activity can be promoted. This increased activity can result in a varied phenotype of osteoblastic, osteolytic, or mixed lesions [12].

The most common mode of metastasis to the spine is arterial, and accounts for the increased frequency of bone marrow involvement. Venous spreading through Batson's plexus has also been proposed as a source of spread. Contiguous spreading can occur as well. The most common area of involvement is the thoracic region (70%), followed by the lumbar (20%) and cervical regions (10%) [1]. Within the vertebral body, about 60% of metastases are localized to the anterior portion, with the remaining 30% affecting the pedicle or lamina.

The presence of an intramedullary spinal cord lesion is a poor prognosticator with an estimated survival of less than a month [13]. The increased prevalence of the spinal metastases necessitates a heightened sensitivity to the patient's signs and symptoms, as undetected spinal cord compression can result in devastating consequences.

19.3 Presentation and Clinical Evaluation

Intradural metastatic spinal cord lesions commonly cause radicular and myelopathic symptoms secondary to spinal cord compression or vascular incompetence. Unlike bony metastases, in which pain is secondary to bony instability, the pain is usually radicular in nature. Intramedullary tumors can also cause unilateral motor and sensory symptoms, such as with Brown-Sequard syndrome [14, 15]. A subset of patients will present with a rapidly progressive neurologic deterioration,

necessitating an urgent diagnosis and treatment [16, 17]. The preoperative performance status is critical to the determination of the treatment protocol; thus, the initial clinical evaluation must be performed with great detail. A thorough history—which includes the duration of systems, systemic cancer history and treatments, and overall quality of life—must be taken into consideration. Next, a detailed neurologic examination with a focus on the motor and sensory function, deep tendon and pathologic reflexes, and rectal tone must also be performed.

Overall performance status is critical in the determination of the treatment plan as patients with metastatic disease may have a shorter life expectancy, making more invasive and time-consuming interventions less ideal since they may harm the patient and decrease quality of life. The typical mode of assessment of performance status is the Karnofsky performance status (KPS) [18, 19], which has been shown to be a good prognosticator of treatment [20–22]. In general, a KPS of less than 40 portends a poor prognosis, as evidenced by a multitude of scoring systems [4–6, 23]. The basic tenant of all these scoring systems is that the overall burden of disease must be considered [5]. While the majority of surgical interventions for metastatic disease are aimed at local control, preservation of neurologic function, maintenance of spinal stability, and life expectancy, KPS must be considered in the overall treatment. Less invasive efforts, such as kyphoplasty, vertebroplasty, or medical management, should be offered in cases with poor prognoses.

19.4 Imaging Studies

In situations in which there is a concern for spinal cord involvement, such as new radiculopathy or myelopathy, the next step in the work-up is to obtain imaging studies. The goal of imaging is to determine the presence and location of a pathological lesion, and to ascertain the degree of compromise to the overall stability based on neural compression and bony destruction. In this regard, computed tomography (CT) and magnetic resonance imaging (MRI) studies are the most informative imaging modalities. These 2 studies will provide the greatest breadth and depth regarding the presence of spinal cord compression and pathologic fractures. Additional information can be obtained with ancillary studies, such as bone scans and positron emission tomography (PET), which provide details on the overall tumor burden. Static X-rays are of limited utility due to its low resolution and poor soft tissue detail. In contrast, dynamic X-rays with flexion and extension could provide some insights to identify additional areas of instability for surgical planning purposes.

Metastases most commonly involve the vertebral body and posterior elements with its affinity for bone marrow. Most tumors are lytic in nature; however, osteoblastic lesions can also occur. Thus, a combination of imaging modalities yields the greatest insights. A recent meta-analysis reviewed the advantages of multi-modality imaging to assist in the diagnosis and treatment of bony metastases [24].

19.4.1 Nuclear Imaging and Positron Emission Tomography

A PET scan is the traditional screening study for metastatic disease involving the spine. This imaging study carries a high sensitivity of 95%. PET scans detect metabolic activity, which can be helpful when bony involvement is minimal, as is the case with isolated bone marrow involvement. Additionally, whole-body imaging is possible to further delineate overall disease burden. However, in contrast to MRI, the spatial resolution is more limited. Various tracers can be used, such as 18F-FDG, 11C-choline, 18F-choline, and MIBG. The optimal tracer can vary depending on the primary tumor, and is currently an area of intense research [25, 26]. Tumor-specific tracers are also in development, and currently in preliminary investigations [27].

19.4.2 Computed Tomography

CT scans are most useful to characterize bony involvement with cortical destruction, demarcation of lesion margins, and tumor calcification. The tumor can also be delineated as a lytic or blastic lesion. These features combined can be utilized to narrow the differential diagnosis, as certain features are pathognomonic for specific lesions. This modality carries a greater degree of spatial and temporal resolution compared with conventional radiography, and has thus supplanted it as primary modality for bony anatomy.

The extent of vertebral involvement is important in assessing the risk for instability. A CT scan is helpful in determining the presence of a compression fractures, trabecular bone thinning, sclerotic pedicles, cortical destruction, and multiple column involvement that increases the risk of pathologic instability [10, 28–30].

19.4.3 Magnetic Resonance Imaging

The most informative imaging modality is a contrasted MRI study, which provides the greatest detail on the location and involvement of the surrounding soft tissues (i.e., paraspinal region). This modality is highly sensitive and specific at greater than 90% for detecting spinal malignancies [31]. The pathologic lesion can be further defined as extradural, intradural, or intramedullary. The degree of spinal cord and nerve root impingement can be characterized. MRI is also the most sensitive in detecting isolated bone marrow infiltration, which permits an earlier diagnosis, in contrast to other modalities that would not be able to detect abnormalities until after at least 50% of the bone is destroyed [10, 30, 31]. As such, it is important to image the entire spine when a metastatic lesion is suspected since concurrent lesions are common. Metastatic lesions are commonly hypointense on T1 and hyperintense on T2 sequences, and will enhance to a varying degree [32, 33]. Restricted diffusion-weighted imaging (DWI) can also be used to differentiate a pathologic from an osteoporotic fracture [34, 35]. The gradient echo sequence provides some insights into the effect of the tumor on bone.

19.5 Treatment Planning

The treatment plan is predicated on the philosophy of "first, do no harm." The initial assessment of the patient must take into consideration the patient's current functional status, systemic tumor burden, overall health/co-morbidities, and patient preference. The complexity of this situation necessitates a multi-disciplinary approach to develop the ideal management strategy. Several studies have highlighted key considerations and developed some algorithms for treatment stratification [36]. One caveat is that these scoring systems apply to the whole population with spinal metastases, of which almost 95% of the patients have vertebral body involvement. In this regard, the applicability to isolated intradural and intramedullary metastases may be limited. However, some insights can be obtained from these scoring systems.

The most common prognostic score is "LMNOP," which represents Location of disease, Mechanical stability, Neurological risk, Oncological parameters, and Preferred treatment [37]. The mechanical stability of the spine is crucial for maintaining neurologic function with instability also resulting in increased pain and disability. Several scoring systems have been devised with the most common system being the Spine Instability Neoplastic Score (SINS) [38–40]. SINS describes 6 categories that can contribute to spinal instability: location, pain, bone lesion, radiographic spinal alignment, vertebral body collapse, and posterior spinal element involvement. A SINS greater than 13 signifies instability, while a score of 7–12 is potentially unstable. The advantage with SINS is a high inter- and intra-observer reliability within and across various specialties [38, 41]. The neurological risk is determined from the current neurologic examination and potential for further neurologic compromise, but also radiographic findings of spinal compression. Unfortunately, no grading system currently exists for intradural lesions. Bilsky et al. developed a scoring system to grade the level of spinal cord compression epidurally [42]. Oncological parameters take into account the tumor type and its responsiveness to radiation therapies. Radio-responsiveness can push treatment recommendations for less-invasive therapies, such as stereotactic radiosurgery. Lastly, the preferred treatment is the compilation of the multiple specialties based on the clinical and radiographic findings previously discussed.

Other scoring schemes for survival estimates from spinal metastases have also been described [4–6, 23], and differ on the weight placed for various factors. A recent meta-analysis aimed at identifying prognostic factors in metastatic spinal disease found 17 poor prognostic factors separated into cancer-specific and nonspecific factors, from which a tumor-specific scoring system was developed [43].

19.6 Treatment/Intervention

Surgery and radiation therapy are the mainstay treatments for spinal cord metastases, and are frequently combined as a multimodal therapy to improve outcome [44, 45]. This was described in the seminal randomized clinical trial by Patchell et al.,

which identified a definitive role for direct decompression surgery with radiation as a superior treatment for spinal cord compression from metastatic lesions [45].

19.6.1 Surgery

The goals of surgery in metastatic spinal disease are diagnosis and decompression of the neural elements to prevent further neurological decline. In the case of intradural lesions, preoperative MRI is critical in the determination of the surgical goals. As previously described, MRI can aid in the determination of the location of the lesion relative to the dura, and if intramedullary infiltration is present. The extent of neural involvement from a clinical and radiographic standpoint will define the degree of resectability, but also the tumor characteristics (i.e., tumor consistency and presence of a tumor margin) found intraoperatively. The ideal situation is for an en bloc resection with clear surgical margins, but this can cause substantial neurologic morbidity. In the setting of intramedullary metastases, a clear margin can be appreciated to facilitate en bloc resection [11, 46]. In cases where en bloc resection is not feasible, subtotal decompression can be pursued and followed with adjunctive radiation therapy.

In the setting of an intradural or intramedullary lesion without osseous involvement, spinal stabilization is not likely necessary. The priority is maximal resection as safely as possible. This is facilitated by intraoperative neurophysiological monitoring. Gross total resection is a priority for intradural and intramedullary lesions. As previously stated, complete resection is often not possible, thus necessitating adjunctive radiation therapy for further tumor control. Cases of intradural-extramedullary and intramedullary metastases are few, but suggest that surgery may be effective to maintain neurologic function [47, 48].

19.6.2 Radiation

Radiation therapy offers a less invasive means of tumor control, and can be utilized as the initial treatment or as an adjunct in the postoperative setting. The decision to use radiation therapy largely depends on factors described in the previous section, namely neurologic compromise, overall performance, and systemic tumor burden. Unfortunately, there is a paucity of rigorous data regarding radiation treatment for intradural and intramedullary spinal metastases. However, many case studies have advocated the use of radiation for patients with intramedullary spinal cord tumors due to their overall poor prognosis [16, 49, 50]. Conventional external-beam radiotherapy (EBRT) is the most common mode of radiation for bony spinal metastases, and consists of daily low-dose radiation in single or daily fractions ranging from 8 to 30 Gy [21]. There are data to suggest that hypofractionation decreases the likelihood of retreatment with improved rates of local control [51, 52]. However, the biggest disadvantage to dose escalation with this modality is the toxicity to the spinal cord at 45–50 Gy.

Stereotactic spinal radiosurgery (SSRS) and spinal radiotherapy (SRT) have emerged as viable alternatives in the treatment of metastatic spinal lesions with the

ability to deliver a very high dose of radiation with improved accuracy, thus decreasing toxicity to local tissues. SSRS is delivered in a single fraction whereas SRT is delivered in 2–5 treatments. Studies for osseous metastatic lesions yield control rates of up to 90% at 2 years for bony metastatic disease [53–55]. Some studies have shown promise of SRS for the treatment of intradural lesions [56–58]. Although no studies for intramedullary lesions exist, the theoretical advantage compared to EBRT is a 3-times higher biologically effective dose. SSRS can also induce a higher rate of deoxyribonucleic acid (DNA) damage, which improves the control rate for traditionally radioresistant tumors [59–63]. The increased accuracy is a function of improved planning with the contouring of the tumor to minimize radiation to the adjacent tissues, namely the spinal cord. This necessitates a thorough understanding of the neuroanatomy, and may require a decompression or separation surgery to delineate the lesion. For this reason, SSRS and SRT require a multidisciplinary team consisting of medical oncologists, radiation oncologists, physicists, and neurosurgeons. Shin et al. previously described the safety of SRS for intradural and intramedullary metastases in a small case series [64]. SSRS and SRT comparisons to EBRT warrants further investigations.

19.7 Multimodal Treatment Algorithm

There is currently a paucity of clinical data to recommend a definitive framework for the treatment of intradural and intramedullary lesions. However, several insights can be obtained from the clinical data and algorithms derived for bony spinal metastases. The degree of neurologic compromise coupled with the acuity of the decline, the systemic tumor burden, and overall performance are important considerations as to the aggressiveness of the interventions. The location and degree of involvement of the neural elements will determine the role of surgery and the timing of radiation therapy as either a primary or secondary treatment. Tumor histology also plays an important role as certain metastases are more radiosensitive, and newer immunotherapies may be utilized to improve outcomes [65, 66].

The combination of surgery followed by radiation therapy has been shown to improve outcomes for spinal metastases [45]. For intradural lesions, gross total resection is favored with adjuvant radiation for any residual tumor. This can also be applied to intramedullary lesions; however, surgical intervention should be pursued with caution in patients with a poor performance status.

19.8 Follow–Up and Further Interventions

Patients with intradural and intramedullary lesions will likely need rehabilitation, which can substantially improve the patient's functional outcomes [67]. Bracing is not necessary, but may provide some relief if there is concurrent osseous involvement. Radiculopathic complaints can improve with pregabalin or gabapentin, and muscle relaxants can help with pain control. Follow-up radiography should be pursued at 3 weeks and thereafter at least every 6 months, but is as the discretion of the multidisciplinary treatment team.

19.9 Conclusions

The treatment of intradural and intramedullary spinal metastases is complex and necessitates a multidisciplinary team for multimodal therapies. Important considerations, such as the patient's performance status, systemic tumor burden, location of the tumor, tumor type and patient preference, are critical to define when developing a treatment plan. Surgery and radiation are the mainstays of treatment, which the few clinical studies available have supported. More rigorous studies are necessary to determine outcomes from these treatments.

19.10 Case Illustrations

19.10.1 Case 1

WY is a 54-year-old woman with a history of metastatic breast carcinoma who had previously undergone a successful resection of a large right cerebellar metastasis. She presented emergently 3 months later with acute onset left-sided hemiplegia. An MRI of her cervical spine (Figs. 19.1 and 19.2) was significant for multi-focal intradural metastases: an intradural extramedullary lesion at C2–3. The patient underwent a multi-level laminectomy and resection of the extramedullary lesion. Postoperatively, her strength improved with rehabilitation. A follow-up MRI of her lumbar spine revealed additional metastases, and the decision was made to place an Ommaya reservoir placement for intraventricular/intrathecal chemotherapy. She underwent adjuvant whole brain radiation therapy with 3000 cGy in 10 fractions, and reduced field boost to the posterior fossa and upper cervical spine of 3900 cGy in 13 fractions. As her systemic disease progressed, she passed about 9 months from her diagnosis of spinal cord metastases.

19.10.2 Case 2

BW is 69-year-old man with non-small cell lung cancer treated previously with resection, irradiation, and chemotherapy presented with left-sided hemiplegia and intramedullary spinal metastasis at the C4–C5 level. The lesion was resected and postoperative irradiation planned after surgery (Fig. 19.3) [68].

19.10.3 Case 3

KS is a 55-year-old woman with a history of renal cell carcinoma and known metastases to the lung. She underwent immunotherapy and was found to be in remission with regards to her systemic disease. She recently developed right-sided leg

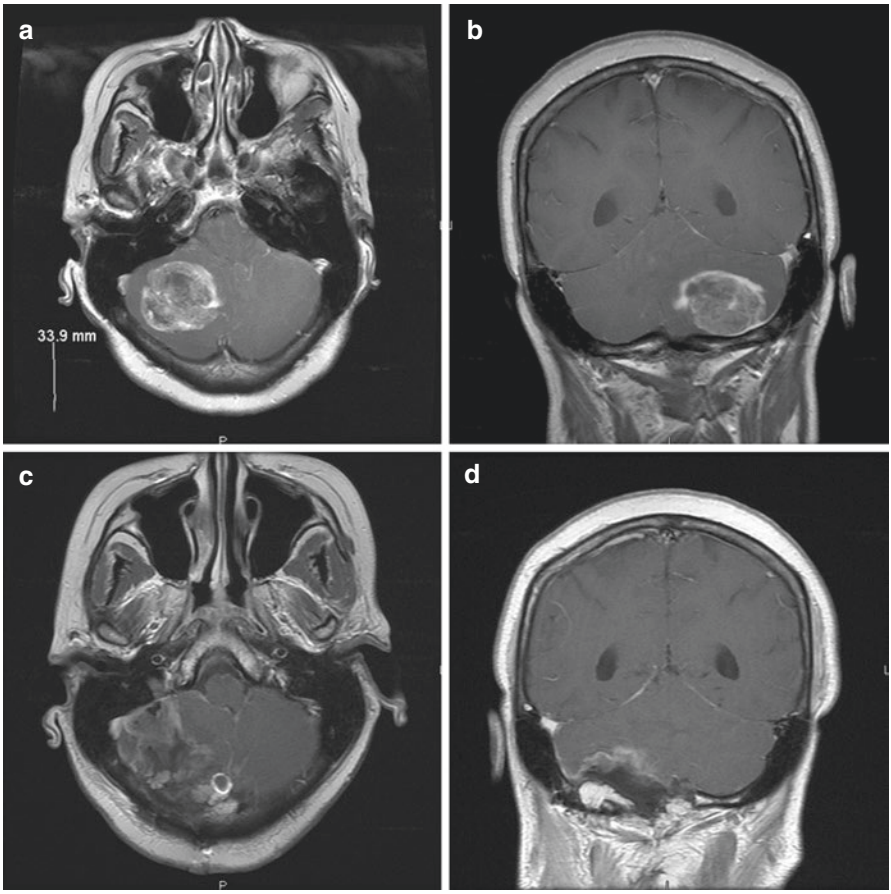

Fig. 19.1 Breast carcinoma metastasis. MRI brain T1-weighted post contrast axial (**a**) and coronal (**b**) images showing a large right cerebellar metastasis. Postoperative post-contrast T1-weighted axial (**c**) and coronal (**d**) MRI of brain showing resection of tumor

weakness for the past couple of weeks that progressed to bowel and bladder dysfunction. An MRI was performed, which was significant for an intramedullary lesion at the conus medullaris (Fig. 19.4). The remainder of her neural axis was without disease.

The patient underwent a multi-level laminectomy with electrophysiological monitoring to resect this lesion, with pathology consistent with renal cell carcinoma. Post-operatively, she experienced some improvement with regards to her lower extremity function, and is currently undergoing rehabilitation. Her future treatment plan is to undergo adjuvant stereotactic radiation.

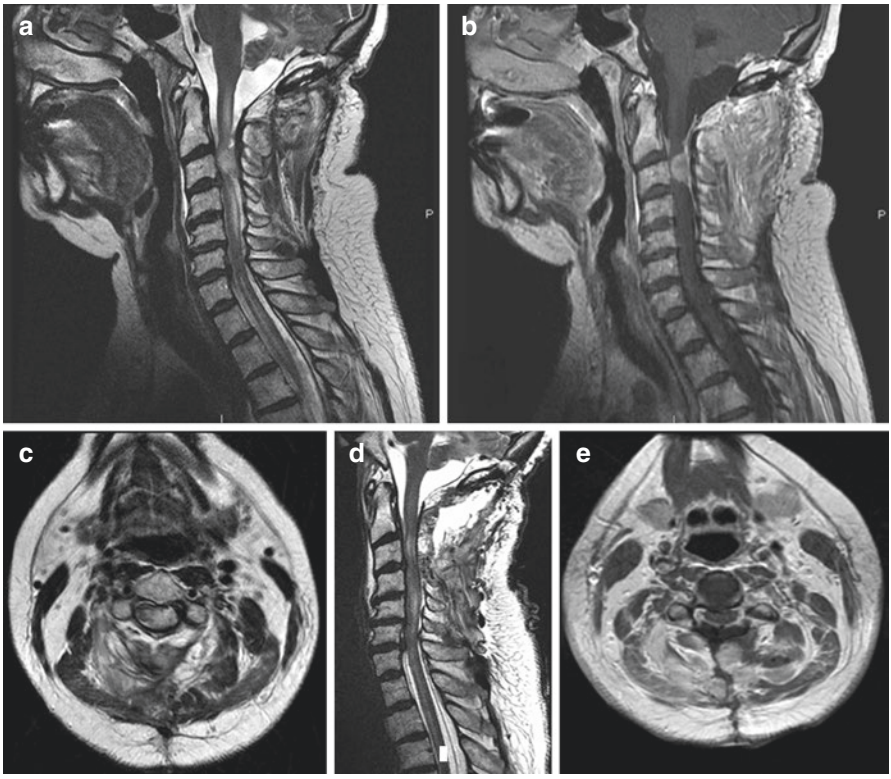

Fig. 19.2 An MRI of cervical spine 2.5 month after initial cerebellar metastasis resection. (**a**) Sagittal T2-weighted MRI. (**b**) Sagittal T1-weighted postcontrast MRI. (**c**) Axial postcontrast T-weighted MRI showing intradural extramedullary tumor at C3. (**d**) Sagittal T2-weighted MRI. (**e**) T2-weighted MRI showing tumor resection

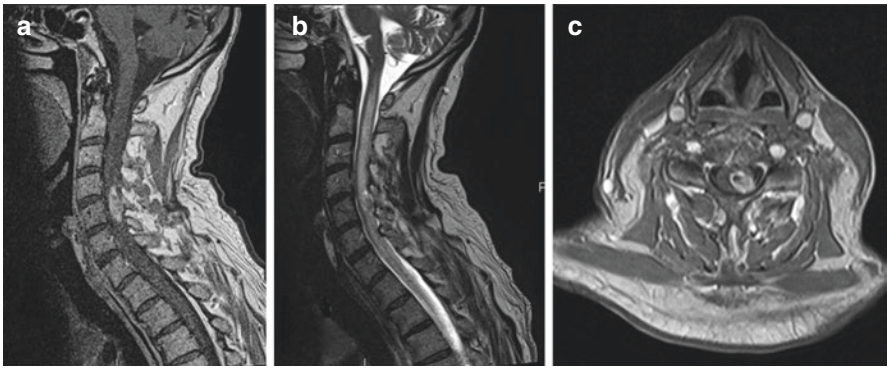

Fig. 19.3 Non-small lung cancer intramedullary metastasis. (**a**) Preoperative T1-weighted post-contrast sagittal MRI of the cervical spine showing tumor at C4–C5. (**b**) Sagittal T2-weighted preoperative MRI showing same tumor and adjacent spinal cord edema. (**c**) Post-contrast, T1-weighted axial MRI showing left-sided intramedullary tumor. (**d**) Post-contrast, sagittal, T1-weighted MRI showing tumor resection. (Note the fat graft dorsal to the dura to avoid cerebrospinal fluid leak or pseudomeningocele.) (**e**) T2-weighted postoperative MRI showing tumor resection and fat graft dorsal to the dura. (**f**) Postoperative, post-contrast T1-weighted MRI showing tumor resection and fat graft

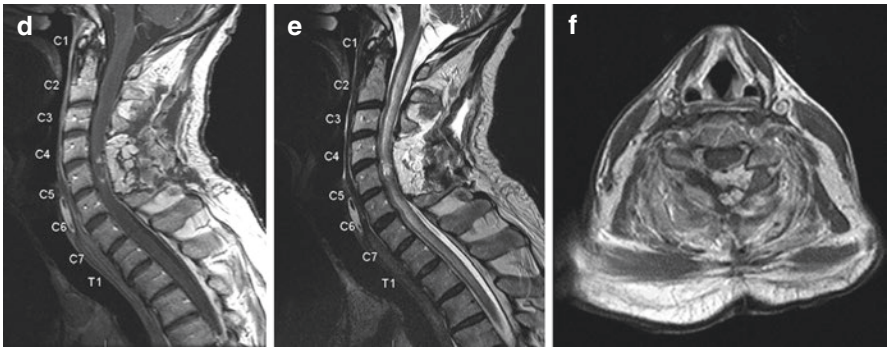

Fig. 19.3 (continued)

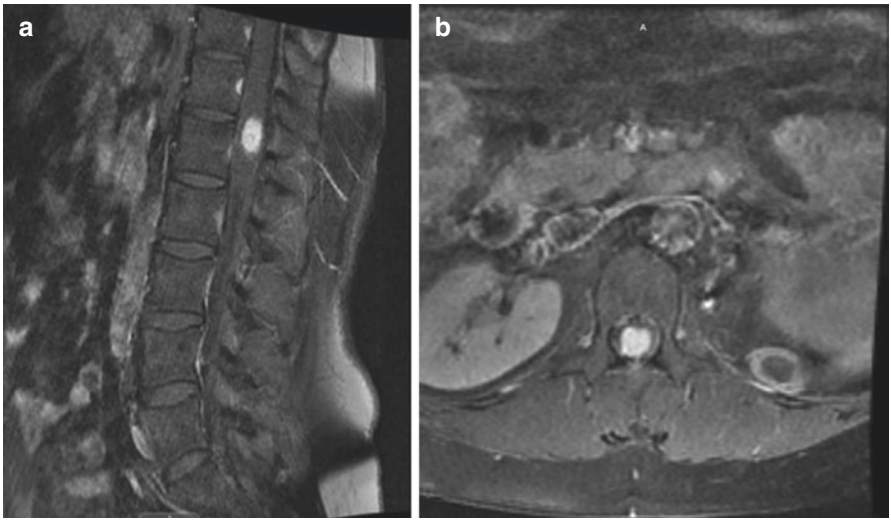

Fig. 19.4 Renal cell carcinoma metastasis. An MRI of the lumbar spine that is significant for an enhancing conus medullaris lesion seen on T1 post-contrast sagittal (**a**) and axial (**b**) cuts

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Sacral Spinal Tumors

20

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20.1 Introduction

Tumors of the sacral spine are rare, comprising up to only 7% of all spinal tumors [1]. They can be broadly categorized into two groups: primary or metastatic. Primary sacral tumors can be further divided into three groups based on origin: congenital, neurogenic, or osseous. The most common primary sacral tumor is the chordoma. The most common sacral tumor is from metastasis.

Identifying the distinction between primary sacral tumors and metastatic sacral tumors is important, as it may have significant implications on the subsequent treatment paradigms and interdisciplinary discussions. A primary sacral tumor for example should be considered for surgical biopsy with specific approach considerations and downstream treatment plans. Contrarily, a widely metastatic tumor with sacral involvement in a patient with a known primary lesion is likely not considered for a biopsy. Rather, deliberations for surgical tumor debulking or palliative treatment plans including radiation or chemotherapy may be more appropriate.

Sacral tumors present significant surgical challenges and require dedicated considerations due to a wide range of presenting symptoms, tumor type, and complex regional anatomy. The anatomy of the sacral spine is unique as it is elegantly intimate with neighboring neurovascular structures, bony elements and joints, and organs of the retroperitoneum, which demand a multidisciplinary approach prior to initiating treatment.

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20.2 Congenital/Neonatal Sacral Tumors

Congenital tumors of the sacral spine in neonates can be defined as tumors detected during pregnancy or within the first few months of life. Thus, neonatal congenital tumors can be identified as teratomas, dermoid cysts, or hamartomas. Though more commonly diagnosed later in life, due to its cellular origins and histology, chordoma also falls within the congenital category. For neonatal congenital tumors, diagnosis is largely based on standardized prenatal and neonatal visits and various implemented advancements in imaging modalities. Treatment paradigms and consequent outcome and prognosis are dependent on tumor type, location, size, age of patient at diagnosis, and associated congenital anomalies.

20.2.1 Sacrococcygeal Teratoma

Sacrococcygeal teratoma is the most common neonatal congenital tumor [1]. The true incidence of this relatively rare tumor is not known but has been reported to range from 1:23,000 to 1:40,000 favoring females (4:1) [2]. These tumors originate at the base of the coccyx and can be benign or malignant. Teratoma tissue involves all three germ cell layers (ectoderm, mesoderm, and endoderm), and can contain skin, teeth, respiratory or gastrointestinal mucosa, and nervous system tissue [3]. They can be categorized into four types: Type I are almost completely external, Type II are external with a pelvic extension, Type III have mostly intra-abdominal components with external components, and Type IV have all internal components without any external components [4].

The diagnosis of these tumors is often established in utero with routine prenatal visits and advanced prenatal ultrasonography. Prenatal magnetic resonance imaging (MRI) has also been assuming a larger role in further defining tumor extent and boundaries when ultrasonography proves inadequate. After birth, if types I–III, these lesions can be seen as an exophytic mass under normal skin, between the coccyx and anus [3]. Signs and symptoms of urinary retention or lack of bowel movements may prompt imaging in the postnatal period.

Due to their relatively large size and location, these sacrococcygeal teratomas have significant secondary effects on neighboring intra-abdominal organ development and consequent overall neonatal development. Resultant issues such as tumor hemorrhage, arteriovenous shunting, and high cardiac output can cause cardiac failure, hydrops fetalis, and prematurity [2]. Large intrauterine tumor growth can preclude vaginal delivery solely due to tumor size. The fetal mortality rate in the perinatal period ranges from 13 to 16% and can be attributed to cardiac failure or tumor hemorrhage [5]. Due to these issues, when diagnosed in the prenatal period, the morbidity and mortality remain high compared to when these tumors are diagnosed in the postnatal period [2].

Once diagnosed in stable pregnancies, close, frequent prenatal visits with serial ultrasounds are warranted. Large tumors or high-risk pregnancies may warrant early cesarean section or intra-uterine or postnatal surgery for tumor removal. Resection should include the coccyx and sacrum depending on tumor extent. Reconstruction

of the posterior peritoneum is critical to prevent delayed hernias. After surgical resection, long-term outcomes are favorable, with a study citing approximately 94% (117/124 neonates) available for 5-year follow-up after tumor resection [6]. Though issues with urinary incontinence, infection, and constipation have been shown to be higher in these patients during childhood, compared with control groups in long-term follow-up [7]. Due the potential for tumor recurrence and malignancy, long-term follow-up is indicated though not specifically defined.

20.2.2 Chordoma

Chordomas are the most common primary tumor of the sacral spine [8]. These tumors rarely present in patients under 40 years of age and are twice as frequent in men than women. They arise from notochord remnant cells, occurring most commonly at the clivus or sacral spine, the embryologic endpoints of the notochord. Chordomas grow slowly but are locally aggressive. Patients present with local mechanical, dull pain, or neurological sequelae, including bowel and bladder dysfunction. Patients with large sacral chordomas can compress abdominal viscera which can cause constipation, urinary retention, and visceral pain [9].

Advanced imaging techniques of the sacrum may be completed for tumor identification and characterization. Magnetic resonance imaging is the preferred imaging modality, allowing the clinician to assess size, specific tumor components, and the extent of soft tissue invasion. Chordomas are usually isointense and hyperintense on T1-weighted imaging and T2-weighted imaging respectively. They heterogeneously enhance with gadolinium. (Fig. 20.1) Computed tomography (CT) can

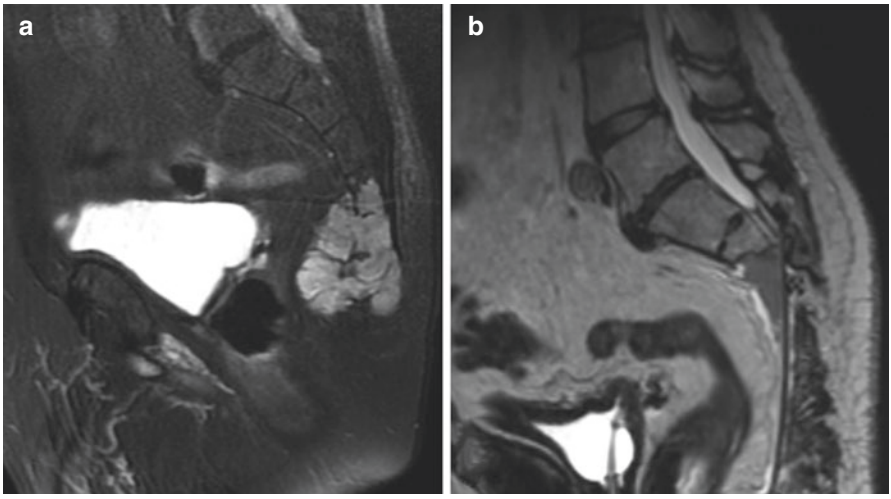

Fig. 20.1 (**a**) MRI pelvis fat suppression sagittal sequence demonstrating a T2 hyperintense distal sacral chordoma. (**b**) MRI T2 image showing a mid-sacral amputation for en bloc resection of the chordoma

demonstrate bone destruction with remodeling, thinning of the sacral cortex, and neuroforaminal widening. Some chordomas may also have calcifications.

Surgical biopsy is almost always indicated to obtain tissue diagnosis and to guide further treatment. If the lesion was presumed to be primarily from the rectum, endoscopy and biopsy of suspicious lesions should be done. Transrectal biopsy should be avoided to not introduce tumor cells into uninvolved tissues. For the remaining lesions, CT guided biopsies now can be done, and the biopsy tract is kept within the boundaries of the following resection.

There are several histologic types of chordoma. Conventional chordomas contain an abundant myxoid matrix and the cell cytoplasm has a "bubble-like" physaliferous pattern. Other types of chordomas include chondroid and de-differentiated types. At a molecular level, chordomas over-express transcription factor T, which produces the brachyury protein. Grossly, chordomas are centrally located, mostly composed of soft tissue, and usually avascular.

The treatment of choice is en bloc surgical resection with wide margins to reduce the risk for local recurrence [3, 9] (Fig. 20.2). Patients can achieve a mean disease-free period of up to 84 months depending on the extent of resection. Intralesional resection with subsequent stereotactic radiosurgery is less optimal, resulting in a less than 50% disease control rate at 5 years after surgery [9]. Adjuvant treatments include radiation and proton beam therapy for subtotal resected chordomas, which have been shown to delay tumor progression. There is no class I evidence to support a role for chemotherapy [9].

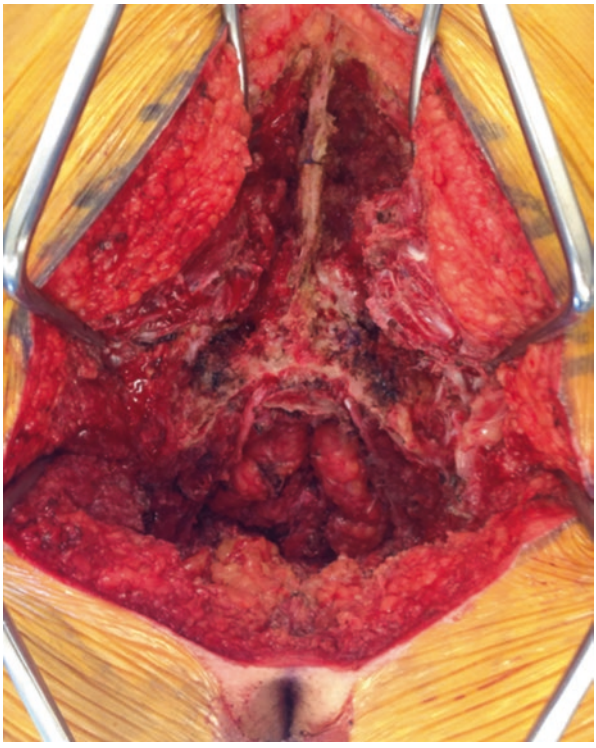

Fig. 20.2 Intra-operative photograph demonstrating en bloc resection of a sacral chordoma via a low sacral amputation. Rectum and peri-rectal fat is visible at the anterior margin of the resection cavity

20.3 Neurogenic Sacral Tumors

Primary neurogenic tumors of the sacrum arise from cellular elements of the peripheral nervous system, including neurons (ganglioneuroma), Schwann cells (schwannomas and neurofibromas) and ependymal cells (myxopapillary ependymoma). While these tumors are typically benign and display indolent growth patterns, they will occasionally undergo malignant dedifferentiation. Complete surgical resection is the treatment of choice in many cases.

20.3.1 Myxopapillary Ependymoma

Ependymal cells give rise to this slowly growing tumor [10]. Myxopapillary ependymomas are the most prevalent type of ependymoma in the caudal spine. These tumors are more common in adults [11, 12]. Myxopapillary ependymomas can arise from the conus medullaris, cauda equina, and filum terminale. They may also form in the presacral space or dorsal sacral subcutaneous tissues, due to the presence of embryonically derived cell rests [13]. Due to its slow growth, an average of 2–3 years may elapse before a tumor becomes large enough for a patient to present with neurologic deficits [3]. These patients may present with lower back pain, radiculopathy in the sciatic distribution, or early signs of cauda equina syndrome, which prompt imaging. Computed tomography of the lumbosacral spine may reveal expansion of the spinal canal. Gadolinium enhanced MRI is the imaging of choice when a myxopapillary ependymoma is suspected. MRI usually demonstrates an isointense and hyperintense intradural mass on T1 and T2-weighted sequences respectively at the level of or below the conus, which commonly homogeneously enhances with gadolinium.

Primary treatment for myxopapillary ependymoma is surgical resection via a posterior approach. Gross total resection is recommended to decrease the risk of local recurrence [3, 13]. This can be ideally achieved by isolating the filum terminale and disconnecting it above and below the tumor. It should be noted to disconnect the filum above the tumor first, as disconnecting the filum below can cause the remaining filum and tumor, to retract cephalad and outside of the surgical field. Violation of the tumor capsule can lead to cerebrospinal fluid dissemination and distant disease recurrence in the spinal. Adjuvant radiotherapy is an option in patients with either incomplete tumor resection, recurrence, or unresectable tumors [3, 13]. Prognosis is excellent after complete surgical resection of myxopapillary ependymomas, as they are recognized as a World Health Organization (WHO) Grade I tumor with an over 10-year survival with complete or partial resection [14].

20.3.2 Ganglioneuroma

Ganglioneuromas are rare, slow-growing tumors that originate from sympathetic ganglion cells, in the peripheral nervous system [3]. These tumors can also occur in the mediastinum and thoracic cavity, as well as the retroperitoneum, sympathetic

ganglia, and adrenal glands [15]. Only 10% of all ganglioneuromas occur in the spine [16]. Patients are usually under the age of 30 years, with an equal incidence in males and females [17].

Ganglioneuromas contain well-differentiated ganglion cells within a stroma composed of Schwann cells and neural processes [18]. These tumors may occur in association with neurofibromatosis type 1 (NF1) [15, 17, 18]. NF1 associated ganglioneuromas may demonstrate intradural invasion.

Grossly, ganglioneuromas may have a dumbbell shape, due to paraspinal expansion and intraspinal extension through the neural foramina. Computed tomography may reveal a well-circumscribed isodense-to-hypodense paraspinal mass with or without calcification. MRI will likely reveal a homogeneously hypointense mass on T1-weighted sequences, which is heterogeneously hyperintense on T2-weighted sequences with variable enhancement patterns.

The treatment of choice is complete surgical resection, and due to its benign, nonaggressive behavior, this will ensure good long-term prognosis, though large prospective, long-term data has not been specifically reported.

20.3.3 Schwannoma and Neurofibroma

Schwannoma and neurofibroma are both categorized as nerve sheath tumors, which comprise 25% of intradural spinal tumors [19]. The peak incidence is between the fourth and sixth decades of life and occurs equally in males and females. Immunohistochemically, they appear to derive from Schwann cells. However, the various morphologies of neurofibromas suggests inclusion of other cells, such as fibroblasts and perineural cells [19].

Schwannomas are benign tumors that rarely expand into the presacral space through the anterior sacral neural foramina [3]. Of all schwannomas, up to 5% occur in the sacral and presacral areas, and overall, schwannomas comprise 25% of all spinal tumors [20, 21]. They grow slowly, but can reach a considerable size before patients become symptomatic from displacement of nerves or visceral organs [20]. Lumbosacral pain is the most common presenting symptom, along with decreased deep tendon reflexes and lower extremity hypoesthesia [22]. Schwannomas are usually well-encapsulated, firm tumors, which can be separated from adjacent tissues.

Neurofibromas contain fibrous tissue, as well as nerve fibers. They can be difficult to distinguish from the involved nerve, as the tumor can cause fusiform, or plexiform, enlargement of the nerve [19]. Both schwannomas and neurofibromas commonly arise from dorsal nerve roots, but neurofibromas can also occur in the ventral nerve roots.

For nerve sheath tumors, computed tomography may reveal a hypodense mass, with or without regional bony remodeling, and intense enhancement with contrast. For schwannomas, MRI will reveal an isointense, heterogeneously hyperintense, and intense enhancement pattern on T1-weighted, T2-weighted, and gadolinium sequences respectively. (Fig. 20.3) Neurofibromas have a heterogeneous enhancement pattern to gadolinium.

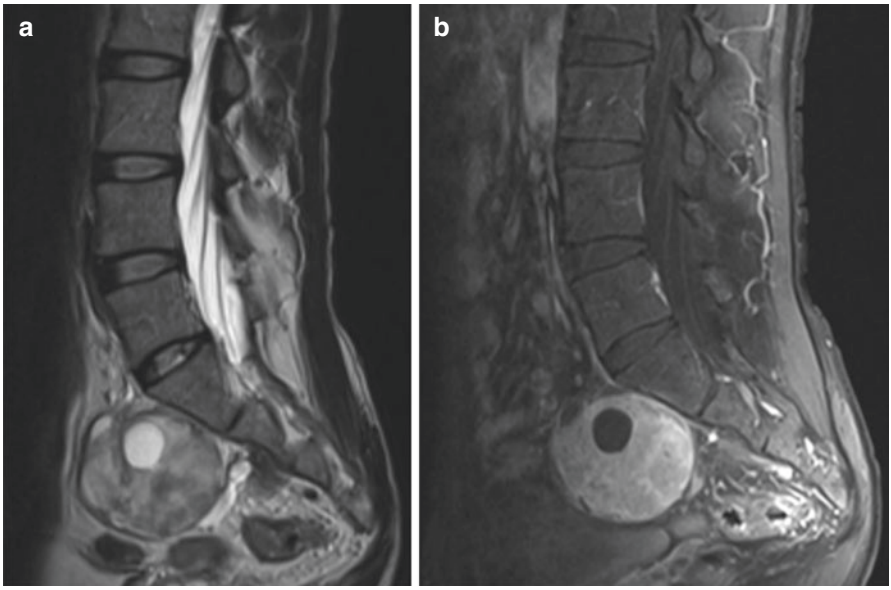

Fig. 20.3 Imaging of a 44-year-old man with enlarging pre-sacral mass. (**a**) Sagittal T2 MRI demonstrating a T2 isointense and hyperintense, heterogenous pre-sacral mass that is partially cystic. (**b**) T1 with contrast administration demonstrates an avidly enhancing mass. CT-guided biopsy results suggested a giant schwannoma versus malignant peripheral nerve sheath tumor

The treatment of choice for benign nerve sheath tumors is complete surgical resection, which greatly reduces the rate of recurrence. A posterior approach with complete or partial laminectomy with or without complete or partial facetectomy is usually enough for complete safe resection depending on tumor size and location. In the case of neurofibromas, gross total resection may not be possible because of the risk of nerve root injury. Intralesional excision can result in more than 50% recurrence rate; therefore, wide en bloc resection is encouraged [22, 23]. Approximately 2.5% of nerve sheath tumors are malignant, and half of these tumors occur in association with neurofibromatosis [24]. With a malignant diagnosis, the overall survival usually does not exceed 1 year.

20.4 Osseous Sacral Tumors

Osseous sacral tumors are primary tumors arising from bony—or cartilaginous—elements of the sacrum. These tumors may be benign or malignant, and diagnosis (via clinical, radiographic and/or histological features) prior to definitive intervention is ideal in order to guide treatment decisions, as treatment may involve medication alone, chemoradiotherapy, or surgical resection with or without pre-operative embolization or neo-adjuvant chemotherapy.

20.4.1 Osteoid Osteoma and Osteoblastoma

Osteoid osteomas and osteoblastomas are solitary osteoblastic tumors occurring in both the long bones and the spine. These two entities share clinical and histological features, and may be considered variants of the same process, with the primary distinction being that osteoblastomas are larger (>1.5 cm) than osteoid osteomas (<2 cm) and feature greater osteoid production and vascularity. Both lesions are most commonly seen in males in the second and third decades of life [25, 26]. Throughout the mobile spine, these lesions occur most commonly in the posterior elements, but in the sacrum, they are seen most frequently within the body [3].

Osteoid osteomas are four times more common than osteoblastomas [26, 27]. They are most commonly found in the axial skeleton, particularly in the diaphysis or metaphysis of long bones [26, 27]. Only 10% of osteoid osteomas occur in the spine (most commonly the cervical spine), and only 2% of spinal osteoid osteomas are found in the sacrum [25]. Osteoblastomas, on the other hand, are frequently seen (>35% of cases) within the mobile spine and sacrum, but may also be found in long bones, craniofacial bones, and the hands and feet [26].

Both osteoid osteoma and osteoblastoma present most frequently with local pain [26]. Osteoid osteomas classically present with pain that is worse at night and relieved by non-steroidal anti-inflammatory drugs (NSAIDs), whereas osteoblastomas often present with a dull, achy, progressive pain that does not worsen at night and persists despite NSAID treatment. With osteoblastoma, local swelling and tenderness may also be seen, as well as neurological symptoms and local deformity when lesions are present within the spine [26].

In both osteoid osteoma and osteoblastoma, plain X-rays may be performed initially, but CT is the study of choice. CT typically reveals a radiolucent nidus surrounded by sclerosis. Osteoblastomas will be larger (>1.5 cm) than osteoid osteomas, irregularly shaped, with a thin shell of surrounding reactive bone and more cortical expansion, with or without ossification/calcifications. Bone scintigraphy is highly sensitive for the detection of both osteoid osteoma and osteoblastoma, as both demonstrate strong uptake at the nidus, but this increased uptake is not specific to either lesion, and as a result does not often aid in differential diagnosis. The use of MRI in the workup of these entities is controversial, as well, as findings are often nonspecific and may lead to misinterpretation, misdiagnosis or overestimation of tumor size [26].

Histologically, both osteoid osteomas and osteoblastomas consist of a central nidus containing osteoblast-lined trabeculae and a fibrovascular stroma surrounded by a rim of sclerotic bone. In osteoblastoma, the nidus exhibits a less-organized osteoid pattern and greater vascularity along with the presence of reactive giant cells and larger osteoblasts [26].

The first-line treatment for pain associated with osteoid osteomas is NSAIDs. If the pain becomes refractory, however, en bloc resection, intralesional curettage, or percutaneous radiofrequency ablation may be used [27]. Osteoid osteoma is not locally aggressive and has no potential for malignant transformation [26]. In fact,

with time, many osteoid osteomas will spontaneously regress [28]. The recurrence rate of osteoid osteomas is 4.5% after wide local excision [3, 29].

Osteoblastoma, on the other hand, while histologically benign, may behave in a locally aggressive manner, and thus surgical treatment is recommended. Intralesional curettage can be performed for less aggressive osteoblastomas, but due to the high recurrence rate, en bloc resection is the preferred treatment choice [27, 30].

20.4.2 Aneurysmal Bone Cysts

Aneurysmal bone cysts are benign osteolytic bone neoplasms that are characterized by blood filled cavities of varied sizes with septations in between. These lesions develop most commonly (65–99%) in children and adolescents because of trauma and local hemodynamic disturbance, although they may also arise due to venous obstruction or an arteriovenous fistula in association with an underlying tumor (e.g., giant cell tumor, osteoblastoma or osteosarcoma) [31].

While aneurysmal bone cysts are typically found in the metaphysis of long bones (e.g., femur or tibia), 12–30% of cases are seen in the spine, and of these, only 20% involve the sacrum [31]. Spinal aneurysmal bone cysts nearly always originate in the posterior elements or sacral alae, but frequently extend to involve the vertebral body.

As with other benign osseous spinal lesions, patients often present with localized pain with or without an associated palpable mass, although with sacral involvement, radicular symptoms or bowel and bladder dysfunction may be seen [32].

Findings on plain films and CT will include a well-defined, expansile osteolytic lesion with thin sclerotic margins. On MRI, fluid-fluid levels can often be seen within the cystic cavities corresponding with blood of variable age, although this is not pathognomonic and may be seen within other tumors (e.g., giant cell tumors and telangiectatic osteosarcoma). Heterogenous gadolinium enhancement may also be seen within the intercystic septations.

Complete surgical resection is the treatment of choice for aneurysmal bone cysts, although with sacral involvement this is made difficult by the surrounding neurovascular anatomy, and in certain cases, embolization, curettage and bone grafting may result in less morbidity. Recurrence rates reported in the literature vary widely after surgical treatment, from 12 to 59% [32].

20.4.3 Giant Cell Tumor

Giant cell tumors are benign but locally aggressive (and occasionally metastatic) osteolytic primary tumors of bone, characterized by a proliferation of mononuclear cells with scattered macrophages and large osteoclast-like giant cells [33]. Giant cell tumors are found most frequently near the articulations of long bones, but may also occur in the spine and sacrum, comprising 4–8% of all primary osseous spine

tumors Females are more commonly affected than males, and these tumors occur most commonly in the second to fourth decades of life [33, 34].

The most frequent presenting symptom is low back pain occurring at night. Pathologic fractures with neurologic compression are less common. Pulmonary metastases may occur, and when present, confer a 25% mortality rate [32].

Giant cell tumors of the spine and sacrum most commonly involve the vertebral body but may extend into the posterior elements or epidural space. MRI will demonstrate an isointense to hypointense lesion with heterogenous contrast enhancement [34]. On computed tomography a moth-eaten, irregular and erosive lesion will be seen, and in some cases, the tumor can expand the contours of the bone. Once the lesion is identified, a CT-guided core biopsy will aid diagnosis.

Histologically, giant cell tumors contain a regular distribution of stromal and multinucleated giant cells, which resemble osteoclasts [33]. Samples may also demonstrate necrosis, hemorrhage, and hemosiderin deposits. Receptor activator of nuclear factor **κ**-B ligand (RANKL) can be detected in the tumor [35].

The treatment of choice is en bloc surgical resection with preoperative selective arterial embolization, although given the propensity for these tumors to grow and involve critical neurovascular anatomy prior to diagnosis, embolization combined with radiotherapy and subtotal resection have been advocated by some as a less-morbid alternative. Denosumab is a monoclonal antibody and RANKL inhibitor that is sometime used as neoadjuvant therapy to shrink the tumor prior to definitive treatment. It can also be used for unresectable or recurrent tumor. Radiation therapy is available as salvage treatment in patients that have contraindications to denosumab therapy.

20.4.4 Cartilaginous Tumors: Chondroma and Chondrosarcoma

Chondromas comprise only 5% of all primary bone tumors and are rarely found in the spine, occurring more commonly in the bones of the hands and feet [3, 36]. Chondromas can be further classified based on their origin: Periosteal chondromas originate from the cortex, while enchondromas originate from the medullary cavity. Men are the most frequently affected; between the third and fifth decades of life [36]. Chondromas are typically solitary, but chondromatosis syndromes such as Ollier disease or Maffucci syndrome may present with multiple chondromas in childhood. While most chondromas are discovered incidentally, patients may present with a palpable mass and focal tenderness. Neurological symptoms may also develop insidiously in patients with spinal chondromas as these slow-growing tumors become exophytic and impinge on nearby neurological structures.

Radiographic findings will include a low-attenuation, erosive lesion with sharply defined, scalloped margins with or without stippled calcifications, neural foraminal widening or local deformity on CT [36]. On MRI, chondromas are typically T1-hypointense and T2-hyperintense. Although chondromas may exhibit variable gadolinium enhancement, this is seen more commonly in chondrosarcoma [36].

Although chondromas are benign entities, they can undergo sarcomatous dedifferentiation. The treatment of choice is surgical resection to establish diagnosis and prevent malignant transformation. The recurrence rate after complete surgical resection is approximately 10% [37].

Chondrosarcomas are cartilaginous tumors of variable malignancy that are often found within the long bones and pelvis of adults. They may arise de novo or via secondary dedifferentiation of a chondroma or other benign cartilaginous neoplasm. Chondrosarcomas constitute 7–12% of all primary spine tumors and 25% of all primary malignant spine tumors [25, 33, 36]. Of these, the large majority are seen in the mobile spine (with a predilection for the thoracic spine). Sacral chondrosarcomas are rare. Males are affected twice as frequently as females, with a typical age of presentation between 30 and 70 years. Growth is often indolent, and the most common presenting symptoms is local pain, although in patients with spinal chondrosarcomas, neurological deficits are also present in 50% of cases at the time of presentation [36].

On immunohistochemical examination, chondrosarcomas are composed of a cartilaginous matrix with hypercellular stroma. There are various subtypes, including central, peripheral, mesenchymal, clear-cell, and de-differentiated. The WHO grade for chondrosarcomas may vary widely (I–IV), and overall prognosis is heavily dependent on grade with 10-year survival for a Grade I chondrosarcoma being 90%, compared with 30–40% for a high grade (III–IV) chondrosarcoma. The large majority of chondrosarcomas (80–90%) are WHO Grade I and may be difficult to distinguish histologically from benign chondromas, but on close histological examination, invasion of surrounding tissues, bony cortical penetration and a prominent myxoid stroma with or without increased cellularity and mitoses will be seen in low-grade chondrosarcomas. With higher-grade lesions, increased cellularity, mitotic activity and metastasis (70%) are often present [36].

Imaging findings will vary with the subtype and WHO grade of chondrosarcoma. Plain films and CT will reveal a lytic bony lesion with heterogenous contrast enhancement, intralesional calcifications (“ring and arc” or “popcorn” calcifications) and endosteal scalloping. In higher grade lesions, a moth-eaten appearance along with cortical remodeling and periosteal reaction may also be seen. On MRI, chondrosarcomas exhibit heterogenous gadolinium enhancement, and are T1 hypointense or isointense and T2-hyperintense. They also will often demonstrate scattered T2-hypointensities and gradient echo or susceptibility-weighted “blooming” artifact related to intralesional calcifications. Bone scintigraphy may also be used when differentiating a low-grade chondrosarcoma from a benign chondroma/enchondroma, as increased uptake is seen more frequently with the former [36].

The treatment of choice is wide en bloc resection, which decreases the chances of local recurrence, and ensures longer disease-free survival. Even minor contamination of the surgical margins with tumor has been shown to confer a less favorable prognosis [36]. Local recurrence occurs in up to 20% of cases despite gross total resection [33, 38]. Chondrosarcomas are relatively resistant to both radiotherapy and chemotherapy [39, 40], but high-dose radiotherapy may slow tumor progression

and has been used in cases of recurrence or for palliation [36]. With aggressive resection, the mean survival for patients with chondrosarcoma is 6 years [41].

20.4.5 Osteosarcoma

Osteosarcoma is the most common primary malignant bone tumor and is found most frequently in the metaphyseal region of long bones and in the pelvis, rarely being seen in the spine (3–5% of cases) [42–45]. Osteosarcoma accounts for only 4% of primary sacral tumors, and many of these occur secondary to degeneration of Paget disease [31]. As opposed to extremity osteosarcomas (which are more common in children and adolescents), osteosarcoma of the mobile spine and sacrum tends to be seen in the fourth decade of life, with an equal incidence in males and females [43, 46].

Axial back pain is the most common presenting symptom, followed by neurologic deficits [43]. Bowel and bladder dysfunction are seen in the later stages of the disease course [46]. By the time of diagnosis, approximately 28% of patients have metastatic disease [43].

CT and plain films may reveal a purely lytic, mixed, or largely osteoblastic lesion with an associated soft-tissue mass, a moth-eaten appearance of bone, an aggressive periosteal reaction and ossification/calcification within the tumor matrix. MRI is useful for local staging and surgical planning and will reveal T1-isointense and T2-hyperintense soft tissue components and peritumoral edema with T1 and T2-hypointense scattered calcifications and soft-tissue enhancement.

The histologic hallmark of osteosarcoma is the presence of trabecular bone or osteoid matrix within a high-grade spindle cell tumor, as the neoplastic cells are of osteoblastic differentiation and able to produce bone without the need for associated cartilage. Cellular pleomorphism, mitoses, vascular invasion and necrosis are also common.

The treatment of choice for osteosarcoma is neoadjuvant chemotherapy followed by wide local surgical excision [46, 47]. Preoperative chemotherapy can prolong survival, although despite aggressive therapy, prognosis is poor, particularly for osteosarcoma of the mobile spine and sacrum [48]. The mean survival for patients with sacral osteosarcoma is 10 months, even after adequate resection [42].

20.4.6 Ewing's Sarcoma

Ewing's sarcoma is a neoplasm that originates from precursor neural cells and is the most common nonlymphoproliferative primary malignant tumor of the spine in children. While seen most frequently arising from the femur, Ewing's sarcoma involves the spine primarily in 3–10% of cases. More often, however, spinal involvement occurs secondarily due to osseous metastases. This tumor occurs during the teenage years, affecting males twice as commonly as females. The sacrum is the most common spinal location affected [46].

Patients usually present with localized back pain, along with neurologic deficits, although bowel and bladder dysfunction are rare. Some patients may also present with fever and elevated sedimentation rate or C-reactive protein, which can confound the diagnostic process.

CT and plain films findings vary, and lytic, sclerotic, or mixed lesions with or without involvement of paraspinal soft tissues and the epidural space may be seen. Soft tissue calcification is uncommon. MRI findings are generally non-specific but will include isointense to hypointense T1 signal and heterogenous T2-hyperintensity with prominent, heterogenous enhancement.

These tumors appear gray-white grossly with areas of hemorrhage and necrosis. Immunohistochemical examination demonstrates small round blue cells with uniform nuclei. At a molecular level, this tumor can be characterized by reciprocal translocations between the EWS gene, located on chromosome 22, and the ETS transcription factor.

The treatment of choice for Ewing sarcoma is systemic chemotherapy. This has increased 5-year survival rates from 10% in the 1980s to 70% presently [49, 50]. Surgical resection improves local control, but may not improve overall survival, and is reserved for cases where residual tumor remains after primary therapy [46]. Ewing's sarcoma is also relatively radiosensitive compared with other sarcomas, and radiotherapy may play a role depending on the location and size of the tumor. Despite advances in therapy, however, 5-year survival is just 33% [42].

20.5 Metastatic Sacral Tumors

Metastases, frequently from hematogenous spread, are the most common tumors to affect the sacral spine [3, 51]. They can derive from breast, lung, prostate, kidneys and the gastrointestinal tract. These tumors can be more rapidly progressive and locally invasive, causing focal back pain or neurologic deficits [52]. Tumors in the pelvic viscera can also locally spread to invade the presacral space [3]. Computed tomography and MRI can reveal large, highly infiltrative masses that have imaging characteristics that resemble the primary tumor. Unfortunately, at the time of the radiographic findings and detection of sacral metastasis, involvement of other organs and other areas of the spine is as high as 60% [53]. Due to these notes, biopsy to obtain tissue diagnosis is not necessary for these patients.

Radiation therapy has been a preferred treatment for sacral metastases, but due to advancements in primary tumor treatments with resultant longer survival, the number of patients with refractory disease has increased. Though the role of radiation therapy for these patients is largely palliative. There are also risks associated with radiation therapy, such as radiation-induced proctitis and enteritis [54–57]. This evolution in the patient population has prompted further exploration of palliative surgery as a treatment option, to decompress neural structures or to reconstruct and stabilize the spine [46].

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Rare Spinal Cord Tumors

21

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21.1 Introduction and Epidemiology

Historically, spinal cord tumors represent approximately 15% of all primary central nervous system (CNS) tumors [1], whereas the newest classification of these intramedullary spinal cord tumors (IMSCTs) encompasses only 2–4% of all CNS tumors. The more prevalent intramedullary lesions include astrocytoma and ependymoma, which are thoroughly described elsewhere in this book. Astrocytoma followed by ependymoma are the most common IMSCTs found in children, while in adults ependymomas are more frequent. The less common IMSCTs are hemangioblastoma and spinal cord metastases, which are much more common in the adult

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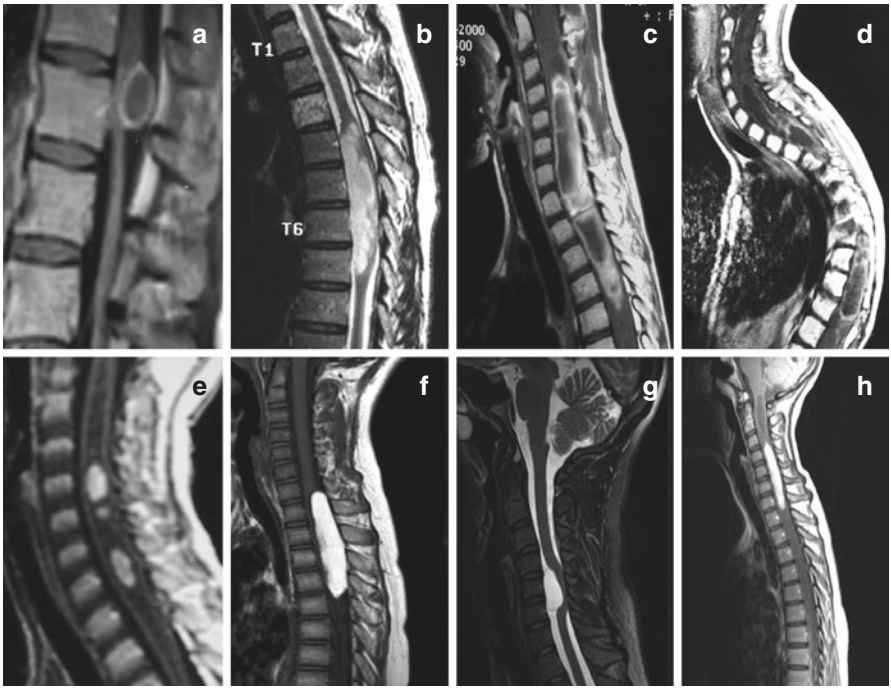

Fig. 21.1 Rare spinal cord tumors. Different sagittal views of some of the different spinal cord tumors discussed in this chapter: (**a**) spinal cord teratoma; (**b**) Spinal cord subependymomas; (**c**) spinal cord gangliogliomas; (**d**) severe scoliosis caused by holocord gangliogliomas; (**e**) spinal cord oligodendrogliomas; (**f**) spinal cord lipoma; (**g**) neuro-enteric cyst; and (**h**) neurocytomas

population. Exceedingly rare lesions, such as lymphoma, primitive neuroectodermal tumor (PNET), lipoma, and neuroenteric cysts, paraganglioma, ganglioneuroma, and oligodendroglioma—among others—have been documented in both the adult and pediatric literature and will be elaborated on in this chapter (Fig. 21.1). Spinal cord hemangioblastoma, spinal cord metastases, and spinal cord cavernous angioma are thoroughly described elsewhere in this book.

21.2 Clinical Presentation

The presenting symptoms for IMSCTs vary based on the type of lesion and the age of the patient; however, these symptoms are usually progressive over the course of weeks or months. The majority of adult patients with IMSCTs have initial complaints of back or neck pain. Other signs and symptoms include unilateral or bilateral weakness, numbness, paresthesia, bowel/bladder dysfunction, radiculopathy, and gait dysfunction [2]. When present in children, these lesions may present themselves as weakness, progressive scoliosis, clumsiness, or other non-descript symptoms [3]. Upper motor signs of Babinski, clonus, or Hoffman's can be seen

on physical exam. Demyelinating disorders must be distinguished from IMSCTs based on clinical exam and symptom presentation. This can be difficult as demyelinating diseases convey a symptom course that is usually relapsing and remitting with intermittent improvement. These types of symptoms can be seen in spinal cord tumors with associated cystic components. Evidence of hydrocephalus may also be present in the setting of IMSCT, occurring in approximately 1% of patients. The etiology likely stems from impaired absorption of cerebrospinal fluid (CSF) by the byproduct of increased protein in the CSF or focal obstruction caused by the tumor [4].

21.3 Evaluation/Diagnostics

Evaluation should first begin with a thorough physical exam with emphasis on identifying upper motor neuron signs, as well as clinical features that pinpoint to a neurologic level of involvement. Once the physical exam has been completed, the diagnostic gold standard is magnetic resonance imaging (MRI). Gadolinium is typically utilized to assess for uptake of contrast material. Prediction of histologic diagnosis can frequently be achieved by assessing the MRI characteristics of the lesion as each has a specific imaging pattern (Fig. 21.1). T2-weighted imaging is the sequence of choice to observe spinal cord enlargement as lesions are classically hyperintense [5]. Primary intramedullary spinal cord lymphoma follows this pattern, appearing to be hyperintense on T2-weighted imaging. Typically, these lesions are poorly defined and multi-focal without evidence of syrinx [6]. There is homogenous contrast enhancement with isointense signal on T1, and without contrast with gadolinium administration [7]. In documented cases of PNETs, the tumor is typically located in the lumbar spine with iso-hypointensity on T1, and heterogeneous hyperintensity on T2. There is heterogeneous contrast uptake into the lesion [8]. These tumors will typically extend into the neural foramen and can involve the vertebral body. Intramedullary lipomas are hyperintense on T1 and T2-weighted imaging and saturate on fat-saturated images [9]. Cord lipomas occur as a single entity; however, they are rarely multi-lobulated in a non-contiguous pattern [10]. Neuroenteric cysts, on the other hand, are usually hyperintense on T2 and hypointense on T1 without contrast enhancement [11]. However, there have been multiple case reports of these lesions presenting with different signal characteristics [11, 12]. Cysts are usually located along the ventral portion of the spinal cord in an intradural-extramedullary location, but can infiltrate intramedullary in rare cases [13]. Subependymomas have a variable appearance on MRI. The lesions are classically solid heterogeneous masses; however, there can be a cystic component. T1-weight imaging with contrast can elicit enhancement along the wall of the cyst [14]. Subependymomas are similar to ependymomas in that they are hypo-to-isointense on T1 and hyperintense on T2 imaging [2].

Ganglioglioma lesions are found in the cervical and thoracic region stretching multiple vertebral segments with a mixed signal on T1 and heterogeneous enhancement. T2 hyperintensity with cord enlargement eccentric to one side without surrounding edema is characteristic of these lesions [15].

When MRI cannot be obtained, computed tomography (CT) myelogram can be used to assess the neuroaxis in adults. CT should not be utilized in the evaluation of pediatric tumors due to radiation exposure unless MRI cannot be obtained.

21.4 Surgical Considerations and Technique

Surgical intervention is the mainstay of treatment, especially in those patients who have symptomatic lesions. Symptoms can evolve from the tumor itself invading neuronal structures (e.g., corticospinal tracts), from mass effect compromising cord vascularization and causing cord ischemia, syrinx, spinal bony deformity (e.g., scoliosis), and tethered cord-related symptoms. In patients who are asymptomatic, close monitoring with serial imaging can be performed, although careful judgement needs to be taken with large tumors or signs of syrinx or cord edema and ischemia. The degree of surgical resection needed is based on histologic diagnosis and the surgical plane presented by the tissue and tumor. For lesions that are non-infiltrating aggressive, gross total resection can be routinely achieved and is recommended. In infiltrating lesions, such as primary spinal cord lymphoma, aggressive resection of the lesion may be more detrimental to the patient than achieving partial resection [16]. Preservation of neurologic function in individuals with infiltrating pathology is of utmost concern for future quality of life.

Due to the positive strides taken in the advances of intraoperative neuromonitoring, surgeons have been able to be more aggressive with surgical resection. Monitoring IMSCTs is now the gold standard of treatment. Somatosensory evoked potentials (SSEPs) and motor evoked potentials (MEPs) along with electromyography (EMG) monitoring are typically used. An epidural lead is placed for cervical and thoracic lesions to monitor D-wave activity—i.e., the integrity of corticospinal tracts. If there is a 50% reduction in amplitude of the D-wave distal to the lesion, this correlates with increased risk of post-operative weakness [17]. When a reduction in MEPs is noted, the surgeon should allow this area of the spinal cord to relax and proceed with resection at a different site of the tumor/spinal cord interface. Consideration must be taken to raise mean arterial pressure goals to greater than 70–85 mmHg (depending on patient age) in the setting of diminish MEPs, and as a general rule for spinal cord lesion surgery. If the signals do not improve, the surgeon must decide whether to proceed further.

Once intraoperative monitoring leads have been applied, the patient in placed in the prone position on gel rolls with a 3-point fixation Mayfield clamp in place for operating on cervical and upper thoracic tumors. The neck is flexed into a military position to bring the cervical cord into a straight line with anesthesia monitoring for signs of airway compromise. A 2-finger width should be present between the chin and the sternum as a surgical pearl to prevent kinking of the endotracheal tube and airway compromise. Care should be taken to ensure the arms and pressure points are padded and the axilla is supported appropriately, thus preventing brachial plexus injury. When needed, the operative level can be marked with the assistance of fluoroscopy prior to prepping and draping the operative site.

The subcutaneous tissue is injected with local anesthetic epinephrine for local pain control and to assist with hemostasis. A midline incision is performed and dissection carried out subperiosteally with the use of monopolar electrocautery. Subperiosteal dissection is undertaken meticulously in order to not disrupt the facet capsules along the lamina and to ensure hemostasis. Laminectomy or laminotomy is performed with the utilization of a bone scalpel or drill 1 level above and 1 level below the lesion. Ultrasound may be utilized for assistance with IMSCT localization once the dura is exposed. Durotomy is performed in a vertical fashion using an 11 or 15 blade scalpel. 4-0 Nurolon sutures (Ethicon, Somerville, NJ) are placed along the incised portion of the dura for retraction. Since the cord is attached to the dura (dentate ligament), care should be taken to any change in monitoring to relieve dural traction as needed. When planning the myelotomy, one should take into account where the tumor presents itself closest to the pial surface of the spinal cord. A midline myelotomy is routinely performed in the posterior median sulcus, but can be done along the dorsolateral sulcus and lateral sulcus as well. Blunt dissection with Rhoton dissectors and a plated bayonet are utilized to find the tumor plane. In larger lesions, it is advisable to consider internal decompression of the lesion using suction or an ultrasound aspirator. This can help to release the tension and eventually can be used to help develop a plane. Pathology should be sent for frozen analysis as this can affect the aggressiveness of resection in certain cases. Once resection has been completed, hemostasis is achieved with thrombin-based products and bipolar electrocautery. The use of bipolar electrocautery should be done very carefully since thermal injury can be devastating. The dura is primarily repaired with either Nurolon or Prolene sutures (Ethicon, Somerville, NJ). The bone is attached using mini-plates as laminoplasty with care to leave extra space between bone and dura to accommodate any possible post-operative cord swelling. Closure of the muscle, fascia, and subcutaneous tissue is completed in a step-wise fashion with water-tight closure. Some physicians elect for 24 h bed rest to help take pressure off of the dural closure for patients who underwent resection of thoracic and lumbar lesions. Postoperative imaging—MRI with and without contrast—is performed within the first 24–36 h.

21.5 Etiologies

21.5.1 Ganglioglioma

Introduction. Gangliogliomas are rare tumors from both neuronal and glial origins that are typically benign but may demonstrate malignant transformation of the glial component of the tumor [18, 19]. They account for only 0.5% of all primary CNS neoplasms. Gangliogliomas are rare, slow-growing primary CNS tumors that most frequently occur in the temporal lobes, typically resulting in seizures [20]. Ganglioglioma of the spinal cord is exceedingly rare with fewer than 70 cases reported, mostly in children or young adults [21]. Only about 3% are located in the spinal cord, with a rate of incidence of about 1.1% of all spinal cord neoplasms [22].

Anaplastic gangliogliomas (AGGs) account for up to 5% of gangliogliomas [23, 24], and tend to appear in adults around the age of 35 [25]. They are very rare and their clinical course is poorly understood; hence, their treatment paradigm is not well established [23]. AGGs can arise as a malignant transformation from low-grade tumor (which is more common in pediatric population), or as a primary AGG tumor, the latter being extremely rare [26]. The World Health Organization (WHO) classifies AGG as Grade III, and their histology exhibits anaplastic features, such as mitotic activity, cytological atypia, and necrosis. Although they can evolve in any location in the CNS, a spinal cord location is very uncommon. When a ganglioglioma arises in the spinal cord, the tumor will be typically located in the cervical region and are typically larger in size on diagnosis compared with other IMSCTs due to its slow-growing nature.

Clinical Presentation. Gangliogliomas affect a wide age range of patients from newborn to elderly, but most cases occur in children or young adults. There has been no gender, race, or ethnic association identified. Patients present typically with progressive myelopathy in addition to other neurological deficits related to the location of the lesion in the spinal cord [27]. The duration of symptoms ranged from 1 month to 5 years [28]. Usually tumors are detected at a late stage because of characteristically slow growth, leading to an insidious progression of neurological deficit.

Imaging. It is nearly impossible to differentiate ganglioglioma from the more common intramedullary neoplasms—astrocytoma or ependymoma—based on imaging alone, as they all share similar features (Fig. 21.2) [29].

Pathology. Histologically, gangliogliomas are composed of both neoplastic glial and ganglion cells, which are disorganized, variably cellular, and

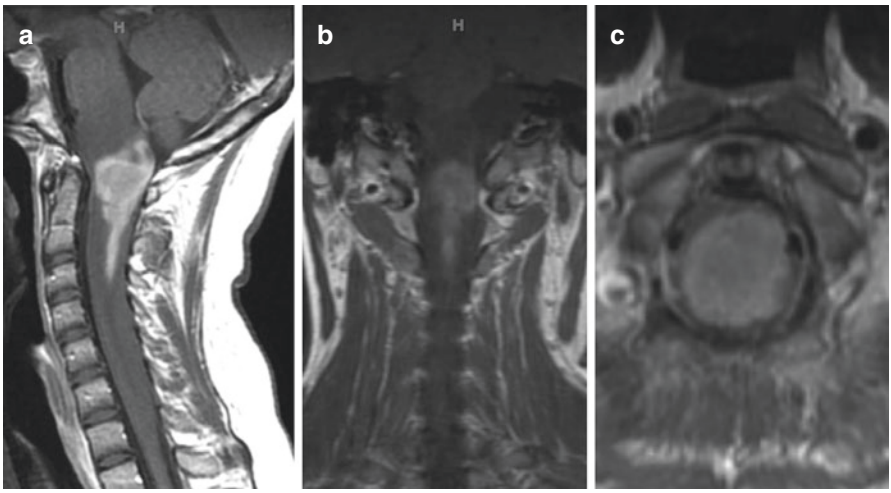

Fig. 21.2 Craniocervical junction gangliogliomas. T1 sequence after gadolinium injection in sagittal (**a**), coronal (**b**), and axial (**c**)

non-infiltrative. Occasionally, it may be challenging to differentiate ganglion cell tumors from an infiltrating glioma with entrapped neurons [29]. In the differentiation of ganglioglioma from regular glial tumor, pathologists look for abnormal clusters of neoplastic ganglion cells. The presence of binucleated and dysmorphic neurons are helpful findings that can help to direct diagnosis towards ganglioglioma [29]. Common features include fibrovascular stroma confined to the neuronal component, perivascular lymphocytic infiltrates, small foci of calcification, and immunopositivity for synaptophysin, neuron-specific enolase, and chromogranin A. More aggressive tumors will usually have elevated Ki-67 and p53 labeling index.

Gangliogliomas are generally benign WHO Grade I tumors; the presence of anaplastic changes in the glial component represents WHO Grade III tumors (anaplastic ganglioglioma), and there is no WHO Grade II for ganglioglioma [30]. In recent years, there are growing data regarding molecular subtyping, specifically with regards to a BRAF mutation. BRAF is an intracellular serine/threonine kinase component of the mitogen-activated protein kinase (MAPK) pathway [31]. Ras protein activates BRAF, which leads to downstream promotion of cell growth, survival, and differentiation. A common mutation is BRAF v600E, which can lead to increased oncogenicity. Almost one-third (in some reports up to 60%) of gangliogliomas harbor this mutation, yet the real prevalence of spinal cord ganglioglioma harboring BRAF mutation has yet to be found [31–34]. There are gangliogliomas that harbor fusion KIAA1549, like pilocytic astrocytoma. H3 K27M (H3.3 K27M) can be found in gangliogliomas as well, and will lead to a much more aggressive tumors, usually AGGs.

Surgical Intervention. The best treatment is gross total resection. Optimal treatment via subtotal resection has not been clearly established yet. According to the few articles available in the literature that discuss spinal cord gangliogliomas, the 5 and 10-year survival rates after total resection were 89% and 83%, respectively [27].

It has been recognized that postoperative results correlate closely with preoperative neurological status, as well as the ability to achieve complete resection [35].

Adjuvant Therapy. With the exception of WHO Grade III anaplastic ganglioglioma, radiation therapy and chemotherapy are generally regarded as having no role in ganglioglioma treatment and have been found to have no treatment advantage [21, 28, 36, 37]. Some physicians advocate against radiation therapy and chemotherapy since they increase the chance for malignant transformation [38]. Most will agree that adjuvant radiotherapy is generally given to patients with incomplete tumor resection or for recurrent tumor (i.e., that cannot be resected), and to those with a tumor histology showing anaplastic features or oligodendroglial-like cells [39]. Adjuvant chemotherapy is advocated by some in partially resected low-grade spinal cord gangliogliomas that show evidence of disease progression [29]. The role of BRAF inhibitors has started to be investigated as well in spinal cord tumors that harbor the mutation or the fusion. Poor prognostic factors for adults with gangliogliomas include older age at diagnosis, male sex, and malignant histologic features.

21.5.2 Paraganglioma

Introduction. Paragangliomas account for 0.3% of all neoplasms. Nearly 80% of paragangliomas develop within or near the glomus jugulare and carotid body [40]. Paragangliomas arise from the paraganglion cells of the neuroendocrine system and can be primary spinal lesions or metastatic from the retroperitoneum. The first case of paraganglioma metastasizing to the spine was reported in 1948 [40]. As few as 30 cases of spinal metastasis of paraganglioma have been reported in the literature [40]. The origin of these tumors is uncertain as the presence of paraganglia cells in the CNS is unclear. Previous publications suggested that a spinal paraganglioma may originate from sympathetic neurons in the thoracic and lateral horns of the spinal cord [41]. Spinal paragangliomas are thought to be of the sympathetic type while carotid and jugular body paragangliomas are of the parasympathetic type [42].

Clinical Presentation. Patients present usually between the ages of 40–50 years; there is a slight male predominance [42]. Paragangliomas are rarely seen in children. Pain is the most common presenting symptom and is usually progressive and insidious in onset [40]. Neurologic symptoms, including radiating pain and limb weakness due to spinal cord and nerve root compression, are also reported [40]. Despite their neuroendocrine origin, these tumors rarely have functional hormonal activity. However, there are some cases of paraganglioma with functional hormonal activity that can induce perioperative vital instability [43, 44].

Diagnostic imaging. MRI is the imaging modality of choice and will demonstrate isointense or hypointense signal on T1, and isointense to hyperintense signal on T2. Paragangliomas will enhance with gadolinium. The presence of signal flow voids may be seen due to high-velocity flow in tumor vessels. A "salt and pepper" appearance on T2 images has been described due their hypervascular nature and the presence of these flow voids [40]. Tumors typically have an irregular oblong shape. Vertebral elements can be involved in cases of metastatic disease; however, bony elements are often spared in primary spinal paraganglioma. When paragangliomas are found in the lumbar spine, they will usually be in the intradural-extramedullary space [40].

Pathology. The stereotypical paraganglioma is the pheochromocytoma, which is found in the adrenal gland and secretes catecholamines resulting in labile blood pressure. Spine paragangliomas sequester catecholamines in cytoplasmic granules; however, they are rarely active in neuroendocrine production [40]. Urine and blood samples of catecholamine and vanillylmandelic acid typically demonstrate normal levels. The "Zellballen" pattern—a nesting or clustering of cell groups and the trabecular cords of cells within thin compartments of connective tissue stroma—is the primary histological feature [40]. The predominant cell type are the chief cells, which are round with eosinophilic cytoplasm and large round nuclei [42]. Chromogranin, synaptophysin, and neuron-specific enolase are positive in paragangliomas. The tumors will stain negative for glial fibrillary acid protein, which will help in differentiating it from ependymoma [40].

Surgical Intervention. Surgical resection is the first line treatment for paraganglioma. For metastatic tumors, the primary retroperitoneal and/or abdominal tumor is typically resected first, unless neurologic symptoms dictate an urgent resection of the spinal tumor [40]. Gross total resection should be the goal of surgery. Preembolization prior to surgery has been described in tumors of the thoracic region to help minimize blood loss and morbidity of surgery [45].

Adjuvant Therapy. Adjuvant radiation therapy is recommended when subtotal resection is achieved (and repeat surgery is not possible), although the role for radiotherapy has yet to be fully determined [40]. Conventional radiotherapy provides control rates of 90–100% and is often advocated as a first-line therapy for asymptomatic patients with intracranial paragangliomas; therefore, its use for spinal lesions may also be promoted [46]. There have been case reports on the use of chemotherapy in paragangliomas with mixed results. Success has been reported with the use of octreotide for metastatic paraganglioma, and with combined cyclophosphamide, vincristine, and dacarbazine; however, there have been multiple series with failure of chemotherapy treatment [40].

21.5.3 Neuroenteric Cysts

Introduction. Neuroenteric cysts are benign congenital lesions that result from abnormal partitioning of the embryonic notochord plate and endoderm, causing primitive endodermal cells to be incorporated into the notochord. The displaced alimentary cells become the cyst wall [47].

Neuroenteric cysts represent 0.3–1.3% of spinal cord tumors. They were first described in 1934 by Puusepp and have been termed enteric cysts, endodermal cysts, gastroenterogenous cysts, gastrocytoma, intestinoma, and archenteric cyst until the term neuroenteric cyst was introduced in 1943 [47]. Associated pathologies include bone, soft tissue, and visceral abnormalities. They are predominantly found in the thoracic cord, followed by the cervical cord, cervicothoracic cord, and the conus medullaris [48]. Most often, neuroenteric cysts are found in the intradural-extramedullary compartment of the spine. Intramedullary neuroenteric cysts contribute to <5% of all intraspinal neuroenteric cysts [48].

Clinical Presentation. Neuroenteric cysts usually manifest before the fourth decade of life (range, 21 days to 68 years) and have a male predominance (male/female ratio of 22:16) [48]. Neuroenteric cysts are typically slow-growing and present with progressive myelopathy [49]. Patients will also present with neurologic symptoms, including weakness, sensory changes, sphincter dysfunction, and pain [48]. It is hypothesized that intermittent symptoms help characterize neuroenteric cysts because the cyst may periodically rupture mucin into the subarachnoid space or by fluctuation in the rate of active mucin secretion and reabsorption by the cyst wall [48]. Cases have been described in infants presenting with meningitis due to cyst rupture into the subarachnoid space.

Diagnostic Imaging. MRI is the diagnostic imaging of choice. Neuroenteric cysts appear typically as non-enhancing cystic lesions that are hypointense on T1

and hyperintense on T2 (Fig. 21.3) [49]. Peripheral enhancement of the cyst wall has been reported in some cases [48]. Cyst fluid will be isointense or hyperintense on T1 and T2, depending on the protein content of the cyst fluid [47]. Neuroenteric cysts are most commonly found in the cervical and thoracic spine, and infrequently in the lumbar spine or conus medullaris [48]. They are often found ventral to the spinal cord and can be misdiagnosed as cystic neoplasms, such as cystic meningiomas or astrocytoma.

Pathology. The cyst is lined by mucin-secreting pseudostratified cuboidal or columnar epithelium of the intestinal or respiratory type. Immunohistochemical staining is positive cytokeratin and epithelial membrane antigen. Staining is negative for glial fibrillary acid protein and S-100 protein. Ependymal cysts will stain positive for glial fibrillary acidic protein (GFAP) and S-100 [48]. Neuroenteric cysts can be classified based on histological features [47]. Type A cysts are simple pseudostratified, cuboidal, or columnar epithelium with or without cilia on a basement membrane. Type B cysts contain mucous glands, serous glands, smooth muscle, fat, cartilage, bone, elastic fibers, lymphoid tissue, or nerve ganglion. Type C cysts will also contain ependymal or glial tissue [47].

Surgical Intervention. Surgical resection is the primary form of treatment for these benign lesions. As neuroenteric cysts are most often located ventrally in the spinal canal, anterior approaches have been reported but are typically more extensive procedures and often require fusion, while the posterior approach is more straightforward—the surgeon can usually find a working corridor due to the cord displacement caused by the cyst and detach the dentate ligament as needed [47]. Surgical methods ranged from cyst puncture and aspiration [50], to resection with cyst marsupialization or cyst-subarachnoid shunting [51–53].

Gross total resection is reported in the literature to range from 71 to 75% in extramedullary locations [48]. Subtotal resection occurs due to poor cyst-cord

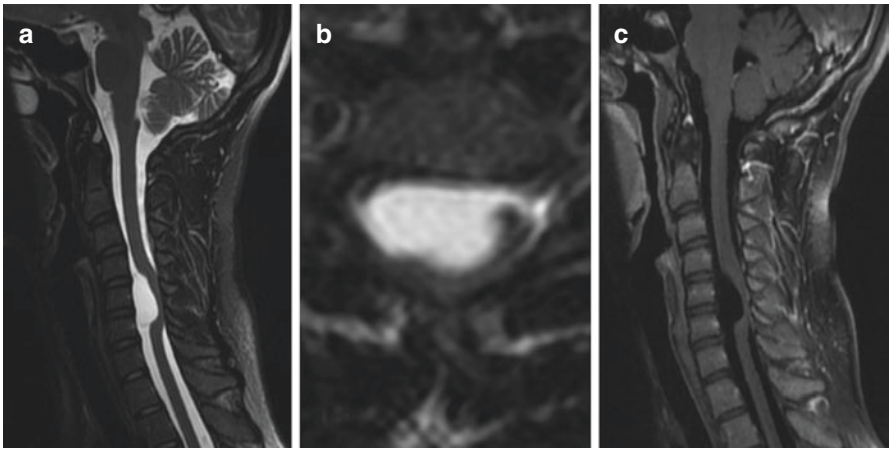

Fig. 21.3 Neuroenteric cyst. Rare lesion, tend to appear hyperintense in T2 weighted images (**a, b**), and hypointense in T1 sequence (**c**)

interface or adhesion to the surrounding neural tissue and in the intramedullary location. Cysts may recur after subtotal resection. The recurrence rate has been reported between 0 and 37% for intradural extramedullary cysts and 20–25% for intramedullary cysts [48]. As with other spinal cord tumors, laminectomy and laminoplasty techniques have been described. surgical fixation and fusion may be required after resection of the cyst due to the potential to remodel the vertebrae, which can cause thinning of the bone [54]. Cyst-subarachnoid shunting has been used in ependymal cysts but remains controversial in neuroenteric cysts due to the thought that the cyst contains caustic mucinous material and may cause irritation to the neural tissue [48].

Adjuvant Therapy. Currently, radiotherapy is not used in the primary treatment of ependymal cysts. Radiotherapy has not been shown to reduce the risk of ependymal cyst recurrence [48].

21.5.4 Primary spinal cord oligodendroglioma

Introduction. Primary spinal oligodendrogliomas (PSOs) are rare tumors represent less than 2% of all intramedullary spinal tumors. There is paucity of literature discussing this entity, with fewer than 70 cases described in the literature [55, 56].

In rare cases, PSOs can be diffuse, even to the extent of the entire cord, leading to symptoms related to increased intracranial pressure [55, 57]. The general treatment paradigm is surgery an adjuvant therapy.

Clinical presentation. PSOs are more common in the adult population, and there is equal distribution among both sexes—the literature to date indicates no significant sex predilection [55]. There are no unique presenting symptoms to PSOs, and they will present in the same way as other intramedullary tumors. Patients usually first describe the appearance of sensory deficits and back pain, and then later describe motor deficits and sphincter malfunction [56, 57]. There were also some reports of oligodendrogliomas involving the entire spinal cord, resulting in increased intracranial pressure as a presenting symptom [55, 58]. Oligodendrogliomas tend to be fairly large tumors upon presentation. In the vast majority of reported cases of PSO, the tumor is between 1 and 5 segments in length—there are some cases in which the tumor occupied >10 consecutive levels [55]. The most reported anatomical location is the thoracic spine [56, 58].

Diagnostic imaging. MRI with and without contrast is the gold standard for diagnosis and surgical planning. CT should be performed in cases with tumors causing skeletal deformation. Oligodendrogliomas are hyperintense on T2 and are contrast enhancing. Usually, heterogeneous hypointense or isointense lesions are observed in T1-weighted images, and a hyperintense lesion is observed in T2-weighted images (Fig. 21.4) [55]. The enhancement can be a mild and nonhomogenous spotty enhancement with hypointense areas usually due to intramural bleeding foci and hemosiderin deposition. Yet in some lesions, enhancement can be much more obvious. Cystic components or cystic necrotic areas are not common feature, and when they appear, they can direct toward a high-grade PSO.

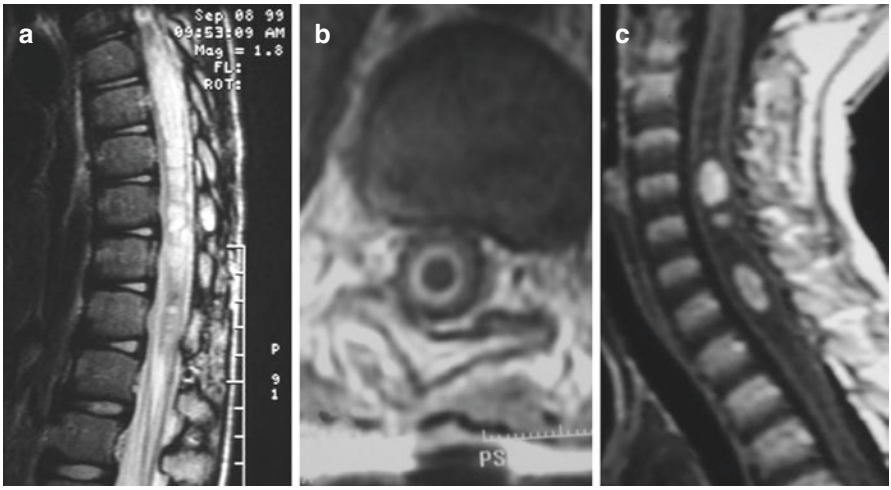

Fig. 21.4 Holocord oligodendroglioma. T2 (**a**) and T1 after gadolinium injection (**b, c**) holocord oligodendroglioma with extensive syrinx

Brain and total spine MRI should be obtained due to the possibility of tumor seeding to different location in the spine and to the brain as well [59].

Pathology. Tumors typically have a high cellularity with characteristic "fried-egg" cells with round nuclei and a clear basophilic cytoplasm, which stain positive for GFAP on immunohistochemical staining. PSOs are usually solid mass tumors and tend to look yellow-gray, pink-gray, or reddish less frequently in macroscopic appearance. Calcifications are fairly common and will appear at an average rate of 30% [56, 60, 61]. Microscopic features of PSOs are typically composed of hyperchromatic neoplastic cells with small spherical nuclei and mitotic figures, depending on the tumor's degree of differentiation. Immunohistochemical analysis of PSOs reveal no reactivity or mild reactivity for GFAP because oligodendrocytes possess no cytoplasmic intermediate filaments [55]. The new WHO classification from 2016 outlines new diagnostic parameter for oligodendrogliomas: an observation of 1p and 19p deletions in fluorescence in situ hybridization [30]. The diagnosis of oligodendroglioma and anaplastic oligodendroglioma requires the demonstration of both an isocitrate dehydrogenase (IDH) gene family mutation, and combined whole-arm losses of 1p and 19q (1p/19q co-deletion) [30]. The WHO classification also recognized that tumors of childhood that histologically resemble oligodendroglioma often do not demonstrate IDH gene family mutation and 1p/19q co-deletion in the pediatric population. But until such tumors are better understood at a molecular level, they should be included in the oligodendroglioma not otherwise specified category [30]. Similar to other pediatric CNS tumors, pediatric spinal oligodendroglioma is a different tumor than adult spinal oligodendroglioma. Since the number of cases of spinal oligodendroglioma and anaplastic oligodendroglioma in the pediatric population is so small (only 4 cases of

anaplastic oligodendroglioma were described in the CCG-945 Children's Cancer Study Group clinical trial), there is a need for wider molecular investigation for all cases in order to tailor the right treatment, including the Ras-mitogen-activated protein kinase (Ras-MAPK) pathway that was found in pediatric spinal oligodendroglioma in some publications [62].

Surgical Intervention. Surgical resection is the mainstay of treatment and when possible, the surgeon should seek to achieve gross total resection. Total resection may not be achievable in a majority of cases as the tumor is often infiltrative and clear surgical margins are not common findings in PSOs [56, 63]. Neurophysiologic monitoring is employed intraoperatively to assist with achieving maximal safe resection, like in every intramedullary tumor resection.

Adjuvant Therapy. Post-operative chemotherapy and radiation have been performed in cases of recurrence [55]. Postsurgical chemotherapy and/or radiotherapy is controversial, and there is agreement that the use of post-resection radiotherapy should be limited to adults or older adolescent cases with a subtotal resection of high-grade tumors and doses not exceeding 40–50 Gy. CT with or without radiotherapy is promising. Nonetheless despite all these treatments, the average survival for a patient with a PSO is 28.6 months [55, 56, 64].

21.5.5 Neurocytoma

Introduction. Neurocytomas are typically located in the supratentorial ventricular system and are primary CNS tumors [65]. They tend to appear predominantly in the lateral and third ventricles in young adults, and account for 0.1–0.5% of all intracranial tumors worldwide [65]. Extraventricular neurocytomas (EVNs) are an even rarer tumor than neurocytoma and was first introduce to WHO classification in 2007 [66]. EVNs are rarely located in the spinal cord with only 24 cases of being reported in the English literature [67].

Clinical Presentation. Age at presentation ranges from 6 to 67 years of age; however, the number of cases of spinal cord neurocytomas is too small to reach any conclusion regarding either age or gender predisposition. Similar to other intramedullary tumors, these tumors are more likely to be located at the cervical or thoracic spinal cord [67].

Like any other spinal cord tumor, spinal cord neurocytomas cause symptoms depending on their location in the spinal cord, the presence of mass effect on the cord, and spinal cord edema. Symptoms may last for several months or years as the neurocytomas grow slowly.

Diagnostic Imaging. MRI characteristics are variable; sometimes it is not possible to distinguish spinal cord neurocytomas clearly from other intramedullary tumors (Fig. 21.5). Characteristics are very similar to ependymomas and oligodendrogliomas, which makes it difficult to make a definite diagnosis only via MRI (e.g., syrinx capping both poles of the tumor) [65, 68]. Therefore, it is necessary to use histopathology and immunohistochemistry features in order to make an accurate diagnosis of a spinal cord neurocytoma.

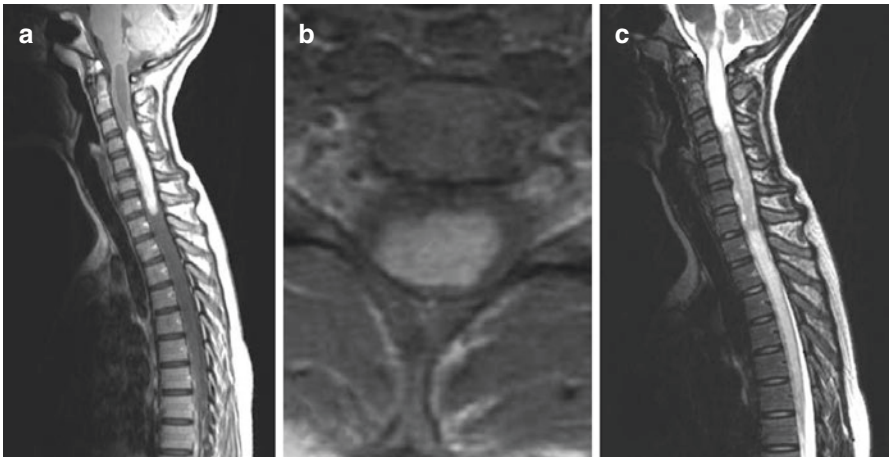

Fig. 21.5 Cervical neurocytoma. Different views of extraventricular neurocytoma. The tumor causes extensive syrinx above and below the lesion and tends to appear hyperintense on T1 (**a, b**), and isointense on T2 weighted images (**c**)

The basic MRI features of primary spinal cord neurocytomas may be isointensity/hypointensity on T1-weighted images and isointensity/hyperintensity on T2-weighted images. After administration of gadolinium, the tumor may show heterogeneous enhancement.

Pathology. Neurocytomas are composed of small round cells with neuronal differentiation. Central neurocytomas correspond histologically to WHO Grade II with a MIB-1 labelling index of <2%. When similar tumors show atypia, mitoses, vascular proliferation and/or necrosis histologically and a MIB-1 index >2%, they are designated as "atypical neurocytomas" [69]. Yet, this description of atypical neurocytoma has not been accepted into the new 2016 WHO classification for brain tumors, although it has been mentioned in different publications [30].

The cells of neurocytomas have a slightly eosinophilic cytoplasm with clear perinuclear halos, which is similar to oligodendrogliomas [65]. For atypical neurocytomas, common histological findings include delicate fibrillary neuropil-like matrices, capillary-sized blood vessels in a branching pattern, foci of calcification (in one-third of the cases), and perivascular pseudorosettes [69]. Because neither imaging nor histopathology help differentiate spinal cord neurocytomas from similar looking tumors (i.e., oligodendroglioma or ependymoma), immunohistochemistry is necessary for differential diagnosis. Neurocytomas are immunopositive for synaptophysin (SYN), which is considered the most reliable immune-marker for the diagnosis of neurocytoma [30, 66, 70] Microtubule-associated protein-2 (MAP-2) is another relatively specific marker for neurocytomas [71]. NeuN and anti-HU antibodies are also considered to be useful and demonstrate nuclear staining in most cases [72, 73].

Surgical Intervention. The treatment of choice for spinal cord neurocytomas is achieving gross total resection. Yet a review of the literature reveals that gross total resection was achieved in less than 80% of cases. Some will therefore advocate the use of radiotherapy as adjuvant therapy [67]. Tumor recurrence rate is more closely related to the histologic atypia and a high MIB-1 labeling index [65]. As for now, the two main parameters that predict progression or recurrence are the extent of resection and histology (i.e., the presence of atypia and a degree of MIB-1). A recent article reviewed EVNs, analyzed their epidemiology, clinical and radiological findings, locations, treatment and prognosis, and concluded that epidemiology was not definitely known because they are quite rare. They are also associated with a poor prognosis compared with o central neurocytomas [74].

Adjuvant Therapy. The use of adjuvant therapy following subtotal resection is still controversial. There are not enough cases to build up solid data to outline a complete treatment paradigm. Even chemotherapy that was shown to have a role in intraventricular central neurocytomas has not been utilized in spinal cord neurocytomas [70, 75]. The use of radiotherapy following subtotal or partial resection is not well established and has shown contradictory results [76, 77].

21.5.6 Subependymomas

Introduction. Subependymomas (WHO grade I) occur very rarely in the spinal cord, accounting for only 2% of all symptomatic cases [78]. Spinal cord subependymomas (SCSEs) are a benign, non-invasive, slow-growing, WHO grade I spinal cord tumor [30]. SCSEs were first reported in 1954 and since then, 72 cases of SCSE have been reported [79]. Like its name, it has some similar features to ependymoma, yet its clinical course and outcome differ. The tumor tends to grow slowly and have a relatively low recurrence rate in cases of subtotal resection. Mixed tumors composed of subependymoma and ependymoma (WHO Grade II) account for approximately 15% of symptomatic subependymoma cases, including all levels of the central nervous system [80].

Clinical Presentation. Like in other intramedullary lesions, signs and symptoms are a consequence of tumor location, amount of cord edema, and mass effect on viable cord. Intramedullary subependymomas usually occur in the cervical and cervicothoracic regions. Patients usually first present with either back pain or sensory deficits [78].

Diagnosis. SCSEs were most commonly located at the cervical spinal cord, followed by the thoracic spinal cord and the lumbar spinal cord. It is very hard to distinguish SCSEs from ependymomas since common MRI findings of SCSEs are iso to low.

Signal intensity on T1-weighted imaging and high signal intensity on T2–weighted imaging, and these features are not different from those associated with a spinal cord ependymoma (Fig. 21.6). However, SCSEs tend to have eccentric locations, relatively poor gadolinium enhancement, and relatively intra-tumoral cysts and calcifications, all of which are different in spinal cord ependymomas [79].

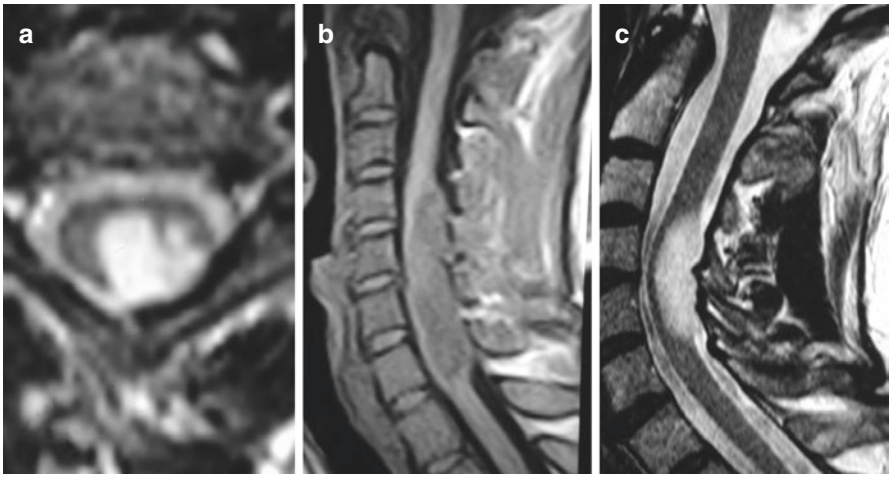

Fig. 21.6 Cervical cord subependymoma. This intramedullary lesion tends to be eccentric (**a**), isointense in T1 sequence (**b**), and hyperintense in T2 weighted images (**c**)

Pathology. The histopathogenesis of a subependymoma has yet to be revealed clearly. An intracranial subependymoma is currently thought to derive from subependymal glial precursor cells, which are bipotential cells with the ability to differentiate into either ependymal cells or an astrocyte [81]. For SCSEs, the description suggested by some publications includes subpial spinal white matter progenitor cells as a possible histogenesis for a better explanation of the predominant peripheral and exophytic location [82]. The macroscopic eccentric location of subependymomas suggests that they might derive from the subependymal cell plate, known as the residual periventricular matrix layer [83]. Other histological features—including sparse cellularity, clusters of nuclei and microcyst formation on a background of a dense fibrillar matrix, and perivascular pseudorosettes—can be occasionally seen and are usually inconspicuous [78, 84, 85]. The immunohistological phenotypes are different from ependymomas by the modest expression of epithelial membrane antigen, probably because there are few ependymal rosettes, and by the expression of GFAP and S-100 [78].

Surgery. Recommended treatments for SCSEs are still not well established. Several publications advocate achieving gross total resection in order to get good clinical outcome [83, 86]. On the other hand, since the literature showed it is hard to achieve a gross total resection in these cases (the rate of gross total resection in previous publications was 73.9% [79], mainly because of the infiltrative nature of the tumor, which leads to poor dissection plane between the tumor and the spinal cord), other authors have shown that subtotal resection or partial resection was sufficient for a good clinical outcome when gross total resection is not feasible. [87, 88].

Adjuvant Therapy. There is no treatment paradigm for SCSEs other than surgery. This is because tumor behavior is very indolent, even with subtotal resection. Hence, there are no data regarding the use of chemotherapy or radiation therapy for spinal cord subependymoma. For intracranial subependymomas, there are more

data suggesting treatment with radiotherapy for subtotal or partial resection, yet radiotherapy did not show a significant association with longer survival [81]. Yet, the use of adjuvant therapy for spinal cord subependymomas is not well established.

21.5.7 Spinal Cord Germinoma

Introduction. Primary intramedullary spinal germ cell tumors are exceedingly rare. As such, there are no established treatment paradigms. Germ cell tumors account for 1% of all CNS tumors, and they are seen more frequently in Japan (3%) and East Asia (12.5%) [89]. The more common anatomical locations are the pineal or suprasellar regions, and less frequently in the brain midline structures. Spinal metastases resulting from germ cell tumor seeding have been well documented in previous publications [90, 91]; however, it is extremely rare that germ cell tumors are be found within the spinal cord as a primary tumor [92].

Primary spinal cord germinomas (SCGs) are very rare. There are fewer than 50 cases published in the literature [93]. Most cases of primary SCGs have been described in young Japanese and adult Chinese patients. Germinomas in the spinal cord can be an intramedullary lesion (majority of the cases) but can also be purely extramedullary in rare cases. The strongest prognostic value was found to be presence of syncytiotrophoblastic giant cells (STGCs), which are associated with a higher rate of recurrence, and hence morbidity and mortality [92].

Clinical Presentation. Primary spinal cord germinomas present in young adults, usually in the second and third decades of life. There is no sex predominance. (Past studies showed a slight male predominance that was not seen in later reviews.) The duration of symptoms is quite heterogeneous, ranging from 1 to 57 months [93]. Like in other spinal cord tumors, the location of the spinal cord germinoma dictated the symptoms and presentation, with back pain and motor and sensory deficits being the most common symptoms and signs of disease. The classic location is the thoracic spinal cord, followed by the transition zones of the cord: thoracolumbar and cervicothoracic.

Diagnosis. There are no specific imaging characteristics of SCGs, hence the differentiation from other spinal lesions like ependymoma and astrocytoma is difficult [93, 94].

The majority of lesions were hypointense to isointense on T1-weighted images, isointense to hyperintense on T2-weighted images, and showed some degree of gadolinium contrast enhancement [95]. Intratumoral and peritumoral cysts can be found [94–96]. Yet, even within the small number of cases described with SCGs, there are a wide range of imaging characteristics, including non-enhancing lesions [96–98]. Hence, the only way to diagnosed and differentiate SCGs from other spinal cord lesions is by biopsy and histologic analysis. As for other ancillary tests, like intracranial germ cell tumors, CSF and serum biomarkers (Alpha fetoprotein [AFP], Beta human chorionic gonadotropin [B-HCG]) can be a significant aid for diagnosis, especially in the case of germinoma (AFP: negative; B-HCG: mildly elevated). Yet in rare cases, SCG can present with elevated AFP.

Pathology. Pathologic and histological features are identical to intracranial germinomas. The presence of STGCs in a pathohistological specimen is an indicator of a more aggressive lesion and poorer prognosis [93].

Surgery. Primary spinal cord germinoma have the same radiosensitivity like intracranial germinomas. Hence, after tissue diagnosis a relevant treatment can be radiotherapy. The known literature about SCGs state that the vast majority of germinomas were without good margins with surrounding tissue [92, 96, 97, 99]. Therefore, achieving a gross total resection without damaging normal structures can be a challenging task for a neurosurgeon, even with electrophysiological monitoring. This paradigm along with the known radiosensitivity led to the fact that a biopsy and a frozen section analysis are recommended [92, 96, 99, 100]. The literature shows that a gross total resection was performed in 23% of cases, a subtotal resection was performed in 52% of cases, and only a biopsy in was performed 25% of cases. We believe that the surgeon needs to bear in mind all these characteristics, and if a frozen section during surgery states germinoma, a careful tumor decompression should be done, relieving tension and mass effect, and leaving as small a tumor load as possible for the adjuvant therapy following surgery.

Adjuvant Therapy. Germinomas are highly responsive to radiotherapy; all patients reported in literature (except one) received some form of radiotherapy. The radiotherapy protocol takes into account the fact that the surrounding tissue is spinal cord and therefore the majority of patients described in literature only received local spinal irradiation. The literature also suggested that local tumor bed irradiation appears sufficient in patients without STCG and with low levels of B-HCG [92].

The role of chemotherapy in spinal germinoma has yet to be defined. Intracranial germ cell tumors are highly sensitive to chemotherapy, especially to platinum and alkylating agents. The common chemotherapeutic agents found to be effective for CNS germinomas are cisplatin, bleomycin, vinblastine, and etoposide [92]. Chemotherapy is described as part of the treatment in 54.5% of cases, with carboplatin and etoposide the most frequently used regimen due to germinoma sensitivity to these agents [93].

The recurrence rate of SCGs is less than 10%, according to the literature, but rises to 50% when STGC is positive. Some publications advocate limited volume radiotherapy combined with systemic chemotherapy in patients with a high risk of recurrence (e.g., positive STGC). To reduce endocrine and neurocognitive side effects, craniospinal radiation should be used as a last resort in patients with recurrence [92].

21.6 Spinal Cord Developmental Tumors

Developmental tumors are slow-growing group and include dermoid tumors, epidermoid tumors, and teratomas. They are generally benign but can reoccur if resection is subtotal or in the presence of more aggressive tumor histology and biology (e.g., anaplastic teratoma). Treatment is resection with a goal of achieving gross total resection, while adjuvant therapy is reserved for recurrent tumors that are not amenable for resection or more aggressive tumor.

21.6.1 Spinal Cord Teratomas

Introduction. Teratomas are germ cell tumors that include all three embryonic germ layers: the endoderm, mesoderm, and ectoderm. Teratomas are extremely rare and account only for 0.1% of all CNS tumors, and except for in the sacrococcygeal region, teratomas constitute less than 0.5% of all intraspinal tumors. Primary cranial teratomas in the CNS are usually known to arise in the pineal gland and suprasellar regions [101, 102]. Teratomas affecting the spine and—more specifically—the spinal cord are very rare. Spinal teratomas can be mature, immature, and malignant based on histological degree of differentiation. Most of the cases of intramedullary teratomas known to literature are of adults.

Clinical Presentation. Spinal cord teratomas (SCTs) are quite rare in adults, and when they do present, it is usually during the third to fifth decades of life [103]. SCTs tend to be located in the thoracic and thoracolumbar regions. Reported cases have demonstrated that intramedullary teratomas are seen predominantly in the thoracic and lumbar region, and only a few reports document spinal teratoma in the cervical spine [104–106]. For adults, a significant difference in the time to diagnosis between both genders has been found, with men diagnosed fairly early in relation to their symptoms duration while women tend to be diagnosed after a much longer period [103]. Actual symptoms depend on the location and extent of disease within the spinal cord, as well as cord edema and mass effect.

Diagnosis. The modality of choice is MRI, with CT scan used as adjuvant test to evaluate bony deformation (Fig. 21.7). In a recent review of thoracolumbar teratomas in adults, 37.5% of the cases had some type of congenital anomaly associated with the lesion, such as an anomalous vertebra fusion, spina bifida, congenital scoliosis, and split cord malformations [103]. MRI characteristics that suggest teratoma

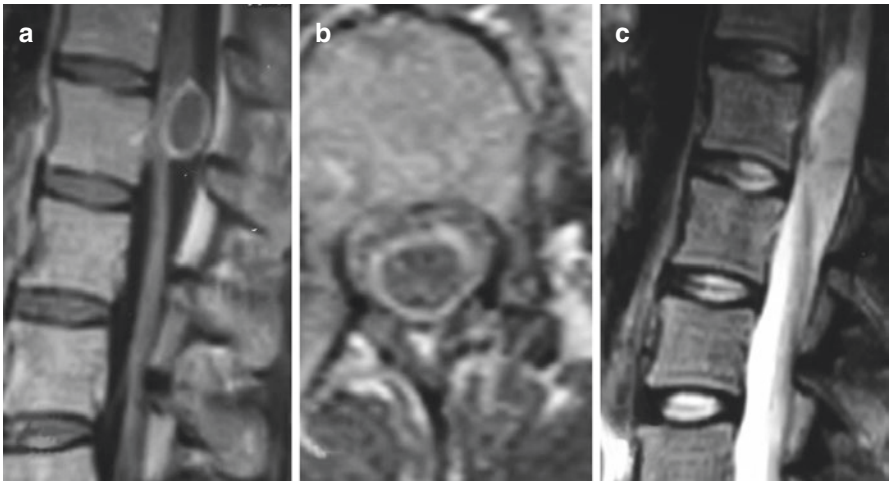

Fig. 21.7 Spinal cord teratoma. Different sequences—T1 after gadolinium injection (**a, b**); T2 weighted images (**c**)—describing spinal cord teratoma

(besides the anatomical location) are tissue heterogeneity manifested by mixed signals with inhomogeneous intensities on T1 and T2-weighted images (the variability could represent different tissue types) [107, 108]. These MRI findings, along with bony deformation as mentioned before, highly increase the suspicion of a possible intramedullary teratoma [107, 108].

Tumor markers in the serum and CSF can assist in diagnosis and to some extent in follow-up. A mild elevation in a tumor marker, such as serum B-HCG in a patient with a spinal teratoma was documented, and the B-HCG levels were shown to decrease to a normal range postoperatively, suggesting that patients with spinal teratomas can have mild elevations in B-HCG due to secreted components of the tumor [109].

None of the modalities can lead to a clear preoperative diagnosis of intramedullary teratoma, and hence histology is still the gold standard.

Pathology. Histopathologic examination is the gold standard for definite diagnosis as mentioned above. Teratomas are classified classically by the presence of all three germ layers. In cases when only 1–2 layers are observed, the diagnosis of teratoma cannot be completely ruled out since overgrowth of one germ line over the other sometimes occurs [110]. Teratomas are classified as lesions composed of all 3 primitive germ layers. The exact mechanism that leads for teratoma formation in the spine cord is not known. Yet, there are two theories proposed to explain the phenomenon: misplaced germ cell theory and dysembryogenic theory [103]. The advocates of the misplaced theory suggest that teratomas originate from disordered migration and misplacement of the primordial germ cells from the yolk sac, typically into a midline location, and are not true neoplastic lesions. On the other hand, the advocates of the dysembryogenic theory suggest that teratomas are caused by disordered differentiation of pluripotent cells in an aberrant developmental environment in the primitive streak or caudal cell mass [103, 111, 112].

Surgery. The mainstay of treatment is still resection of the tumor with relief of mass effect. The goal of surgery is gross total resection, if possible. Based on previous data with gross total resection, only one case was reported with recurrent tumor 10 years after surgery [103]. Yet, a review of the literature showed that avoiding recurrence was achieved only in half of the cases, and then depends on actual histology and tumor characteristics; adjuvant treatment may then be warranted. Close follow-up can be used in cases in which some residual tumor is present but the mass effect on the cord is resolved, the symptoms and signs are resolved, and no malignant characteristics are found in the histology. When looking at the different types of teratomas, mature types have been shown to have a benign postoperative course during long-term follow-up, even with partial resection. On the other hand, recurrences were most commonly encountered with immature or malignant teratomas with a recurrence rate of about 10% (these data are combined for any spinal teratoma, not just intramedullary) [113].

Cases with elevated B-HCG before surgery can serve as a tumor marker for monitoring tumor recurrence, but the full utility of this has yet to be studied.

Adjuvant Therapy. In cases in which the teratoma harbors malignant histologic features, radiotherapy is recommended as an adjuvant therapy to prevent

recurrence, even if gross total resection was achieved by post operation imaging [109]. In the presence of benign histology, avoiding radiotherapy after initial surgery seems to be appropriate. In cases of tumor recurrence or progression and a previously benign histology, it is better to choose surgery first as a treatment modality before considering radiotherapy, which even then may have doubtful efficacy [109]. In some cases, chemotherapy should be considered, with cisplatin-based chemotherapy regimens as for other germ cell tumors mentioned before.

21.6.2 Spinal Cord Dermoid and Epidermoid.

Introduction. Intramedullary dermoid and epidermoid cyst are very rare. There are several publications concerning intramedullary dermoid cysts, but almost no publications about epidermoid cysts [114, 115]. Yet, management of the two is similar; hence, the reader can regard the management of dermoid and epidermoid cysts in a similar way. Spinal epidermoid cysts are relatively rare lesions and constitute 0.6–1.1% of all intraspinal tumors [114, 116]. The vast majority of intraspinal epidermoid cysts are seen in intradural and extramedullary locations. Intramedullary epidermoid cysts are very rare, and the majority of cases are associated with a dermal sinus or an extramedullary extension [116, 117].

Intramedullary dermoid cysts are benign and rare spinal lesions with an incidence of 5–7% of all primary intradural tumors in the pediatric population [118]. Dermoid lesions are commonly associated with the dermal sinus, which is seen in half of the cases [119]. The most common location for dermoid lesion is the lumbar spine and conus medullaris area [118, 120].

Clinical Presentation. Dermoid and epidermoid lesions can present as any other spinal cord lesions, causing symptoms in relation to their location and concomitant mass effect and cord edema. They infrequently present acutely because of either rupture within the cord or infection from the associated dermal sinus, causing recurrent meningitis or, rarely, an intramedullary abscess. There are only isolated reports in the literature of ruptured or infected dermoid cysts with an acute presentation [121]. In children, a dermal sinus is the most common source of an intramedullary abscess and the cause of intramedullary abscesses in 45% of pediatric patients. In contrast, a dermal sinus is the cause of only 24% of intramedullary abscesses in adults [121–123].

Dermoid lesions associated with a dermal sinus will most likely present within the first decade of life because of infection-related pathologies (e.g., sinus causing recurrent meningitis, or intradural and intramedullary abscess) [124]. When not associated with a dermal sinus, most patients with a dermoid cyst present because of mass effect on neural tissues, causing lower back pain or radiculopathy [125]. Other important presenting scenarios are of chemical meningitis, hydrocephalus, and other complications secondary to ruptured cysts [125, 126].

Diagnosis. MRI is the modality of choice in both cases for making diagnoses, as well as thorough inspection of the back for evident skin malformations that suggest dermal sinus. Radiological findings of intramedullary epidermoid cysts may be

quite variable because of the disparity in signal intensity secondary to the variable lipid and protein composition of these lesions. On MRI, non-homogeneous hypointensity on T1-weighted images and hyperintensity on T2-weighted images are characteristic, but varying signal intensity between the different cases as well as between the different parts of the same cyst is not uncommon [114, 116]. These lesions are usually fairly well-defined with no surrounding edema and minimal peripheral enhancement after the gadolinium injection. Yet, sometimes it is hard to define the borders or visualize a plane between the lesion and the cord because of repetitive inflammation at the margins of these lesions, and may lead to gliosis along the margins [115].

For dermoid lesions, a dermoid cyst without infection can be recognized by the signal characteristics of fat, lack of enhancement, and heterogeneous intensity seen in T1 and T2-weighted images [121]. In case an intramedullary abscess is present, there will be findings of enhanced intramedullary mass with peripheral rim enhancement and cord edema appreciated in T2-weighted images [127]. In cases with a dermal sinus, the abscess can usually be seen in T2-weighted images as a tract connecting the canal to the skin.

Pathology. Dermoid tumors are of ectodermal and mesodermal origin and are more developed [128]. Epidermoid tumors are of ectodermal origin and contain an inner layer of stratified epithelium and a fibrous capsule [128]. The distinction between types is somewhat blurry. In general, an epidermoid tumor is ectodermal in origin and contains an inner layer of stratified epithelium and a fibrous capsule [129]. A dermoid tumor is an orderly group of ectodermal and mesodermal elements. The cyst wall consists of the epidermis, corium, and cutaneous appendages (sebaceous glands and hair follicles) within the lining of stratified squamous epithelium and often pockets keratins, cholesterol crystals, and hairs [128, 130]. The embryologic theory regarding the creation of these 2 lesions is still debated. The dermal sinus, regardless to the presence of dermoid or epidermoid cyst, is formed by the failure of separation of the surface ectoderm from the neural tube [131]. Already in the nineteenth century, it was thought that dermoid and epidermoid cysts were formed as a result of a defect in neural tube closure, which occurs between the third and fifth gestational weeks [115, 118]. Epidermoid and Dermoid cysts can be congenital as well as acquired, most likely derive from totipotent ectoderm inclusions, which can give rise to all the epidermal and dermal elements found within these cysts [118]. Epidermoid cysts, especially intramedullary epidermoid cysts (which are usually congenital), are frequently associated with developmental abnormalities such as spina bifida, dermal sinus, meningomyelocele, diastematomyelia, and enterogenous cysts [114, 132]. Microscopically, the epidermoid cyst is lined by a thin fibrous outer layer of stratified or flattened epithelial cells, and filled with soft, flaky, and pearly material composed of keratohyalin granules, ghosts or skeletons of epithelial cells, debris of dead cells, and some fat [133, 134]. The cyst normally does not contain any liquid component; however, free fatty acids and cholesterol can be carried into the mass by inflammatory cells in response to necrosis of the degenerating squamous cells. In addition, less frequently in comparison to dermoid cyst, epidermoid cysts very rarely will degenerate into an abscess, which is almost

always associated with a dermal sinus [115]. When it does, usually a dermal sinus will be found [135].

The predilection of the lumbosacral region and of the conus medullaris for dermoid cysts is a result of the caudal neuropore being the last to close in the formation of the neural tube and the conus medullaris developing from the caudal mass of cells by secondary neurulation [121]. For epidermoid cysts, the most common location is the thoracic spine [114].

Surgery. Surgical resection is the preferred treatment modality. For epidermoid lesions, radical removal of the cyst should be the goal of surgical intervention. Yet, total removal of the epidermoid cyst is seldom accomplished in the majority of cases, and a high rate of tumor recurrence has been subsequently reported. Usually, decompression of the cyst content is easily done. However, the cyst wall is adherent to surrounding cord parenchyma, hence making the excision of the cyst wall dangerous with a high likelihood to cause neurological deficit [114, 135].

For dermoid lesions, in case there is involvement of intramedullary abscess, most publications in the literature support early intervention with resection of the abscess, sinus tract, and the dermal cyst wall, if possible [121]. The major factor preventing the total excision of an intramedullary dermoid cyst is dense adhesion of the wall of the cyst to the surrounding neural structures. The cyst wall should be excised in order to prevent recurrence. Yet, especially in the context of intramedullary infection, removing the cyst wall can be very difficult and might end up with permanent deficit.

Adjuvant Therapy. Surgical resection—and if needed, repeat resection—is the mainstay of treatment. The use of adjuvant treatment, like radiotherapy, is anecdotal and debated [136].

21.6.3 Spinal Cord Lipomas

Introduction. Spinal lipomas are usually extramedullary lesions and are typically found in the lumbosacral spine with spinal dysraphism. Truly intramedullary spinal cord lipomas are rare, comprising less than 1% of all spinal cord lesions [137]. After surgical intervention, debulking, and excision, patients may only exhibit partial recovery because of the intramedullary location of these tumors, and close follow up with further surgical intervention is sometimes warranted.

For lumbosacral lipomas, two types have been described by Pang, et al. Dorsal lipomas have a lipoma-cord interface on the dorsal surface of the lumbar canal and an intact distal conus and intact sacral nerve roots [138]. A transitional lipoma will involve the conus as it grows ventrally and is often described as asymmetric. These types of lipomas are formed as part of a neurulation defect, allowing mesenchymal cells into the neural groove and contact ependymal cells. On the other hand, although true intramedullary spinal cord lipomas are rare, they are also typically associated with spinal dysraphism. It is hypothesized that mesenchymal cells become misplaced during neural tube development and migrate into the developing neural tube before it closes, which then later develops into a lipoma [139]. Another theory

suggests that adipocytes may arise from the cells giving rise to spinal cells. Mesenchymal cells form spinal blood vessels due to the direction of neural crest cells. However, if neural crest cells are defective, they are unable to inhibit the mesenchymal cells to prohibit them from developing into other cell types, such as adipocytes [139]. Lipomas associated with spinal dysraphism are—in fact—considered to be hamartomas, while lipomas not associated with dysraphism are considered true neoplasms. In the literature, intramedullary spinal cord lipomas are represented through scattered case reports of single patients and their presentation and treatment. One case series six patients treated in an 8-year period at a single institution [140]. While another series demonstrated 14 patients over a period of 12 years [141]. Both series described the need for surgical resection to preserve neurologic function.

Clinical Presentation. Intramedullary lipomas present either in early infancy or in adults in the second or third decade of life. Children and infants present with "floppy baby syndrome" due to spinal cord damage resulting from birth trauma. Adults usually describe an indolent course with slowly progressive neurologic deficit. Neurologic deficit can present as numbness, weakness, pain, atrophy of muscles, or myelopathy. Deficits may worsen as adipocytes grow due to fat deposition in normal metabolic fat cells [139]. Intramedullary spinal cord lipomas are usually present in the thoracic spine, followed by the cervicothoracic junction, and less frequently as isolated cervical spine pathologies [142].

Diagnostic Imaging. MRI remains the most sensitive imaging modality for diagnosing intramedullary lipoma. Fat is hyperintense on T1, hypointense on T2, and does not enhance with contrast (Fig. 21.8). Fat suppression sequences can be performed to help differentiate fat from blood or calcification, which will remain hyperintense on T1 fat suppressed images.

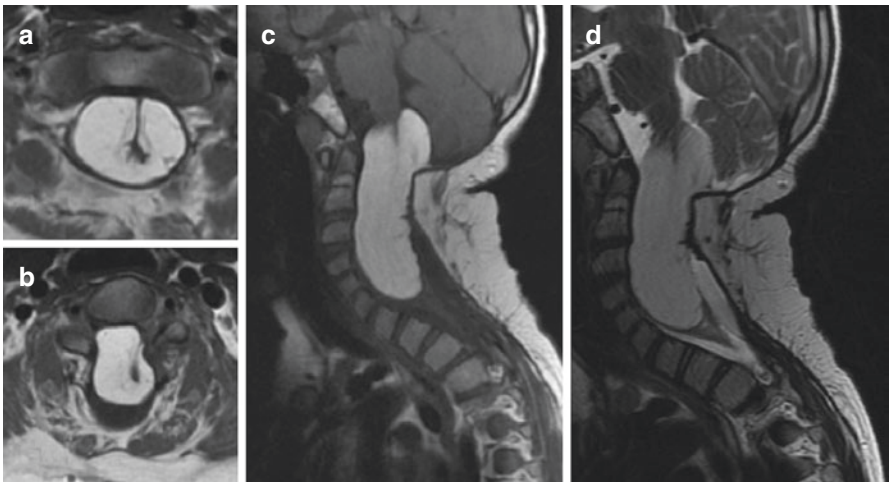

Fig. 21.8 Cervical spinal cord lipoma. True intramedullary lipomas are rare lesions. They tend to appear hyperintense on both T1 (**a, b, c**) and T2 (**d**)

Pathology. Intramedullary lipomas are similar in pathology to extradural lipomas in that they are comprised of mature adipocytes with no atypical cellular features [142]. The cells grow in fibrous connective tissue. Other cells, such as muscle, bone, and neural tissue, may also be found within lipomas.

Surgical Intervention. Management strategy for spinal cord lipomas are tailored to each individual patient. Oftentimes, observation is utilized when the lipoma is diagnosed incidentally. The lipoma can be observed for long periods of time until there is neurologic deterioration. When patients develop neurologic symptoms, spinal decompression with subtotal resection is considered due to the risk of further neurologic decline from surgical removal of the tumor itself. The tumor is often adherent due to the "sticky" nature of adipocytes with surrounding neural tissue. Intraoperative ultrasound can be used to delineate the extent of the lesion as the lipoma is anechoic [139]. Lasers can also be used intraoperatively as the laser will vaporize the adipocytes due to their high water content. Intraoperative physiologic monitoring is recommended to achieve maximal safe resection.

Intraspinal lipomas can replace normal tissue during development instead of compressing it as in other neoplastic processes. Therefore, there is less redundancy in functional pathways and a greater chance of permanent neurologic injury after surgical resection [139]. It is also, therefore, cautioned that while observation is a valid option upfront, surgical decompression is recommended at early signs and symptoms of tumor growth before spinal cord damage occurs as it may be irreversible [139].

Reoperation may be necessary on remnant tumor, if symptoms reoccur due to hyperplasia of the adipocytes. Additionally, tethering of the cord may occur due to the adherent nature of the surgical cavity and also decreased movement of the cord in the dural sac due to the cord's bulk prior to tumor removal [138].

Adjuvant Therapy. There are no studies in the literature advocating for adjuvant therapy for intramedullary spinal cord lipomas. Intramedullary lipomas are slow growing tumors and, therefore, not good targets for radiation or chemotherapy.

21.6.4 Holocord Intramedullary Tumors

Introduction. This section is deals a phenomenon that can occur with different pathologies rather than with a specific tumor. The first report of a holocord tumor was made by Cushing in 1927; histology showed it was ependymoma. The incidence of longitudinally extensive tumors involving the cervical, thoracic, and lumbar spine is very low (<1% of intramedullary lesions); hence, few studies in the literature exists on the management [57]. The agreed definition of holocord intramedullary tumor is for a lesion that harbors the majority of the spinal cord. It is acceptable that the approach should be established upon the treatment of other intramedullary tumors [86, 143].

Clinical Presentation. Presenting symptoms can be as for any other intramedullary tumor. Yet in some cases, the decompensation of the neurological status can

affect several regions of the spinal cord at once, leading to diffuse deficits. Since in most of the cases the pathologies that tend to lead to holocord tumors are of low-grade tumors, patients tend to present late with large and extensive tumors.

Diagnostic Imaging. The main tool as for other intramedullary tumors is MRI. The characteristics are similar to the non-holocord tumors but with the same histology. Large areas of cysts can be found in holocord tumors that can be indistinguishable from solid tumors on T2-weighted studies owing to high protein content (Fig. 21.9). Yet after gadolinium injection, these cysts do not enhance [144, 145].

Pathology. From the scant literature available on this topic, there is a wide variety of tumors that present as holocord tumors, including astrocytoma of different kinds, and ependymoma. In any case, the majority of the cases of low-grade tumors present with relatively favorable biological behavior.

Surgical Intervention. There is not enough literature to establish an evidence-based approach, yet most publications from programs with extensive experience in surgeries of the spinal cord advocate aggressive surgical resection of these lesions [57, 146]. Early treatment remains necessary in preventing further progression of symptoms and possibly to improve neurological function [59, 146–149]. However, there are additional challenges that face the surgeon performing the extensive resection required in removing a holocord tumor. Some of these challenges are related to potential surgeon fatigue, thus mandating multi-stage procedures [57, 150]. The staged procedure is advocate in cases in which there is extensive tumor (usually more than 15 spinal levels), and the patient has big body dimensions. The

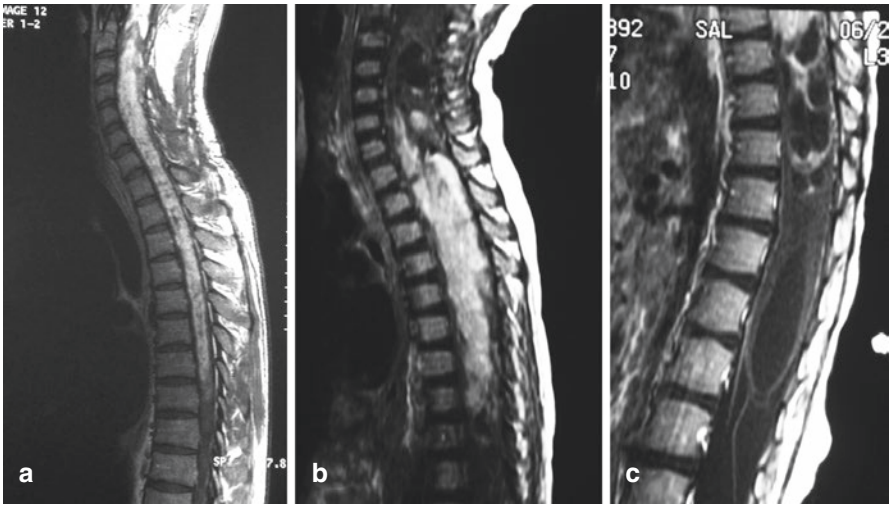

Fig. 21.9 Holocord intramedullary tumors. Large tumors that harbor the majority of the spinal cord and can be with different histology: (**a**) astrocytoma; (**b, c**) Ganglioglioma. The tumor can harbor large cysts that are very hard to distinguish on regular T2 weighted imaging, but will not enhanced on T1 after gadolinium injection

advantages for staging are in focusing on a smaller lesion each time, which will cut down on anesthesia time, and this may result in a more complete resection. Surgeon fatigue should be taken into account as well, since the goal is to achieve gross total resection, while still preserving function. Long operations can hinder in achieving this goal. The two operations will typically entail a cervical operation and a thoracic operation [57]. Follow-up for these patients requires special attention to spinal deformity and instability due to the extensive bony opening needed for the initial surgery. This represents an increased source of morbidity for patients with holocord tumors.

Adjuvant Therapy. As written before, there is no clear established treatment paradigm for holocord tumors. Most oncologists will treat their patient according to the actual pathology regardless for the size of the tumor. Previous publications described the use of neoadjuvant radiotherapy but without any significant benefit [151]. More established practice is the use of adjuvant radiotherapy when gross total resection is not achieved. Recommendations are partially based on expert experience published as case series over the years, but it is based mainly on the treatment paradigm for the same non-holocord tumor histology. Hence, if gross total resection is achieved, most experts will recommend close follow-up without adjuvant treatment. If the resection is partial and the pathology is favorable (e.g., pilocytic astrocytoma), most experts will recommend continued follow-up without treatment and redo surgery as needed to decompress the cord when symptoms ensued. The use of chemotherapy, like temozolomide, is anecdotal as well and were tested mainly in very young children in order to postpone radiation therapy or a more aggressive resection.

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Dumbbell Tumors of the Spine

22

Mirza Pojskić and Kenan I. Arnautović

22.1 Definition

The term "dumbbell tumor" was initially introduced by Heuer in 1929 to describe spinal tumors that acquire an hourglass shape as they encounter an anatomic barrier, such as dura mater, a nerve-root foramen, or other bony elements, as they grow [1–3]. Spinal tumors with significant intraspinal and paravertebral involvement are classified into four types based on the location of the tumor: intramedullary, intradural extramedullary, epidural, and dumbbell-shaped [4]. Dumbbell tumors can be assigned to various groups according to the constricting structure and other details of tumor location [5]. These days, the term "dumbbell tumor" does not refer to the hourglass shape, but rather acts as a stand-in conceptual term referring to separate tumors that connect and comprise two or more separate regions, such as the intradural or epidural space, or locations outside the spinal canal [6].

Schwannoma and meningioma are the two most common intradural spinal tumors. Ninety percent of spinal dumbbell tumors are schwannomas [4], and up to 33% of schwannomas have a dumbbell form [7]. Multiple schwannomas more frequently represent a clinical manifestation of neurofibromatosis type 2 [8]. Non-schwannoma non-neurofibroma dumbbell tumors of the spinal cord include 28 different pathological entities: hemangioma [9, 10]; meningioma [11]; malignant peripheral nerve sheath tumors [12]; neurogenic paravertebral tumors with origin from neurogenic elements within the thorax [13], including neuroblastoma [14], ganglioneuroblastoma [14], and ganglioneuroma [15]; hemangioblastoma [16];

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liposarcoma [17]; lipoblastoma [18]; angiomatosis [19]; angiolipoma [20]; rhabdomyosarcoma [6]; spine extraosseous chordoma (SEC) [21]; mesenchymal chondrosarcoma [22]; soft tissue chondroma [23]; osteochondroma [24]; malignant glomus tumor [25]; malignant solitary fibrous tumor [26]; plasmacytoma [27]; metastasis [28]; Ewing sarcoma [29]; atypical teratoid rhabdoid tumor [30]; lymphoma [31]; lymphangioma [32]; meningeal melanocytoma [33]; small cell malignant tumor [34]; and peripheral primitive neuroectodermal tumor (PNET) [35]. In addition, malignant dumbbell tumors accounted for 64% of cases in pediatric patients and 2.8% in adult patients [6].

22.2 Epidemiology

In large series of spinal cord tumors, the incidence of dumbbell shaped lesions varies between 6% [3] and 24% [2, 6–8, 36, 37]. There is a significantly higher rate in the cervical spine of up to 44% [6].

22.3 Classification

The first classification of dumbbell tumors was the Eden Classification, which served as the gold standard for decades [2]. Eden designated four cross-sectional configurations for dumbbell tumors in 1958, a time at which neither computed tomography (CT) nor magnetic resonance imaging (MRI) had been developed (Fig. 22.1). Although this is a morphological as opposed to a surgical classification, it was postulated that Type I, II and III tumors can be operated on through a posterior route, and that the anterior approach is appropriate for Eden Type IV tumors. In cases of Type II and III tumors (i.e., the extraspinal component of the tumor compresses and shifts the vertebral artery and extends anteriorly beyond the vertebral artery), combined anterior and posterior approaches can be considered [38]. One series of 118 cases showed that Type III tumors were the most frequent type (53%) followed by Type II (33%), Type I (9%), and Type IV (5%) [6].

There are seven other classifications of dumbbell tumors, in addition to the Eden Classification. Liu et al. introduced an anatomic classification of dumbbell tumors in 2017 [34]. The largest transverse section of the tumor was divided into four areas; each area needed different surgical procedures. A modification of the Eden classification due to CT and MRI advances was provided by Toyama et al. [39]. In addition to an axial configuration, Toyama et al. categorized dumbbell tumors in an imaging-based anatomic 3-dimensional classification according to the number of intervertebral and transverse foramina involved for each tumor, which was better suited for surgical planning [5]**.** Special sub-classifications for cervical dumbbell tumors of the spine were developed by Hiramatsu [40], which classified both the horizontal and craniocaudal spread of dumbbell tumors. Jiang et al. developed the so-called Peking University Third Hospital (PUTH) anatomical classification of the cervical dumbbell tumors in 2009 [41], which differentiated between erosive or compressive

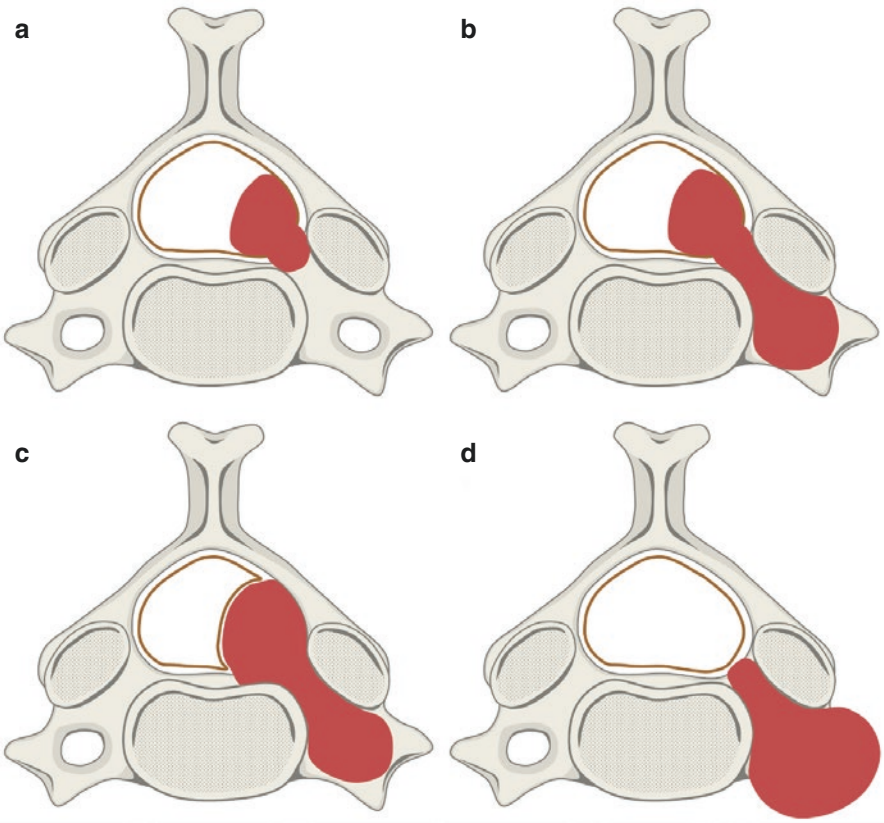


Fig. 22.1 Eden Classification of the dumbbell tumors of the spine. (**a**) Type 1: intradural and extradural. (**b**) Type 2: intradural, extradural, and paravertebral. (**c**) Type 3: intradural and paravertebral. (**d**) Type 4: Foraminal and Paravertebral

bony change. This classification included intraspinal lesions in front of the spinal cord, and standardized surgical procedures according to category. Sridhar et al. proposed a 5-type classification system that was limited to giant invasive dumbbell spinal schwannomas [42]. Modifications of the Shridhar et al. classification were provided by Park et al. [43] and Kotil et al. [44].

22.4 Differential Diagnosis

22.4.1 Symptoms

Presentation of spinal dumbbell tumors depends on the size and location of the tumor. Most patients with spinal dumbbell tumors present with similar symptoms, regardless of the underlying pathology. Non-radicular pain is a common symptom,

followed by sensory deficits and gait disturbances, radiculopathy, motor weakness, ambulation, and bowel and bladder-function impairment [45, 46]. Non-radicular pain can persist through the follow-up, while radiculopathy tends to completely resolve following surgery [46]. Extraforaminal thoracic giant dumbbell tumors (e.g., giant schwannomas) can compress the lungs and vascular structures, and giant lumbosacral tumors can compress abdominal and visceral structures, resulting in urination problems and constipation [47]. Furthermore, tumors that are located in the cauda equina can cause vertebral erosion, resulting in instability and pain [47]. Vascular lesions can present with bleeding that mimics spinal subarachnoid hemorrhage or leads to progressive neurological deficits [48, 49]. Known primary tumor in the patient history could indicate the presence of metastasis. In pediatric patients, rare childhood tumors—like neuroblastoma, ganglioneuroma, atypical rhabdoid theratoid tumor, Ewing sarcoma, or lymphoma—should be taken into consideration. Multiple schwannomas can indicate the presence of neurofibromatosis type 2. Dumbbell tumors among pediatric aged patients are more likely to be malignant than among adult patients [6].

22.4.2 Radiological Presentation

More than half of dumbbell tumors are completely restricted to the extradural space, although preoperative MRI in some cases suggests the presence of intradural/extradural tumors [50, 51]. A wide variety of unusual lesions, which can cause neural foraminal widening, need to be taken into consideration, including the following: neoplastic lesions, such as benign/malign peripheral nerve sheath tumors (PNSTs), solitary bone plasmacytoma (SBP), chondroid chordoma, superior sulcus tumor, and metastasis; and non-neoplastic lesions, such as infectious process (tuberculosis, hydatid cyst), aneurysmal bone cyst (ABC), synovial cyst, traumatic pseudomeningocele, arachnoid cyst, or vertebral artery tortuosity [52].

It is often impossible to differentiate between dumbbell-shaped schwannoma, meningioma, or vascular lesion. MRI yields no definitive findings—both neurogenic tumors and hemangiomas are isointense-to-hypointense in T1 imaging, and homogeneously hyperintense in T2 imaging [53]. Regular enhancement is seen upon gadolinium administration. As a general rule, a schwannoma diagnosis should be made when a spinal intradural extramedullary tumor shows hyperintensity on T2-weighted imaging or intense enhancement without dural tail sign; otherwise meningioma is a more probable diagnosis [54]. Positive predictors of meningiomas are the dural tail-sign on contrast-enhanced T1-weighted imaging and calcification on CT scans [55]. For schwannomas, fluid signal intensity of the tumor on T2-weigthed imaging, rim enhancement on T1-weigthed imaging with gadolinium-diethylenetriamine pentaacetic acid (Gd-DTPA), and bone scalloping on CT scans with bone windows are predictive factors [55]. One characteristic of spinal meningiomas is the so called “gingko leaf sign” [56] seen on axial post-contrast T1 imaging: the distorted spinal cord pushed to one side of the theca by the meningioma depicts the “leaf”-shape, and the stretched dentate ligament depicts the p “stem” of

the leaf (seen as a non-enhancing "streak") [56]. In large tumors, cystic and necrotic zones can be observed [57]. Intracranial schwannomas are more likely to accompany spinal schwannomas [57], which is one reason for why we recommend MRI of the head and total spine prior to surgery.

Vascular lesions are particularly important when making a differential diagnosis since they can present with bleeding [48]. It is also important to take vascular tumor in consideration when planning surgery. A cavernous hemangioma should be included in the differential diagnosis of dumbbell-shaped spinal tumors when the p intervertebral foramina is not highly dilated and a non-enhanced nerve root is identified in the tumor with a lobular contour [58]. One of the signs most indicative of hemangioblastoma is the presence of blood flow voids on T2-weighted MRI [59].

Differentiation between benign and malignant lesions on MRI could be made using dumbbell scoring system [27]. Tumors larger than 5 cm or that increase in size on follow-up, irregular boundaries with perilesional edema, irregularly lobulated shaped, and osteolytic p bone destruction could point to a malignant lesion [27] and could be important in decision-making and for indications for a biopsy. The occurrence of paraspinal infiltration along the muscle fascicles suggests the possibility of lymphoma, which can be decisive in treatment since lymphomas are extremely chemo-sensitive and radiosensitive [60].

We recommend CT studies in all cases in which bony erosions are suspected. The extent of widening and erosion of one or more neuroforamina can provide insight into the instability of the spine and the need for stabilization following resection. Bony erosions can result from large benign tumors due to the compression effect of the tumor, but also due to aggressive malignant neoplasms. In most cases, the bony change is simply compressive with the widened intervertebral foramen [41]. However, in some special cases, the tumor erodes the p vertebral body, the facet joint, or—less commonly—the lamina. Sometimes the tumor makes small but deep nidus in the bone. In these two circumstances, radical bony lesion resection is mandatory; a less aggressive bone lesion resection could lead to tumor recurrence [41]. Standard X-ray images, including anterior-posterior (AP), lateral, and flexion and extension dynamic X-ray evaluation should always be performed prior to surgery in order to a) help localize the segment where the surgery is going to be performed, and b) assess instability p with functional X-ray, especially in cervical spine.

22.5 Specific Pathological Entities in the Spine which can Present as Dumbbell Tumors

22.5.1 Schwannomas and Neurofibromas

Approximately 90% of schwannomas are solitary and sporadic; 4% arise in patients with neurofibromatosis type 2, and another 5% are multiple but unassociated with neurofibromatosis type 2 [61]. The vast majority of spinal schwannomas develops from the dorsal roots and is intradural. Dumbbell schwannomas have been reported

as a separate group of spinal tumors, which characteristically involve both the intradural and the extradural compartments, occupying the intervertebral foramen, and more frequently located in the cervical spine [6, 62]. Giant schwannomas always have an extraspinal part with widening of the neuroforamen, which makes them dumbbell-shaped tumors. The surgical method should be tailored to each individual case (Figs. 22.2, 22.3, 22.4 and 22.5 demonstrate two cases of dumbbell schwannomas of the cervical spine operated on by the senior author of this chapter [KIA]. Details of the surgical resection of cervical dumbbell schwannoma are contained in the surgical video section of the online edition of this manuscript.) Spinal nerve sheath tumors showing an intradural location can be resected via a posterior standard or via a unilateral approach with modifications, such as partial facetectomy or a spinal cord rotation technique with resection of the dentate ligament [63]. Extradural dumbbell extension exposure of the tumor along the surgical plane of the dural or perineural boundary (particularly originating from the C1 or C2 level) is the key procedure required to accomplish radical and safe resection of the tumor with use of anterior access in selected cases [63].

Spinal extradural schwannomas are a distinct pathological entity of dumbbell schwannomas and can be distinguished from other nerve sheath tumors growing inside the spinal canal by their clinicoradiological features, including large tumor size with erosion of the vertebral body and an unlikely nerve root origin. Schwannomas tend to occur in thoracic and lumbar areas, and neurofibromas are usually associated with neurofibromatosis type 1 and tend to occur in the cervical area [45, 64]. In dumbbell neurofibroma cases, the majority of the nerve fibers are entrapped within tumoral tissue. It is frequently impossible to remove the tumor without sacrificing the nerve root; aggressive surgery may, therefore, result in severe neurological deficits [65, 66]. Neurofibromas were associated with higher rates of recurrence and lower rates of gross total resection than other tumor types, particularly in patients with neurofibromatosis types 1 or 2 [45].

22.5.2 Meningioma

Meningiomas compose up to 5% of spinal dumbbell tumors and are an important entity in differential diagnosis [6]. Dumbbell meningiomas probably originate from the arachnoid villi at the nerve root exits [4]. They are mostly located intradurally but occasionally exhibit an extravertebral extension with a dumbbell-shaped form [4, 67, 68]. The meningioma's extravertebral extension could include tumor growth through the intervertebral foramina, but usually only to a minor extent [69]. Because there is little intraspinal space for tumor growth, a meningioma at this location is prone to grow through the dura and, subsequently, to the extradural/extravertebral space [70]. The most common location seems to be the thoracic spine as there are several reports of thoracic dumbbell meningiomas resected with a combined posterior and thoracoscopic approach [11] or with additional thoracotomy [67]. Cases of dumbbell meningiomas in the cervical spine were also described [69, 71]. (Fig. 22.6 demonstrates a case of dumbbell meningioma of cervical spine operated by the senior author [KIA]).

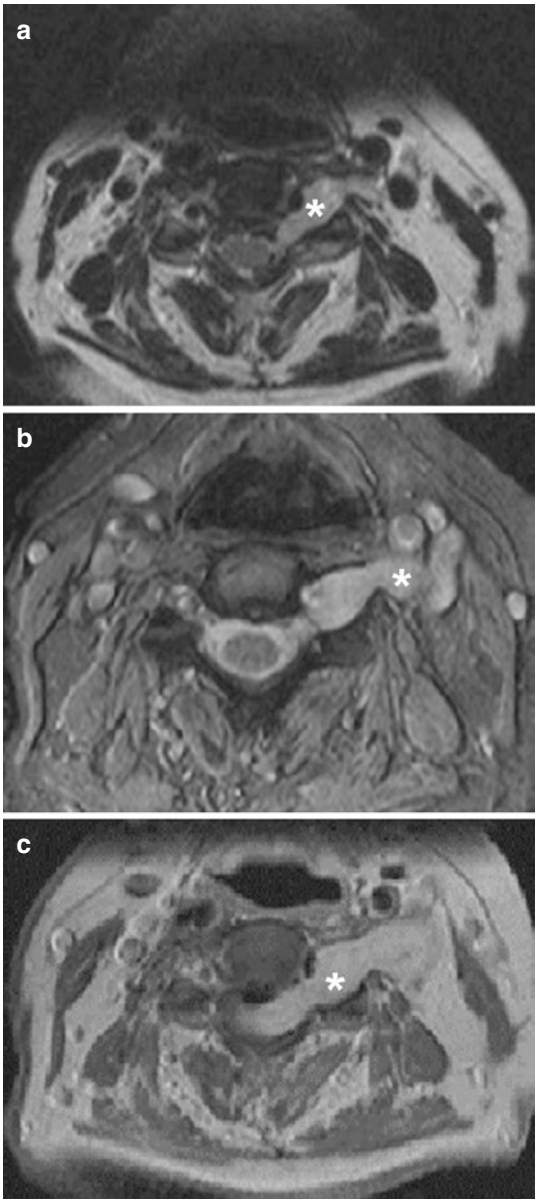


Fig. 22.2 Imaging of an 84-year-old female patient with left-sided radiculopathy and mild quadriparesis. She was diagnosed with a left-sided C3/4 dumbbell tumor (asterisk). The tumor was followed for 3 years where it showed progressive growth. (**a**) Initial T2-weighted axial MRI of the cervical spine showing homogeneously hyperintense dumbbell lesion in C3/4 foramen on the left side. (**b**) T2-weighted axial MRI of the cervical spine at 1-year follow up showing progressive growth of the extraspinal tumor component. Since the patient was clinically stable, surgery was not indicated. (**c**) Axial T1-postcontrast MRI of the cervical spine at 3-year follow-up showing dumbbell lesion with intense contrast enhancement and progressive intraspinal tumor growth with compression of the spinal cord and myelopathy. At this point, the patient had worsening quadriparesis

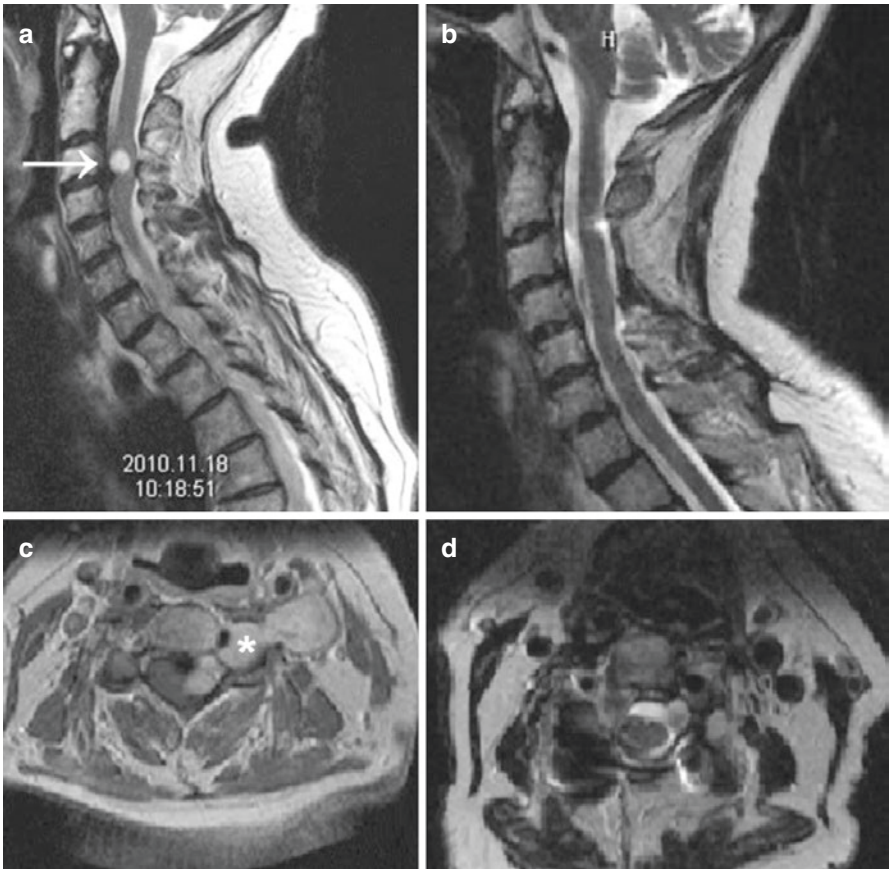


Fig. 22.3 Imaging of gross total resection of dumbbell lesion in left C3/4 neuroforamen via the posterior approach with laminectomy and unilateral facetectomy. The pathohistological diagnosis confirmed the diagnosis of schwannoma WHO I. Additional stabilization with lateral mass screws C2–5 was performed. (**a**) Preoperative sagittal T2-weighted MRI of the cervical spine showing an intradural homogenously hyperintense extramedullary tumor at C3/4 (arrow). (**b**) Postoperative sagittal T2-weighted MRI of the cervical spine showing complete resection of the tumor without any signs of myelopathy. (**c**) Preoperative axial T1-weighted post-contrast MRI of the C3/4 level showing the intraspinal and extraspinal expansion of the schwannoma with homogenous contrast enhancement (asterisk). (**d**) Postoperative axial T2-weighted MRI of the C3/4 level showing no sign of remaining tumor

22.5.3 Vascular Lesions

Capillary hemangiomas are benign vascular malformations most often found in the skin or soft tissue throughout the body of younger patients. They are histologically characterized by nodules of capillary-sized vessels lined with flattened endothelium, and often regress spontaneously. There have been more than 40 intradural

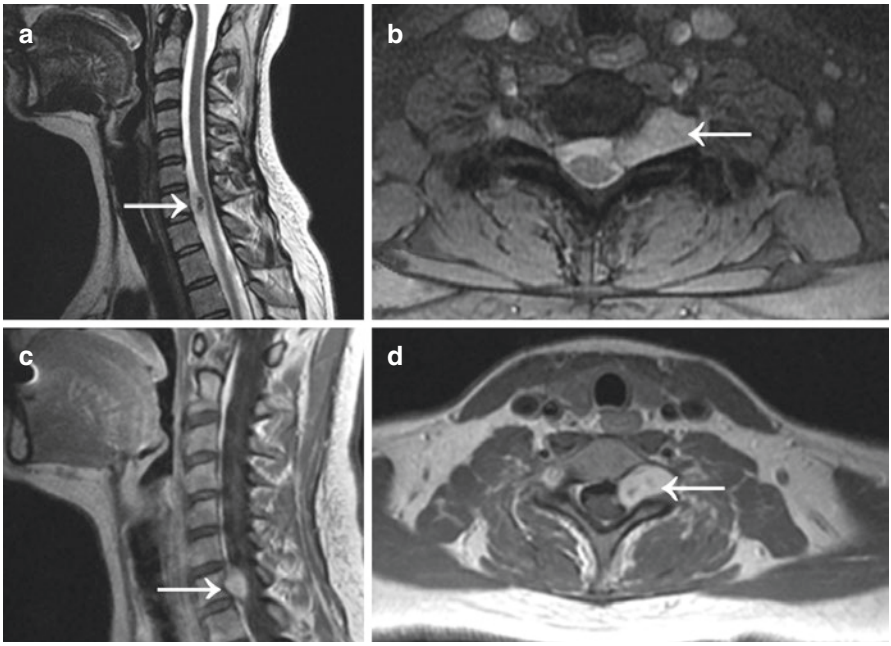


Fig. 22.4 Imaging of a 33-year-old patient with left arm numbness and weakness. (**a**) Preoperative sagittal and (**b**) axial T2-weighted MRI of the cervical spine showing hyperintense dumbbell tumor with (**c**) sagittal and (**d**) axial T1-weighted post-contrast MRI of the cervical spine demonstrating dumbbell tumor (arrow) with homogenous contrast enhancement at C7/T1 on the left side

spinal capillary hemangiomas described in the literature [72]. Extradural-only cases with spinal cord compression have also been described [10, 73], as well as cavernous hemangiomas with both intradural and extradural growth [9]. The majority of extradural cavernous hemangiomas are composed of an extension from a vertebral hemangioma into the spinal canal with extradural-only locations representing 1–2% of spinal hemangiomas [74]. These tumors commonly affect the vertebral bodies and extend into the epidural space, and are less commonly found within the thoracic cavity [75, 76]. Typical CT findings for hemangioma are lobulation, heterogeneous enhancement with contrast media, multiple ring-like calcifications, and an intact intervertebral foramen when the tumor extends to the spinal canal; however, these findings are not always observed [77]. On MRI, both neurogenic tumors and hemangiomas are isointense-to-hypointense on T1 images, and homogeneously hyperintense in T2 images [53]. They are usually presented as a progressive myelopathy, so early treatment may prevent permanent neurological deficits. Endovascular embolization has been recently used to remove a hemangioma, successfully minimizing blood loss during the operation. However, this management carries a risk of spinal infarction [78].

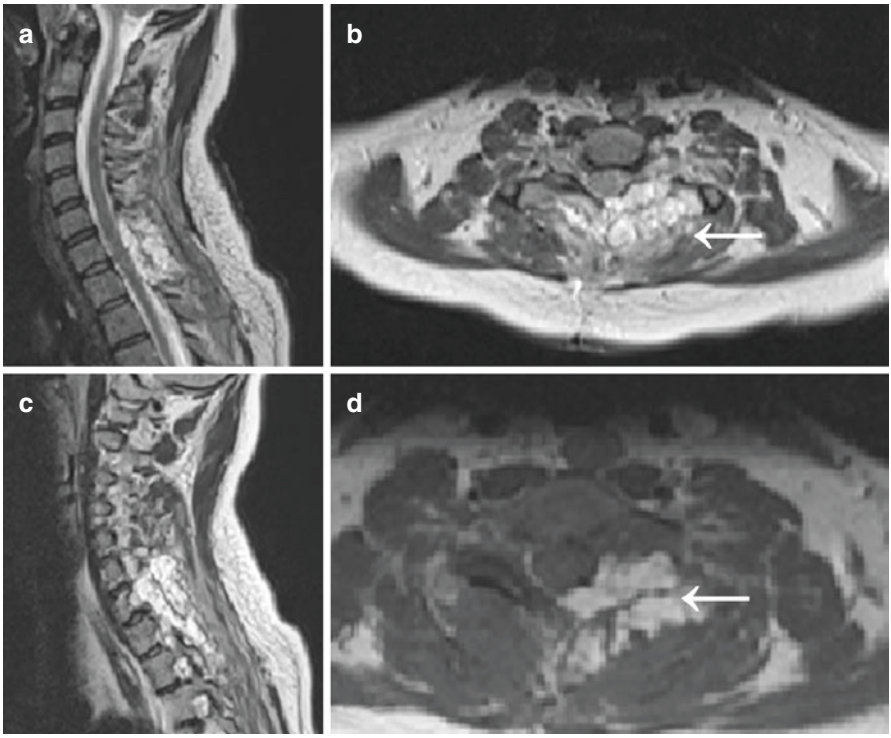


Fig. 22.5 Imaging of tumor gross total resection via posterior approach with unilateral facetectomy. The pathohistological diagnosis was schwannoma WHO I. (**a**) Postoperative sagittal and (**b**) axial T2-weighted MRI of the cervical spine with (**c**) sagittal and (**d**) axial T1-weighted post-contrast MRI of the cervical spine demonstrating complete resection of the tumor. Additional stabilization was unnecessary. Arrow shows abdominally harvested fat graft applied to dural suture in order to prevent cerebrospinal fluid leak

Gross total resection is the preferred treatment for these lesions. In the thoracic spine there are several approaches: a posterior approach, a posterior approach with thoracotomy, a thoracoscopic approach, and a combined posterior approach with thoracoscopy. Some authors suggest performing thoracotomy before posterior surgery because it allows for ligation of the involved arteries and prevents bleeding in the spinal canal [79]. Management of intraoperative bleeding and sufficient hemostasis are the pitfalls of successful surgery of these lesions. Details of the surgical resection of dumbbell hemangiomas are described in the surgical video section of the online edition of this manuscript. (Figs. 22.7 and 22.8. demonstrate the case of dumbbell hemangioma of the thoracic spine depicted in our surgical video in which the patient underwent a 2-stage procedure of intraspinal resection by the senior author (KIA) followed by thoracoscopic resection of the intrathoracic part of the tumor.

Hemangioblastomas located extradurally account for 8–12% of all spinal hemangioblastomas. They are more prevalent in patients with Von-Hippel Lindau disease [49]. There are several case reports describing these lesions. It is

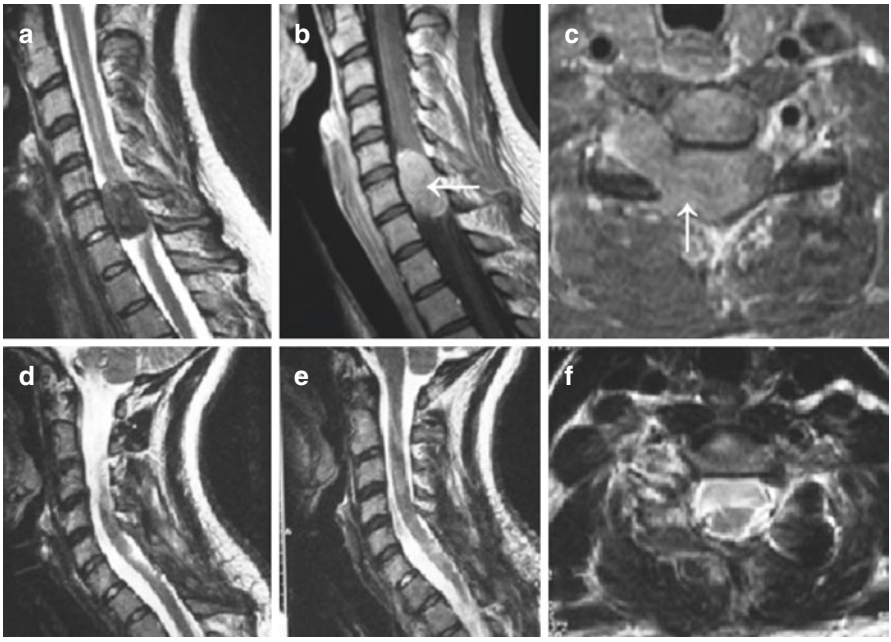


Fig. 22.6 Imaging of a 24-year-old female with quadriparesis and T1 sensory level, inability to walk, and intermittent urinary incontinence. (**a**) Preoperative T2-weighted sagittal MRI of the cervical spine demonstrating intradural extramedullary tumor with (**b**) homogenous contrast enhancement in sagittal T1-weighted post-contrast series and (**c**). axial T1-weighted post-contrast MRI of the cervical spine showing the dumbbell form of the tumor (arrows). The tumor underwent gross total resection via the posterior approach with laminectomy at C6/7 with unilateral facetectomy. The pathohistological diagnosis was meningioma. Additional stabilization of the C6/7 segment was performed. Postoperative (**d**, **e**) sagittal and (**f**) axial T2-weighted MRI of the cervical spine showing complete resection of meningioma. The patient fully recovered

recommended that resection of hemangioblastomas arising in the cervical spine be done via the lateral approach, which provides control of the vascular feeders [16]. Hemangioblastomas can also manifest subarachnoid hemorrhages in the cauda equine [49]. To avoid excessive blood loss, preoperative embolization and angiography to confirm the location of main feeder should be considered when hemangioblastoma is suspected. To prevent massive hemorrhage during surgery, early identification of feeders and blood flow direction with extracapsular resection needs to be carried out [49].

22.5.4 Paravertebral Neurogenic Tumors with Intraspinal Extension

Because the paravertebral space is rich in neurogenic tissue, primary neurogenic tumors originating here are the most common types of tumors, representing 90% of primary tumors of the posterior mediastinum, 63% of the retroperitoneal space, and

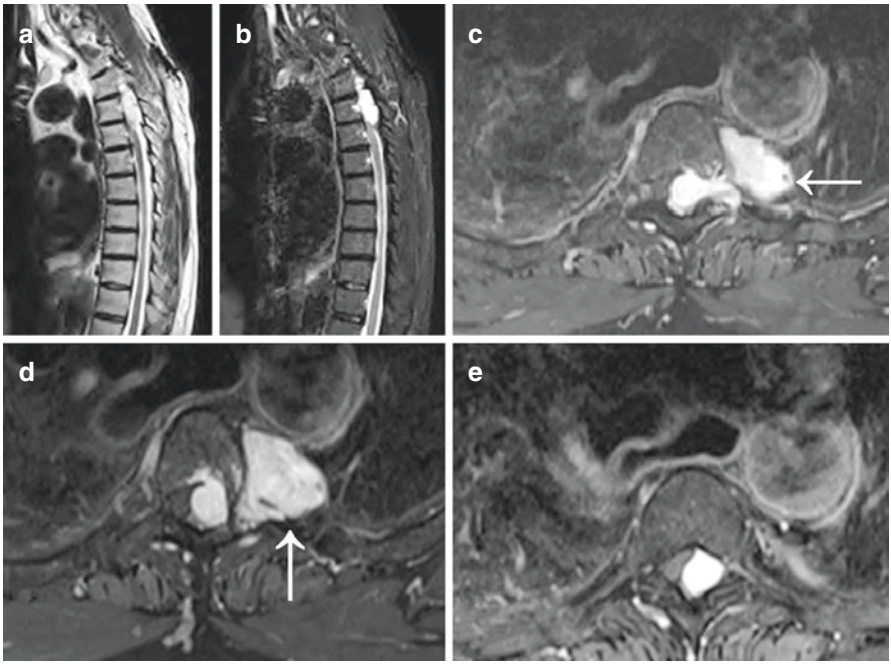
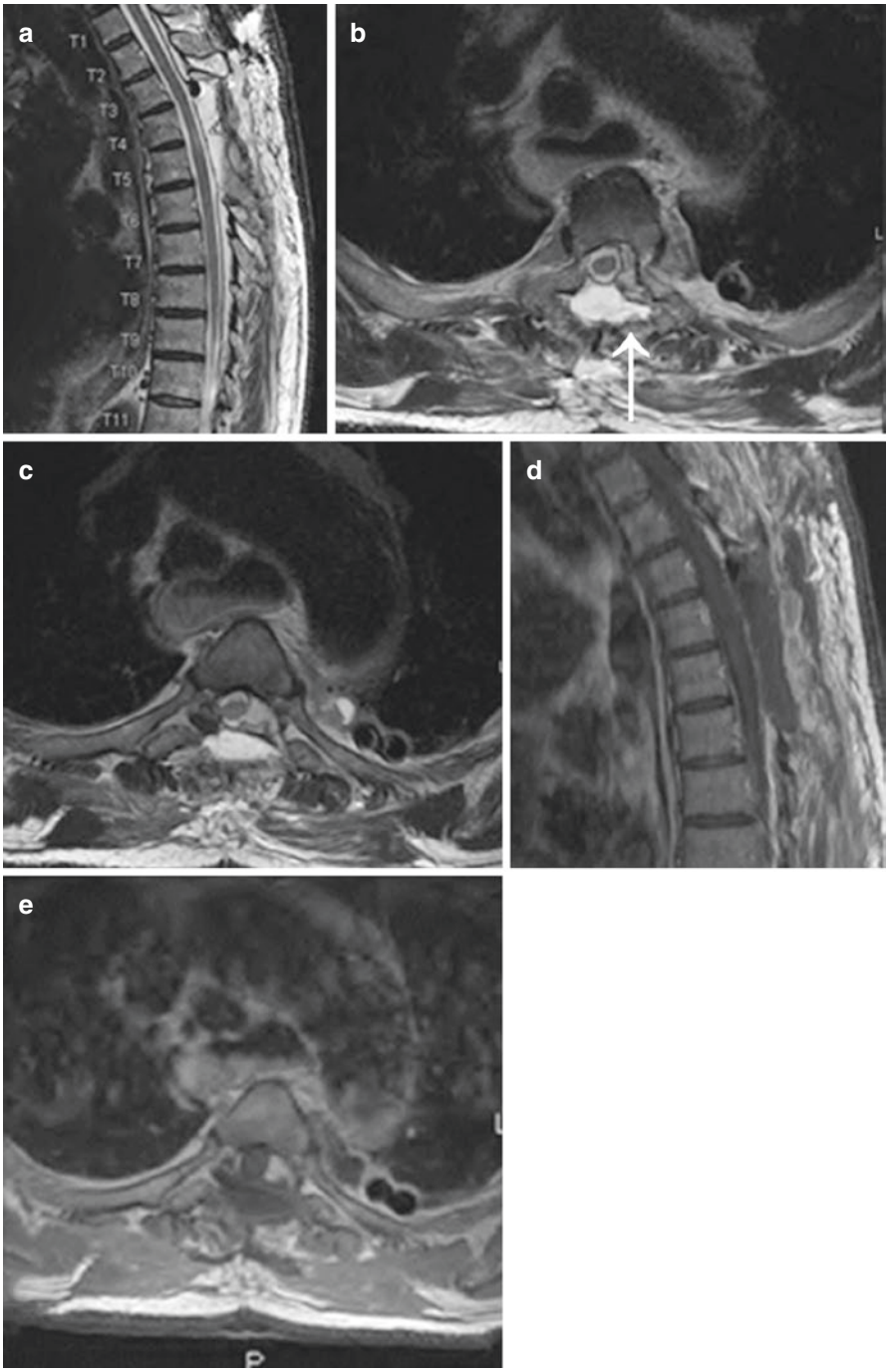


Fig. 22.7 Imaging of a 78-year-old patient with progressive paraparesis and ataxia of the thoracic spine. (**a**) T2 weighted sagittal sequence showing the hyperintense intraspinal tumor T3–5; (**b**) postcontrast T1-weighted sagittal sequences showing homogenous enhancement of the tumor; (**c, d, e**) postcontrast T1-weighted axial sequences revealing dumbbell-shaped tumor extending intraspinally with displacement of the spinal cord to the right and growth through the intervertebral foramen of T4 into the left middle thorax. Note the lobular contour of the mass, which can be a clue to the diagnosis of hemangioma (arrows)

Fig. 22.8 Further imaging of the 78-year-old patient undergoing a single 2-stage surgery, which included posterior microsurgical and transthoracic endoscopic resection of the tumor. For the posterior approach, a partial hemilaminectomy and facetectomy with partial costotransversectomy was performed, which revealed a highly vascular epidural tumor with spinal cord compression extending into the neuroforamen. Gelfoam powder (Pfizer, New York, NY) and extensive coagulation were used for hemostasis of this vascular tumor. The intraspinal epidural part of the tumor was completely resected with foraminotomy. A fat pad (arrow) was placed in the foramen as a marker for the extent of the thoracoscopic procedure. Second stage surgery included thoracoscopic resection of the extraforaminal part of the tumor. The fat pad was visualized endoscopically in the neuroforamen at the end of the resection providing an important orientation. Histopathological evaluation revealed capillary hemangioma. Postoperative MRI of the thoracic spine: (**a**) T2-weighted sagittal sequence showing the complete resection of the tumor; (**b, c**) T2-weighted axial sequences; (**d**) postcontrast T1-weighted axial sequence showing no signs of contrast enhancement; and (**e**) postcontrast T1-weighted axial sequence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10% of the neck [80]. The most common pathological type for patients age 2 year or younger is neuroblastoma of the suprarenal gland or paraganglionic retroperitoneal sympathetic tissue, while the most common type for adults is schwannoma in the retroperitoneal space or posterior mediastinum [8, 81]. Neurogenic tumors, especially neuroblastoma and extradural schwannoma [82] in the paravertebral gutter, have a predilection to spread through the intervertebral foramen to inside the spinal canal (i.e., forming a dumbbell-shaped tumor), which causes myelopathy due to either direct or indirect compression on the spinal cord [83, 84]. **Ganglioneuroma** is a rare, differentiated, benign, and slow-growing tumor that commonly arises from sympathetic ganglion cells. In rare cases, they can grow through the intervertebral foramina and present with a dumbbell shape. Most of these tumors are retroperitoneal and are more common in children and young adults [85]. On CT, these tumors show punctuate calcifications in pre-sacral region and sometimes present with extensive osteolytic bone destruction of the sacrum [86].

22.6 Malignant Spinal Dumbbell Tumors

22.6.1 Metastasis

A differential diagnosis of leptomeningeal metastasis includes ruling-out a wide range of malignant and benign conditions, such as congenital and degenerative lesions, infectious and autoimmune diseases, and neurinoma [8]. The radiologic distinction between metastases and neurinomas is based primarily on definite neuroimaging features, particularly the number of lesions, size and growth pattern [87]. Whereas metastases are often encountered as multiple small nodules at lower spinal structures (e.g., the cauda equina)—presumably—due to gravity, neurinomas appear as single lesions in the neuroforamen and might present at any height [8]. The clinical presentation of leptomeningeal metastases depends on the location and growth-pattern often resulting in general symptoms, such as nausea and headaches due to interruption of the cerebrospinal fluid (CSF) flow and, later signs of myelopathy due to compression of the spinal cord [87]. In patients with breast cancer, overall survival with current treatments remains limited to less than 6 months on average [88]. Surgical treatment combined with adjuvant or neoadjuvant therapy can improve neurologic function and lessen pain [28].

22.6.2 Malignant Peripheral Nerve Sheath Tumors (MPNSTs)

MPNSTs account for 3–10% of all soft tissue sarcomas, and are commonly located in the trunk, limbs, head, and neck, although there are some rare spinal cases [89]. MPNSTs have high metastatic potential and surgical resection is the preferred treatment of choice, if the tumor is resectable; however, there is no effective systemic therapy currently available. Surgical treatment of these lesions is defined by Enneking criteria as either Enneking appropriate (i.e., en bloc resection with wide

or marginal margins) or Enneking inappropriate (i.e., piecemeal or an intralesional resection) [90, 91], although a multicenter study showed similar rates of recurrence and survival for the two groups [90]. Prognosis of unresectable or metastatic MPNSTs is extremely poor, particularly in the spinal region, where the associated mortality rates are as high as 80%; larger lesions are also more likely to be related to higher malignancy [12, 92, 93]. Adjuvant photon beam therapy showed better local control, but carbon ion radiotherapy leads to better local control and increases in overall survival and progression-free survival [94].

Spinal extraosseous chordoma (SEC) is usually located in the cervical and epidural region and is extremely rare. SECs are less aggressive, have a lower rate of recurrence and metastasis, and have a better prognosis than those of the osseous origin [21].

Mesenchymal chondrosarcoma is a rare malignant tumor arising from bone or soft tissues. Calcification can be seen in tumors, which may influence or reflect the growth of tumor and disease progression. Gross total resection should be followed with adjuvant radiotherapy and close follow-ups due to the possibility of recurrence [22].

Myxoid liposarcoma (MLS) is a soft tissue sarcoma usually located in extremities. One-third of patients develop distant metastases and there are several reports that present as dumbbell-shaped spinal lesions [17, 95]. Treatment consists of surgical resection followed by adjuvant chemotherapy [17].

22.7 Surgical Technique

The best surgical approach for these tumors is dictated by the location and size of the tumor. Tumors located entirely or partially within the spinal canal can be accessed through the midline-posterior approach. In a large series reported in the literature, up to 80% of dumbbell tumors—predominantly schwannomas—were resected using only a posterior approach [6]. When the posterior approach is used, every effort should be made to maximize the excision of the paraspinal tumor through the same approach [46]. In cases in which an anterior approach is employed, the operation should be performed with surgeons who specialize in the region-specific approaches, such as head and neck, thoracic, and abdominal surgeons.

In the **cervical spine**, the posterior-midline approach is the standard common approach for intraspinal lesions [3]. McCormick (1996) has described a posterior-midline approach with partial laminectomy and complete unilateral facetectomy [65]. Further possibilities include a combined posterior and anterior approach [40], an anterior approach with corpectomy [38], a lateral approach with oblique corpectomy [96], an extensive posterolateral approach involving total lateral mass resection and laminectomy [97], and an anterolateral-transuncodiscal approach [68]. The location of the vertebral artery (VA) is important during resection of cervical dumbbell tumors [98]. When the VA is encased by the tumor, a posterior approach carries high risks [34]; the anterior approach may be more adequate in these cases.

McCormick [4] has also described a modified version of the lateral-extracavitary approach for removal of dumbbell and paraspinal tumors of both the thoracic and lumbar spine. For the **thoracic spine,** there are several surgical techniques available including the following: a combined posterior microsurgical approach for resection of the intraspinal part followed by subsequent video-assisted thoracoscopic surgery for intrathoracic part of the tumor [99, 100], a posterior-only approach [101], a single posterolateral approach [102], a posterior approach combined with thoracotomy [67, 79, 81, 103], a 1-step removal via posterolateral thoracotomy and extended foraminectomy [104], a transclavicular approach for tumors of the cervicothoracic junction [105], an extended lateral cavitary approach [4], and a thoracoscopic-only approach [106].

Posterior approaches for resection of dumbbell tumors of the **lumbar spine** include a posterolateral-transforaminal approach [57], a transparaspinal approach [107], a posterior approach with laminoplasty [108], a posterior approach with hemilaminectomy, facetectomy and stabilization [6], a posterior dual approach [109], and a mini-open [44] minimally invasive technique with [110] or without stabilization [111] (i.e., using tubular retractor). Giant lumbar schwannomas eroding the vertebral body and expanding into the retroperitoneal space requires a 2-stage surgery—a decompression and partial resection with root transection posteriorly, followed by an en bloc resection through the retroperitoneal approach by vascular surgeon [112].

Gross total resection should be performed whenever possible as long as there is no risk of vascular or neurologic injury since the risk of recurrence rises with subtotal resection [45, 113]. Subtotal resection is usually performed in cases when risk of vascular injury or neurological deficits is high as suggested by intraoperative nerve monitoring. Preservation of the involved nerve root should always be attempted when removing neurogenic dumbbell tumors [41]. In a large series in the literature, complete resection has been achieved in 86 to 100% of patients [4, 5, 8, 96, 98].

Spinal reconstruction surgery using instrumentation should be considered when the spinal column is weakened structurally during tumor removal when the tumor invades at multiple levels, such as with malignant neoplasms, neurofibromas, extradural-intravertebral tumors, and multidirectionally eroding tumors [5]. The cervical spine seems to be more prone to the development of the postoperative instability [5, 41]. Facetectomy with costotransversectomy in the thoracic spine may require additional stabilization. If bilateral laminectomy on more than two levels is performed or more than half of the lumbar vertebral body is compromised by the tumor, instrumentation and reconstruction may be considered [34].

22.8 Complications

Dumbbell lesions are associated with higher rates of CSF leakage, pseudomeningocoele, and wound infection compared with non-dumbbell spinal nerve sheath tumors [114]. Complications include surgery site infections [57], CSF leak, injury

to the surrounding structures in the neck, thorax and abdomen when using a combined approach (i.e., injury to the carotid artery, esophagus, recurrent laryngeal nerves, chylothorax, pneumothorax, colon perforation, ureter injury, retroperitoneal hematoma, injury of the aorta and iliac arteries), spinal cord edema, spinal cord ischemia due to injury of Adamkiewicz artery [115], pseudomeningocoele [116], and extensive bleeding in the case of vascular lesions. Complication rates increase as the size of the total excised tumor increases [57].

One of the important questions in surgery of dumbbell spinal tumors is how to deal with dural defect in intradural-extradural tumors (Eden Type I and II). Suturing autologous fascia over the dural defect, and then applying of several layers of dural graft and fibrin glue is one possible method [98]. A "separate-dural-incision method" is another type of dural incision and closure procedure for preventing postoperative CSF leakage during the surgical removal of dumbbell-shaped spinal tumors [117]. Adequate visualization of the intradural and extradural components of the tumor is achieved with the use of separate dural incisions. First, the dura mater is opened along the dural theca to provide adequate visualization of the intradural portion of the mass; then, a second incision is made along the nerve root to remove the extradural component. Meticulous suturing is essential in intradural lesion cases; however, the dura mater is usually thin and fragile in such cases. During suturing with a needle and thread, the dura mater can become lacerated proximal to the needle holes and result in CSF leakage. Instead of using a needle and thread for this technique, non-penetrating vascular clips were used to close the dural incisions [117]. A third technique that showed good results in prevention of the CSF leak in spinal surgery is the application of a previously harvested abdominal fat graft onto the dural suture [118]. After tumor resection, it may be very difficult or impossible to achieve watertight dural closure. Application of the fat graft application, along with fibrin glue, incorporated in dural closure may eliminate the risk of CSF leak.

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Instrumented Fusion after Spinal Cord Tumor Resection

23

Michael A. Galgano, Jared S. Fridley, and Ziya L. Gokaslan

23.1 Introduction

The indications for concomitant instrumented fusion after intradural spinal cord tumor resection is a topic that is not routinely covered when discussing the concepts of spinal biomechanics. While there is a fair amount of evidence supporting restoration or maintenance of the posterior tension band in the pediatric population after laminectomy, similar evidence is lacking in the adult population [1, 2]. Performing a laminectomy at 3+ levels or at a junctional level, >50% unilateral or bilateral facetectomy, C2 laminectomy, previous deformity (such as kyphosis in the cervical spine), persistence of deformity after 1 year of the original surgery, and operating on the "younger adult population" (33 +/− 4.2 years), appear to be the general indications for supplemental spinal fusion based on retrospective analyses of various case illustrations [2].

The majority of spinal cord tumors are resected via a posterior approach. Traditional dissection entails traversing the dorsal fascia, reflecting the paraspinal musculature, and creating a window within the posterior osseous elements to ultimately gain access to the intradural contents. Disrupting the posterior elements, particularly the posterior spinal ligaments, may have negative biomechanical consequences in terms of the spine's ability to maintain sagittal alignment in the postoperative state. This may cause the patient significant symptoms related to spinal deformity or instability. These posterior spinal ligaments connecting adjacent spinal levels between the boney posterior elements, which include the supraspinous ligament, interspinous ligament, and ligamentum flavum, are individually relatively weak. However, when intact the sum total length of these ligaments spanning from

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the cervical spine to the sacrum creates a long moment arm that confers a biomechanical advantage as a highly functioning posterior tension band [3]. The capsular ligaments of the facet joints have a short moment arm, but individually are strong, and thus provide a robust stabilizing effect when left intact [3]. It has also been shown that there is a direct relationship between the width of the laminectomy and post-operative iatrogenic instability. This is likely from increasing disruption of the facet joints with wider laminectomies [4, 5].

23.2 Spinal Cord Tumor Resection and Biomechanical Stability

Comparatively, the cervical spine tends to be more prone to post-operative instability than the thoracic and lumbar spine, likely secondary to its relative mobility [3]. It is well-established in the literature that the pediatric population is especially susceptible to post-laminectomy kyphosis after resection of intradural spinal cord tumors [6, 7]. Within the pediatric population, it is thought that the viscoelasticity of the remaining posterior ligamentous complex structures, horizontal facet orientation, in addition to the incomplete ossification of the vertebral bodies may be responsible for post-laminectomy kyphosis in children. It is also postulated that anterior horn injury along with muscle denervation may lead to paraspinal muscle weakness and deformity. It is also felt that post-operative radiation may play a role in post-operative kyphosis [8].

Ahmed and colleagues performed a univariate and multivariate analysis of predictors of post-operative instability in patients <21 years old with intramedullary spinal cord tumors. They found that preoperative kyphoscoliosis ($p = 0.0032$) and laminectomy/laminoplasty performed at more than four levels ($p = 0.05$) were independently associated with development of post-operative sagittal deformity that subsequently necessitated instrumented fusion [9]. Knafo and colleagues performed a similar analysis on 63 patients, which revealed increased post-operative sagittal deformity in patients ≤30 years old (21.9° vs. 13.7°; $p = 0.04$) who either underwent a laminectomy involving ≥4 levels (19.3° vs. 12.1°; $p = 0.04$), or had a laminectomy that included the cervicothoracic or thoracolumbar junctions (20.8° vs. 12.4°, $p = 0.02$). Multivariate analysis showed that only age ($p = 0.01$) and the number of spinal levels involved in the laminectomy ($p = 0.014$) were significant and independent predictors of postoperative sagittal deformity [10]. Hersh and colleagues looked at 66 consecutive pediatric patients with cervical and thoracic intramedullary spinal cord tumor resections. Whether undergoing laminectomy or laminoplasty, patients had similar rates of post-operative deformity, eventually necessitating spinal fusion [1]. Raab and colleagues, however, have advocated the utilization of osteoplastic laminotomy in the pediatric population during resection of spinal cord tumors. Their case series has shown a decreased incidence of post-operative spinal deformity in this patient population (27.1% vs. historical mean of 46%) by preserving the normal architecture of the posterior elements [11]. McGirt and colleagues examined the sagittal alignment of 58 patients pre-operatively for spinal cord

tumors. Five (36%) of 14 patients with preoperative scoliosis or loss of lordosis developed postoperative progressive spinal deformity compared to only 6 (13%) of 44 patients with normal preoperative sagittal and coronal balance ($p = 0.06$). Patients <13 years of age were more than 3-times more likely to develop postoperative progressive deformity, ($p = 0.05$). Decompression spanning both the axial cervical spine (C1–C2) and the cervicothoracic junction (C7–T1) increased the risk for progressive spinal deformity fourfold ($p = 0.04$). Number of spinal levels decompressed, revision surgery, radiotherapy, involvement of C1–C2 or C7–T1 alone in the decompression, or any other recorded variables were not associated with progressive postoperative spinal deformity. It was concluded that patients possessing one or more of these characteristics should be monitored closely for progressive spinal deformity after surgery [12].

Within the adult population, careful examination of pre-operative upright cervical alignment should be appreciated. A pre-operative kyphotic alignment should signal to the surgeon that a laminectomy alone without instrumented fusion may yield worsening sagittal alignment in the post-operative state.

High cervicomedullary intradural tumors may necessitate violation of the occipital-cervical joint for maximal safe resection. Debate exists as to how much of the joint can be tolerated without needing an occipital-cervical instrumented fusion. Some authors feel that sparing 50% of the occipital-cervical joint does not lead to instability, whereas removing 75% yields a statistically significant increase in motion when extension is coupled with axial rotation [13]. Other authors feel that resection of ≥50% of the joint leads to instability [14]. Patients undergoing a partial condylectomy without supplemental fusion should be counseled prior to surgery that there is a possibility they may require additional fusion after surgery if they develop clinical occipital-cervical instability.

Katsumi and colleagues have shown that violation of the C2 dorsal elements including the semispinalis and lamina may lead to post-operative instability [15]. Resection of a C2/3 ventral meningioma for example, would necessitate a C2 laminectomy and subsequently a C1–C3 fusion [16].

Bony remodeling from longstanding intradural tumor expansion may be another indication for consideration of supplemental instrumentation. Pedicles can become progressively narrowed over time (Fig. 23.1), making them more prone to fracture from minor trauma (Fig. 23.2). Bruzek and colleagues describe a case where a cervical intra- and extramedullary neurenteric cyst caused the associated vertebrae to become extensively thinned. The necessary removal of the posterior elements to gain access to the cyst coupled with the thinned out vertebrae pushed the surgeons to provide supplemental fixation [17].

The decision to provide supplemental fixation after resection of a multicompartmental nerve sheath tumor has long been a subject of debate. Although many nerve sheath tumors are relegated strictly to the intradural space, some will harbor an extradural extension through the neural foramen (Figs. 23.3, 23.4, 23.5 and 23.6). This begs the question how necessary it is to remove all overlying bone and joint in an effort to maximize resection of the tumor. Some authors have proposed the “dual approach” for resection of dumbbell schwannomas, whereby two

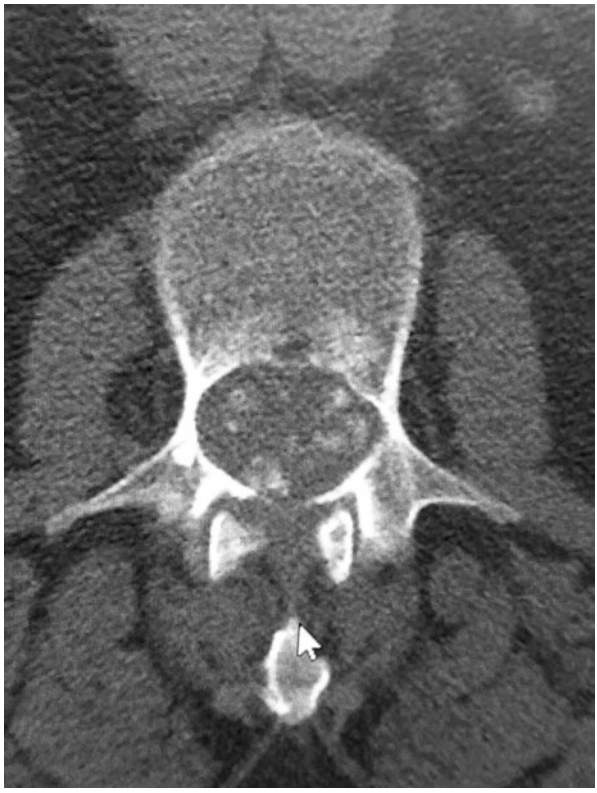

Fig. 23.1 Lumbar Spine CT. Axial lumbar spine CT scan revealing a partially calcified intradural tumor, with associated thinning of the pedicles

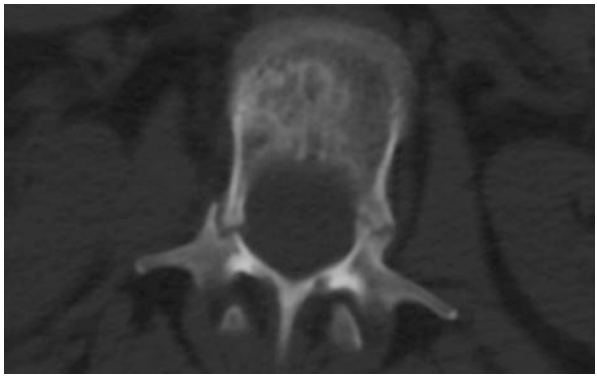

Fig. 23.2 Lumbar Spine CT. Axial lumbar spine CT showing bilateral fractured pedicles

separate surgical corridors are accessed to resect the tumor in an effort to avoid a fusion. This particular approach is a pars and facet-sparing procedure [18]. Ahmad and colleagues looked at 48 cases of spinal nerve sheath tumors [19]. Seven of these cases necessitated a partial facetectomy, and none of the patients went on to require a fusion from instability at the 3-year follow-up. They did find that surgeons were more likely to provide supplemental instrumented fixation if there was pre-existing

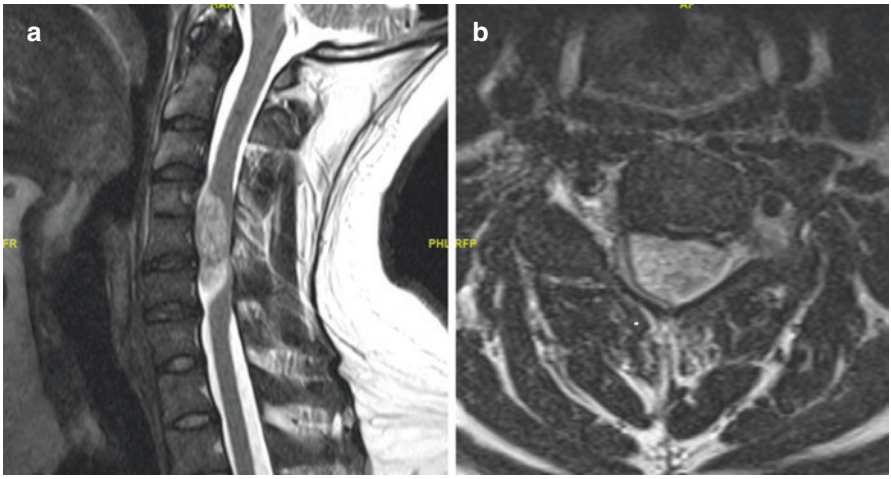

Fig. 23.3 Cervical Spine MRI. Pre-operative T2 sagittal (**a**) and axial (**b**) MRI images of the cervical spine showing a large intradural, extramedullary mass from C4–C6 with extension into the left neural foramen, consistent with a nerve sheath tumor

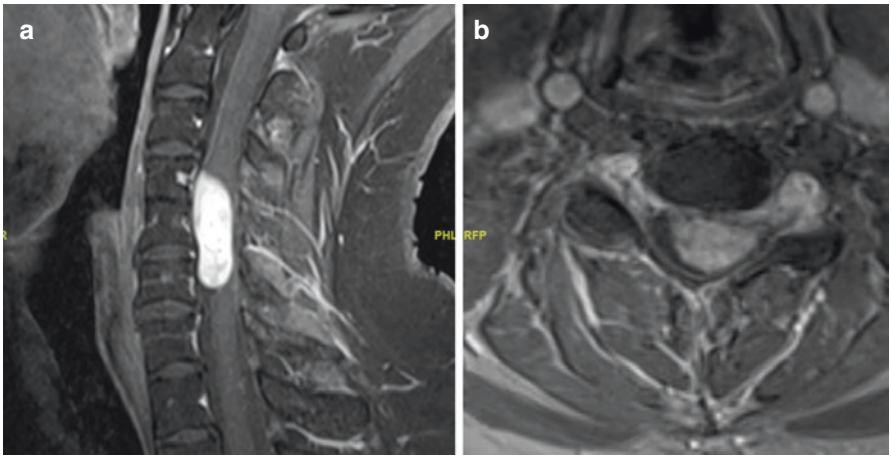

Fig. 23.4 Cervical Spine MRI. Pre-operative Contrast-enhanced T1 sagittal (**a**) and axial (**b**) MRI images showing a large contrast enhanced tumor from C4-C6 with extension into the left C5 neural foramen, consistent with a nerve sheath tumor

deformity or instability, a history of neurofibromatosis type I combined with a tumor in the cervical region, those undergoing a total facet resection, and those patients with malignant nerve sheath tumors. They also found that removal of one third or even half of a facet joint complex appears to be well tolerated with no instability seen on follow-up [19]. A finite element model has shown that bilateral total facetectomy simulated at L4-L5 and L5-S1 levels increased spinal instability significantly under extension and axial rotation and not under flexion [20].

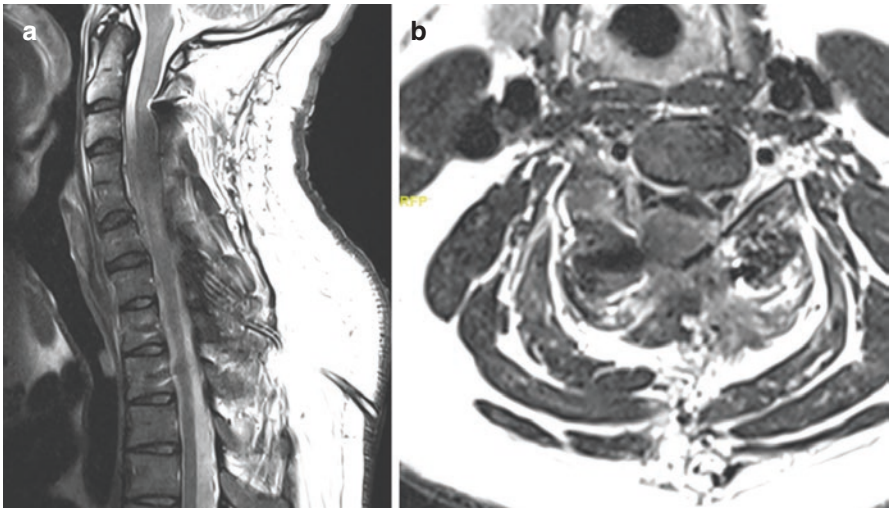

Fig. 23.5 Cervical Spine MRI. Post-operative T2 sagittal (**a**) and axial (**b**) MRI cuts revealing a gross total resection of the tumor

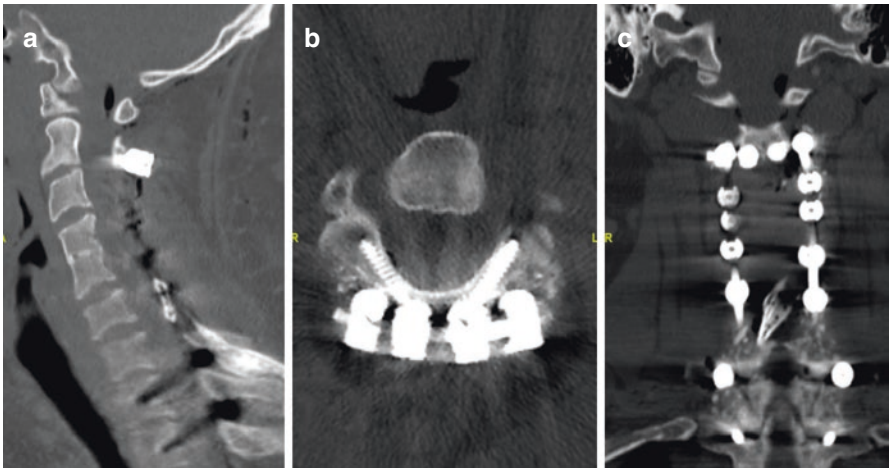

Fig. 23.6 Post-operative CT scan following cervical spine tumor resection and C2-T2 instrumentation. Sagittal (**a**) and axial (**b**) and coronal (**c**) demonstrate extant of bony removal and hardware placement

The thoracic spine classically is viewed as the most stable region of the vertebral column, due to the ribs connecting the dorsal elements to the sternum. This however, does not hold true for the lower thoracic ribs which are "floating" due to their early termination and lack of sternal articulations. Questions exist whether this calls for more frequent supplemental fixation of the lower thoracic spine when compared to the upper and mid-thoracic spine after aggressive bone/joint removal to access a

multi-compartmental intradural-extradural spinal cord tumor. A biomechanical cadaveric study showed that adding dorsal fixation increased segment rigidity and reduced overall range of motion of the lower thoracic spine to a greater extent than did instrumenting the thoracic spine levels with true ribs [21]. Despite a lack of true ribs, the lower thoracic spine did not differ significantly when compared with the upper thoracic spine in flexion/extension and lateral bending after decompression, although trends existed toward significance for greater axial rotation after decompression [21].

It should be noted that instrumenting the spine during resection of intradural spinal cord tumors does not come without additional risks. Osseous malunion and hardware misplacement are two potential complications related to instrumentation. After resection of intradural tumors, most neurosurgeons will implement routine magnetic resonance imaging (MRI) to assess for recurrence. Spinal hardware will most definitely yield artifact on the MRI, which can make radiographic appreciation of residual or recurrent tumor problematic.

23.3 Surgical Treatment of Post-Operative Deformity

While an extensive discussion regarding treatment of post-operative deformity is beyond the scope of this chapter, a few principles should be highlighted. One of most important studies that can be performed to assess the kyphotic deformity is a dynamic X-ray. This will often give vital information as to the flexibility of the kyphosis. In turn, this can help guide the surgeon in determining a treatment plan. Symptomatic rigid deformities may necessitate osteotomies and ligamentous release posteriorly, anteriorly, or both depending on the amount of correction desired. Symptomatic kyphotic deformities that are more flexible may benefit from posterior fixation alone to recapitulate the dorsal tension band. It should be kept in mind that revision operations in a previously laminectomized area are more prone to unintended durotomies, as the virgin anatomy has been disrupted and midline landmarks are no longer present.

23.4 Future Trends

Neurosurgeons have always tried to preserve as much of the natural integrity of the spine as possible [22]. Although select cases do necessitate supplemental instrumentation, soft tissue/bone-sparing techniques are becoming more popular amongst spine surgeons. Certain cases that traditionally would have been done with instrumentation are now being done with joint-sparing techniques. Muscle- and facet joint-preserving laminectomies have been advocated to maintain cervical lordosis [23]. A traditional laminectomy may also not be necessary if an intradural tumor displaces the cord to one side. A minimally-invasive unilateral approach may be successfully utilized in certain cases [22, 24–28]. The broad use of the endoscope has now expanded to use for the resection of select intradural tumors [29, 30].

The mini-open interlaminar and trans-spinous approaches have also been utilized [31–33]. Some authors feel that regardless of sagittal extension of the tumor, a schwannoma with an axial diameter of 16 mm located in the lumbar spine can be effectively treated with the MIS approach, including foraminal extension [34]. Despite the growing popularity of less-invasive techniques for the resection of spinal cord tumors, the surgeon should make certain that the safety profile of the surgical resection and oncological outcome is not sacrificed in return for using a tissue-sparing technique.

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Radiosurgical and Radiation Considerations for Residual, Recurrent and Malignant Spinal Cord Tumor

24

Jason Weaver

24.1 Introduction

Radiation therapy has emerged as a viable option for the treatment of residual and recurrent intramedullary spinal cord tumors. Although the literature is limited owing largely to the low prevalence of primary spinal cord tumors, some evidence can be extrapolated from the treatment for residual and recurrent metastatic disease affecting the spinal cord. In this setting, radiation plays a crucial component in pain management, prevention of pathological fractures, and preventing neurological decline [1–4]. The planning and implementation does necessitate a multidisciplinary team to develop a comprehensive strategy, which accounts for the complexity of metastatic disease to improve outcomes and minimize complication rates.

Surgery is the mainstay of intervention for tumors that compromise the spinal cord with radiation serving as an adjunct, especially in the setting of residual and recurrent disease. The most rigorous clinical studies have been for the treatment of spinal metastases, but some concepts can be extended to spinal cord tumors since the goal of spinal radiation is tumor control and symptom relief. Patchell et al. definitively established the role for radiation as an adjunct in the postoperative setting for spinal metastases [5]. A multitude of radiation modalities have been utilized to treat spinal metastases over the decades, and have generated rigorous algorithms based on a multitude of clinical studies [6–9]. Contemporary radiation strategies integrate newer technologies and regimens are proving to be advantageous for metastatic lesions; however, they necessitate a greater understanding of the rationale and

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evidence. Despite this, the management of residual and recurrent disease continues to be challenging, owing largely to the proximity to the spinal cord. Thus, the dosing and target are critically important.

This chapter will focus on the role of radiation in the management of residual and recurrent spinal cord tumors. Some insights and management strategies will be extrapolated from the radiation strategies of spinal metastases.

24.2 Epidemiology

Intramedullary spinal cord tumors are rare group of histologically distinct tumors that comprise of 4–10% of all primary intracranial neoplasms, and an estimated 10–35% of all intraspinal tumors [10, 11]. Large clinically robust studies are difficult due to the heterogeneity and infrequency of these tumors. Despite these limitations, some retrospective studies have provided some key insights into the epidemiology of intramedullary tumors. Progression-free survival and long-term outcomes are dependent on age, location of tumor, histopathology, degree of resection, and preoperative functional status [12, 13].

Up to 90% of intramedullary tumors are gliomas, of which about 70% are ependymomas and the remainder are astrocytomas [14]. Ependymomas are graded from World Health Organization (WHO) Grades I to III, and subtypes include ependymoma, subependymoma, and myxopapillary ependymoma. Intramedullary ependymomas are most common in middle-aged males. In ependymomas, histopathology and extent of resection are the most important factors associated with outcomes [15, 16]. However, some studies have indicated that histological grade is not associated with aggressiveness [17]. Regardless, recurrence rates are up to 40% in cases of subtotal resection with 10-year survival at 80% [16]. A thoracic region ependymoma was also associated with a worse outcome [18, 19]. Astrocytomas typically also occur in middle-aged males, in the thoracic region. Histopathology is the most important prognosticator of outcomes, as WHO grade predicts the presence of an intraoperative dissection plane [11, 20–23]. In contrast to ependymomas, the possibility of gross total resection is much less, and yields a recurrence rate of up to 50% in 5 years. The difficulty with surgical intervention of a spinal astrocytoma is the invasiveness of the tumor, which increases the risk of neurologic morbidity. Advancements in intraoperative monitoring techniques have greatly facilitated more aggressive resection while decreasing morbidity. Despite this, a recent review of the Surveillance, Epidemiology, and End Results (SEER) database revealed a median survival of 13 months and a 5-year survival of 18.7% [24]. As such, adjuvant radiation therapy can play an important role [19, 21, 25, 26].

Aside from gliomas, the next most common tumor is hemangioblastoma, which constitutes up to 8% of all intramedullary spinal cord tumors, and is associated with von Hippel-Lindau syndrome [27]. Other tumors include gangliogliomas, neurocytomas, lymphomas, and metastases, which in total comprise of about 5% of all intramedullary spinal cord tumors.

24.3 Clinical Presentation

Clinical presentation is largely dependent on the location of the tumor, and similar to metastatic lesions; back pain is most pronounced in the recumbent position and is the most common symptom followed by radiculopathy [11, 28]. Radiculopathy can manifest as dysesthesias or motor weakness. Bilateral sensory or motor symptoms without cranial involvement and myelopathic findings are consistent with spinal cord lesions. Additionally, the asymmetric location of the tumor within the spinal cord can differentially affect various spinal tract. Spinothalamic tract compression can alter pain and temperature fibers whereas corticospinal tract involvement results in an upper motor neuron deficit. Dorsal column tract involvement decreases gross sensation. Lesions in the cervical spine and upper thoracic spine can compromise respiratory function, whereas sacral lesions can affect the bowel/bladder function. If the lesion extends into the brainstem, cranial nerve, respiratory, circulation, and overall consciousness can also be affected.

Spinal cord lesions can cause hydrocephalus in up to 15% of patients secondary to cerebrospinal fluid outflow obstruction or decreased reabsorption [29–31]. The onset of symptoms can range from rapid to insidious, but are invariably progressive in nature. In this regard, surgery is recommended for good outcomes [32–34]. There is, however, a subgroup of patients who do not develop symptoms, except for pain, with suboptimal surgical outcomes [35]. Risk factors for symptom onset and timing are age, associated degenerative spinal column disease, and medical comorbidities. Regardless, as with metastatic cancer, early diagnosis and timely intervention can improve survival [36, 37].

A multitude of scoring systems have been developed to assist in the characterization of the associated deficits [38, 39]. A common grading system is the McCormick classification, which ranges from grade I (neurologically nonfocal) to grade IV (severe neurologic compromise, not independent) [39].

24.4 Types of Radiation

Radiation can be delivered to the spinal cord and its proximity through three modalities: conventional external beam radiation therapy (EBRT), stereotactic radiosurgery (SRS), and stereotactic body radiotherapy (SBRT). Each modality can theoretically be utilized as a primary treatment, or as an adjunct postoperatively. Patchell et al. was the first to definitively establish a role for radiation in spinal metastases [5]. The goals of radiation are for tumor control to prevent neurologic sequelae, and to relieve pain. Each modality offers specific advantages with certain limitations. SRS and SBRT have emerged as viable modalities in the treatment of spinal lesions as the integration of newer technologies have improved outcomes and decreased complications [40, 41]. More rigorous comparison studies between the three modalities are needed.

The treatment strategy has largely evolved from strategies used to treat spinal metastases. In this section, we describe each modality as it relates to the treatment

of spinal metastases in order to highlight the logic and limitations of each modality.

24.4.1 Conventional External Beam Radiation Therapy

Conventional EBRT consists of two treatment beams that deliver up to 30 Gy in up to ten fractions. EBRT has been a standard for palliative radiation in patients with spinal cord tumors as the primary indication has been for pain control [42, 43]. EBRT fractionation can increase the total dosage to 30 Gy in ten fractions up to 14 days with equivalent outcomes [44–47]. Most recently, the American Society for Radiation Oncology recommended 8 Gy in 1 fraction for bony spinal metastases [46]. At this dosage, up to 70% of patients will achieve pain relief and 40% local tumor control at 1 year [48, 49]. However, the efficacy of EBRT is more limited with complete and partial response rates seen in up to 20% and 60%, respectively [50]. Tumor type is a major component in the ability to control the tumor, as certain tumors are radioresistant. The greatest disadvantage is the large field of treatment—about a 5 cm margin around the tumor—that does not spare the spinal cord. Thus, the radiation dosage to the tumor is imprecise and results in poor local control for spinal metastases [51–53]. A lower radiation dose is often pursued (i.e., 8 Gy in 1 fraction), and about 20% will eventually require a second dose as symptoms progress [54]. The overall effectiveness of EBRT is a factor of tumor histology as it relates to radiation sensitivity and dose limitations due to its proximity to critical structures. As such, radioresistant metastatic tumors have a poor long-term control [55, 56].

24.4.2 Stereotactic Radiosurgery and Stereotactic Body Radiotherapy

SRS and SBRT have emerged as promising modalities in the treatment of spinal metastases. Treatment plans are delivered in conjunction with image guidance to minimize toxicity to the local tissues, especially the spinal cord [41, 57–61]. This permits the delivery of very high doses of radiation with improved accuracy, and can be contoured around the spinal cord [40, 41]. With the improved accuracy, the theoretical advantage compared with EBRT is a 3-time higher biologically effective dose to induce a higher rate of deoxyribonucleic acid (DNA) damage, which would be especially beneficial for radioresistant tumors [40, 62–65]. For spinal metastases, SRS may also be used in place of surgery, depending on the patient's neurologic status, the proximity to the spinal cord, and the tumor type. In this setting, the targeted therapy that SRS provides yields minimal complications with good local tumor and pain control rates [40, 41]. In the postoperative setting, SRS can also improve local control rates [66, 67].

The administration of the radiation treatments is more involved compared with EBRT. Patients must be immobilized in a rigid external frame to optimize

the stereotactic accuracy, which may be difficult for patients with spinal pain. The most common method of delivery is intensity-modulated radiation therapy (IMRT), which consists of multiple beams converging on the target from various angles to limit collateral injury to the surrounding tissues. Dynamic arcs can also be integrated with IMRT to deliver volumetric modulated arc therapies (VMAT), which may improve the safety profile with increasing radiation conformity and homogeneity of the delivery [68, 69]. The IMRT and VMAT formats have greatly increased the flexibility and durability for treatment options for fractionation [66, 70, 71]. SRS is delivered in 1-to-2 fractions, whereas SBRT is delivered in 2-to-5 fractions. Studies for osseous metastatic lesions have yield control rates of up to 90% at 2 years for bony metastatic disease [41, 72, 73]. Harel et al. recently published their experience with spinal SRS, which yielded a control rate up to 97% [68]. Several other studies have also reported on favorable outcomes with minimal side effects for spinal metastases [41, 65, 74, 75]. Gerszten et al. did also find an 84% clinical improvement in those patients that presented with a progressive neurological decline [41]. The feasibility of SBRT for the treatment of spinal tumors has been validated in patients with recurrent disease [54, 76, 77].

The complexity of SRS and SBRT necessitates a thorough understanding of the neuroanatomy, and may require a decompression or separation surgery to delineate the lesion. For this reason, SSRS and SBRT requires a multidisciplinary team consisting of medical oncologists, radiation oncologists, physicists, and neurosurgeons.

24.5 Management Strategies

Similar to patients with spinal metastases, the treatment regimen for patients with primary spinal cord tumors can be complex and may require a multi-disciplinary treatment strategy. In the setting of residual and recurrent disease, the situation can be more complicated. Patients must undergo a thorough intake and examination to determine the timing and severity of the symptoms. Radiography with magnetic resonance imaging (MRI) is utilized to determine the extent of disease. With this initial information, patients can be risk being stratified by determining the patient's clinical performance status and radiographic findings for neurological risk. A comprehensive scoring system that includes the neurologic status, radiographic findings, and histopathology does not currently exist for primary spinal cord tumors. However, a multitude of prognostication scores for spinal metastases have been developed to assist in determining the ideal treatment algorithm [6–9]. The most common scoring systems are the "LMNOP" system, which stands for location of disease, mechanical stability, neurological risk, oncological parameters, and preferred treatment [78]. An alternative framework is "NOMS," which stands for neurological, oncological, mechanical and systemic evaluation [79]. These scoring systems can be utilized to a limited extent to delineate a role for additional surgery versus radiation.

The role of radiation is to control pain, and to prevent neurologic decline from either tumor progression or osseous instability. Radiation therapy is versatile but—in the setting of primary spinal tumors—is used as an adjunct to surgical resection. In contrast to surgery, radiation therapy does possess a theoretical advantage with a more favorable safety profile, and has traditionally been offered to patients with a substantial risk to undergo surgical intervention. In this regard, radiation therapy can be integrated into the treatment plan very easily. Patchell et al. solidified its role as an effective adjunct to surgical decompression for spinal metastases [5].

The success of radiation therapy depends largely on tumor histology and radiation-specific variables (i.e., mode, dosage). Radiation is best suited for to relieve pain [80]. In this regard, the radiation treatments can be administered for palliation [50]. A more robust outcome of tumor response necessitates the consideration of the tumor biology/histology and mode of radiation delivery. Certain tumors are more radiosensitive than other tumors, which is an important distinction to define since it establishes treatment expectations. Additionally, the modality of radiation delivery is critically important, as has been shown for metastatic spinal tumors. Conventional EBRT yields a poor response for radioresistant tumors [50], whereas SRS and SBRT has a more biologically favorable profile for the traditionally radioresistant tumors with fewer complications [3–5, 81, 82]. In the setting residual and recurrent disease, SRS or SBRT may serve as the better option compared with EBRT to attain an optimal biologically effective dose.

The greatest drawback to radiation therapy is the time needed to obtain a response, which can take months [83]. As such, patients with an acute decline in neurologic status with radiographic evidence of spinal cord compression should be strongly considered for surgical decompression [5], unless the tumor is very radiosensitive (i.e., lymphoma or multiple myeloma). An additional consideration is the patient's risk of mechanical instability. If the risk of a fracture or spinal cord compression is imminent, then surgical decompression and stabilization may be prudent to prevent a catastrophic neurologic compromise prior before the benefits from radiation can take effect.

Ultimately, the decision to incorporate radiation therapy into the treatment plan is dependent on the life expectancy of the patient. With residual and recurrent tumors, radiation can be delivered quite easily, but must be weighed against patient-specific factors of impending neurologic compromise, life expectancy and quality of life. Irradiation of recurrent spinal disease can increase the risk of spinal cord toxicity, but can be minimized with SBRT [54].

24.6 Outcomes

The management of spinal cord tumors is complex due to its proximity to critical structures. Radiation therapy is a viable treatment option after attempted surgical resection. There are no studies that have evaluated the role of radiation therapy as a primary treatment modality. As such, surgery remains the first choice for the treatment of intramedullary tumors. Its role as an adjunct for spinal metastases after

surgical intervention has been established. In a randomized study by Patchell et al., a significantly larger proportion of patients (84% vs. 57%) were able to improve and maintain ambulation status after the combination of surgical decompression with postoperative radiation compared to radiation alone [5].

EBRT was the first radiation modality utilized for the treatment of diseases involving the spinal cord. Several studies have evaluated its efficacy in the setting of spinal cord compression from spinal metastases as a primary treatment, and in combination with various surgical approaches [84]. EBRT alone resulted in a mean functional improvement in only 44% of patients, whereas up to 36% eventually worsened neurologically [84, 85]. The limitations of EBRT have been the large field of radiation and poor targeting; the dosages can be quite limited and certain tumors can be resistant to the tumor. EBRT is commonly used for palliative therapy, with several studies indicating lower rates of complete pain response and local control [44, 86–88]. This is likely secondary to lower tolerable dosages with an increased risk of radiation myelitis with recurrence. Isaacson et al. published a meta-analysis that identified several studies of EBRT providing only modest control and improvement in overall survival for spinal ependymomas and astrocytomas with radiation dosages limited by risks of radiation myelopathy, and gastrointestinal and fertility issues [89]. As such, EBRT is of limited utility for intramedullary lesions.

Spine SRS and SBRT are emerging modalities that are alternatives to conventional EBRT. These strategies are image-guided radiotherapies that can deliver higher biologically effective dosages (BED) to improve cytotoxicity while sparing the adjacent normal tissues [90]. The addition of the IMRT paradigm also enhances its treatment profile. These modalities were initially utilized in spinal metastases as a treatment for residual and recurrent tumors that were radioresistant to EBRT. Gerszten et al. reviewed their experience with SRS for spinal metastases and found good long-term pain improvement and radiographic control of up to 96% and 100%, respectively, for various tumor types [41, 91–93]. Newer studies have evaluated its efficacy as a postoperative adjuvant and neoadjuvant therapy for spinal tumors [94–96]. The limitations with these studies are the retrospective nature in heterogeneous populations, non-standardized treatment protocol (i.e., fractionation and dosage) and metrics for outcomes such as pain control. Regardless, local control rates were up to 90% at 1 year and complete control of pain. Five-year outcomes for SRS showed good continued control [97]. Retreatment rates with SBRT were also effective overall [98]. Complication rates were low with a 0.2% risk of neurologic injury and 9% rate of compression fractures [96]. Clinical trials are currently underway to further characterize the role of SRS and SBRT for spinal metastases [65, 99–101].

SRS has also been shown to be a safe modality for residual and recurrent primary spinal cord tumors with low rates of progression in the short-term [77, 102–104]. Toxicity to the spinal cord was not observed in the treatment of intradural spinal cord tumors [102, 103]. A recent meta-analysis reviewed the overall safety profile and determined its effectiveness in tumor control for the management of intramedullary tumors with overall favorable clinical and radiological outcomes [105]. This study included a wide range of pathologies, with an overall local control rate of up

to 82% and a low incidence of radiation-induced toxicity of 4%. Monserrate et al. reported on utilizing cone-bean CT-guided SRS as a safe and accurate option for patients with intradural tumors [104].

SRS for recurrent and residual ependymomas is feasible and safe [106–108]. Lobón et al. published a 20-year experience of re-irradiation for recurrent spinal ependymomas in 32 pediatric patients and found a median progression-free survival and overall survival of 1.2 years and 3.5 years, respectively [107]. In those who progressed through the first radiation treatment, 15 patients achieved a greater progression-free survival after the second radiation treatment. In a retrospective study, Oh et al. defined a role for adjuvant radiation in delaying recurrence after subtotal resection of spinal cord ependymomas [108]. They reported on a cohort of 47 patients with subtotal resection who received adjuvant radiotherapy and found that progression-free survival was significantly prolonged compared with those patients who did not receive radiotherapy with a hazard ratio of 2.26 [108]. In contrast, other studies showed that radiation was not beneficial in patients who achieved gross-total resection for spinal ependymomas [109]. As such, reoperation should be weighed against radiation for residual or recurrent disease. Additionally, these studies are limited by the short-term follow-up and bias from a retrospective perspective. Larger more rigorous clinical studies are warranted.

SRS has also been applied to the treatment of spinal hemangioblastomas with favorable outcomes [110–114], and is well-tolerated [113]. These lesions can be multiple, as up to 30% of patients are diagnosed with von Hippel-Lindau (VHL) disease and thus must undergo a more thorough clinic-radiographic examination [115]. Pan et al. reviewed their experience of SRS for the treatment of spinal hemangioblastomas, which included 46 tumors in 28 patients [110]. The local control rate at 5 years was 92.3%, which are comparable to the control rates for intracranial hemangioblastomas. Patients with VHL also experienced an 81% improvement in symptoms. There were no complications noted in this study. Two recent meta-analyses indicate excellent long-term outcomes of up to 96% [116, 117]. Some controversy does exist regarding the timing of SRS for spinal hemangioblastomas in patients with VHL. Chang et al. have published extensively on their experience with SRS for hemangioblastomas, of which a small proportion of these patients have received SRS upfront as a primary treatment with good control rates [110]. However, a meta-analysis addressing this question did not find enough evidence to support this treatment, and highlighted the need for a prospective pooled analysis [117].

24.7 Conclusion

Radiation therapy is a viable option for the treatment of recurrent and residual intramedullary spinal cord tumors, but surgical resection remains the primary mode of treatment at the outset. EBRT is the traditional treatment modality, but contemporary therapies of SRS have emerged as a very promising therapy with good control rates and minimal toxicity. More studies are needed to define the role of radiation therapy in the treatment of residual and recurrent spinal cord tumors.

24.8 Case Illustrations

CS is a 31-year-old man who presented with complaints of spasticity, bowel and bladder dysfunction, and weakness in his legs. A contrasted MRI had shown a large expansile intradural mass from L3 to S2 (Fig. 24.1). He underwent a multi-level laminectomy for resection of this lesion and tolerated the procedure well. Final pathology was a grade I myxopapillary ependymoma over 5 years ago. On routine serial tumor surveillance MRI, he was found to have an interval growth of a small left L5–S1 component intradurally (Fig. 24.2). Given the progression, he underwent a conventional external beam radiation consisting of 16 fractions totaling 40Gy with a stereotactic boost to the tumor of 700 cGy (Fig. 24.3).

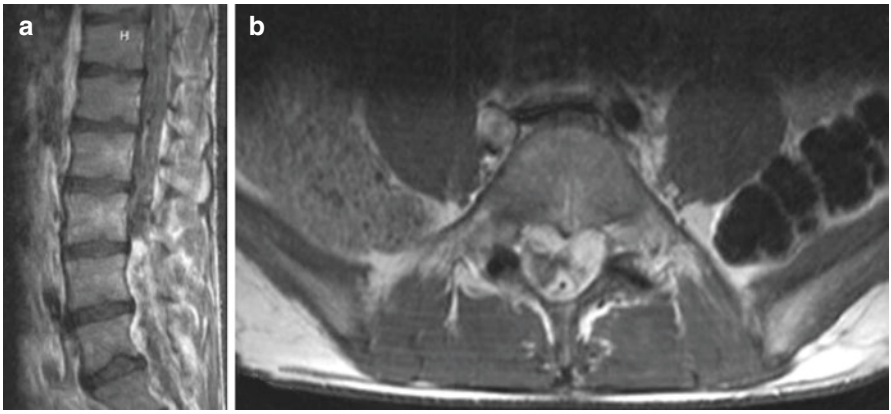

Fig. 24.1 Sagittal (**a**) and axial (**b**) MRI showing a large expansile intradural mass in a 31-year-old man from L3–S2

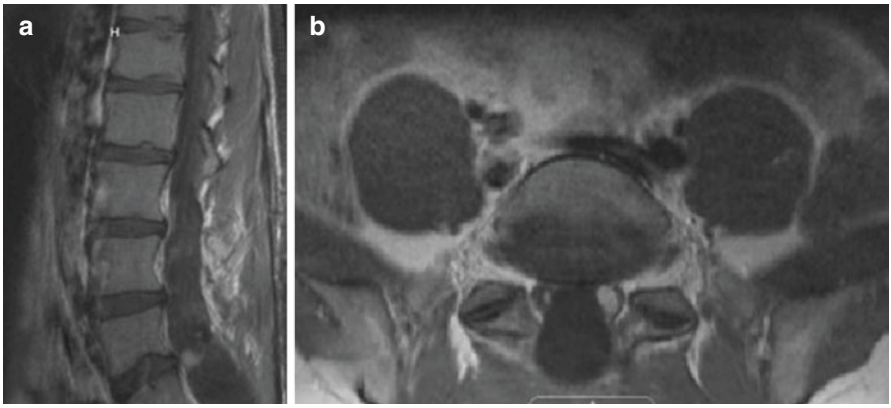

Fig. 24.2 Sagittal (**a**) and axial (**b**) MRI showing intradural growth of small left L5–S1 component

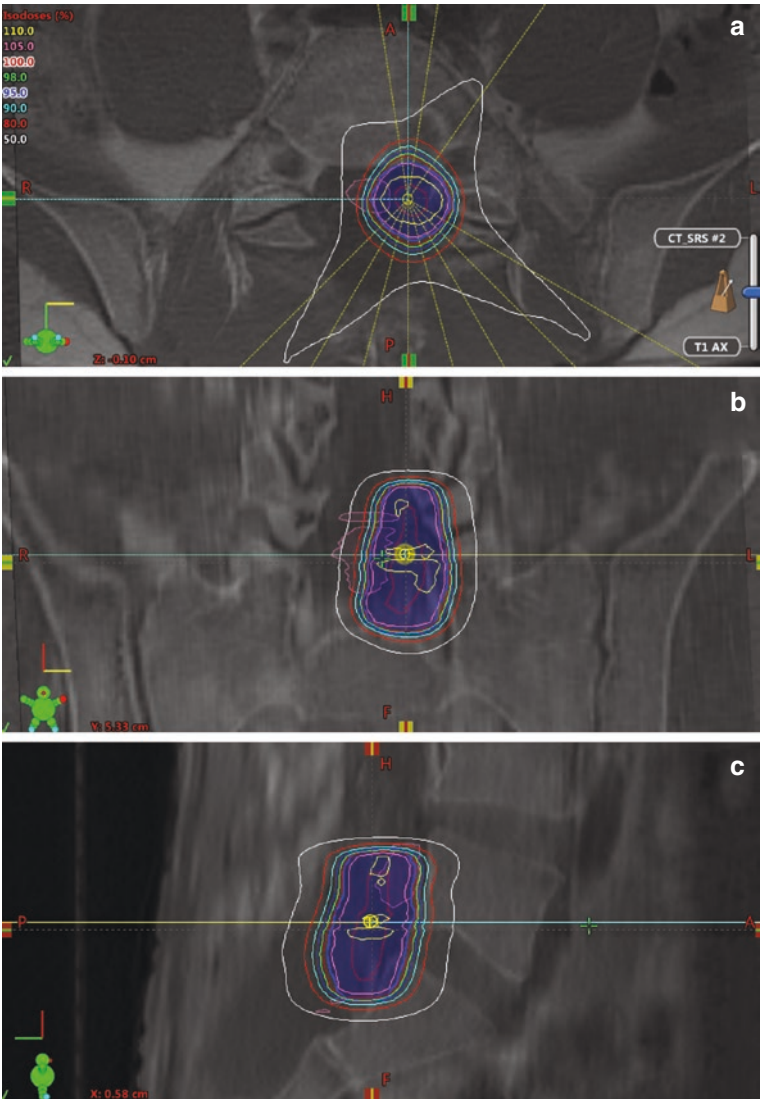

Fig. 24.3 (**a**, **b**, **c**) Conventional external beam radiation consisting of 16 fractions totaling 40 Gy with a stereotactic boost to the tumor of 700 cGy

Serial MRI surveillance showed radiographic stability until 7 years post-radiation, which showed interval growth (Fig. 24.4). After an extensive conversation of the options, the patient elected to undergo surgical resection. He tolerated the procedure well, and to date does not show recurrence 6 months out (Fig. 24.5).

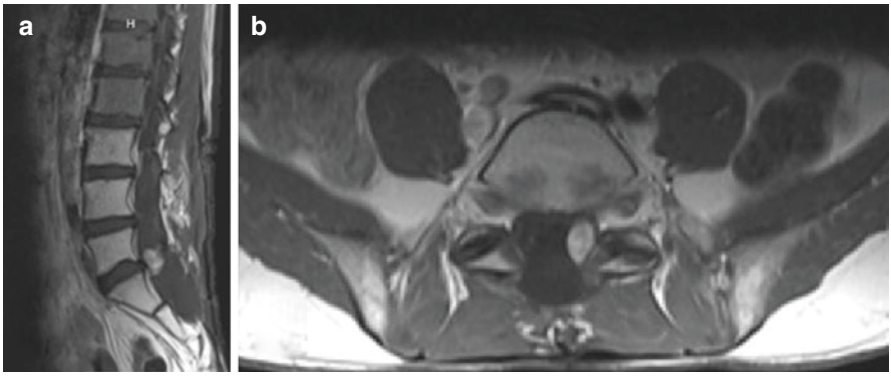

Fig. 24.4 Sagittal (**a**) and axial (**b**) MRI showing radiographic stability 7 years post-radiation, which showed interval growth

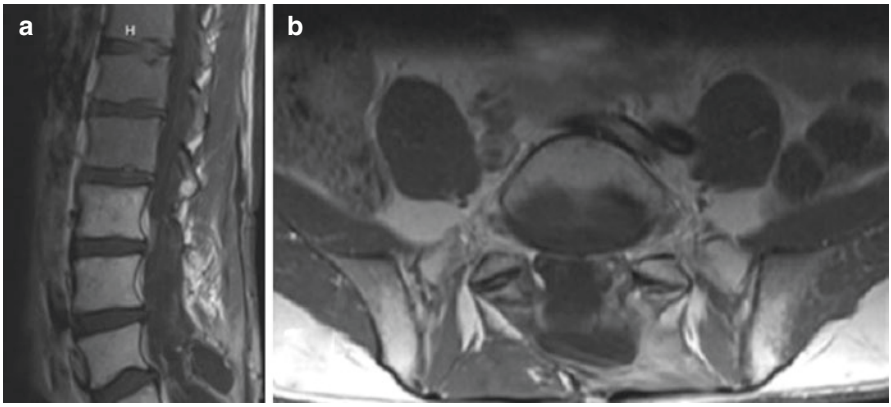

Fig. 24.5 Sagittal (**a**) and axial (**b**) MRI showing no tumor recurrence at 6-month follow-up

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Complications in Treatment of Spinal Cord Tumors and Prevention Surgical Strategies

25

Marko Kovacevic, Bruno Splavski, and Kenan I. Arnautović

25.1 Introduction

Both extramedullary and intramedullary intradural spinal cord tumors (SCTs) will often create early neurological signs and symptoms due to the infiltration and/or compression of neural structures in small spatial compartments, such as the spinal dural sac or a vertebral canal. Gross total tumor resection, whenever possible, is the goal in surgical treatment in order to relieve symptoms and preserve or improve neurological function, as well as to avoid tumor recurrence and repeated surgery. However, in cases of malignant or infiltrative tumors, radical resection may not be possible and may not prolong survival [1, 2]. In their classic work, Yasargil et al. [3] reported a successful radical removal of intramedullary spinal tumors using microsurgical techniques with favorable neurological outcomes. Since then, there have been many other studies of SCT reporting satisfactory outcomes [4–21].

Postoperative functional outcome mainly depends on tumor histology, molecular biology, genetic basis, tumor size and location, preoperative neurological status, utilized surgical technique, and postoperative care [12, 16, 22, 23]. Patients with severe preoperative neurological deficits may not recover functioning after surgery;

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their functioning may even worsen. Good results with better postoperative recovery and better functional outcome are more common in patients with short-term neurological deficits [11]. Upper thoracic lesions, for example, are associated with the highest rate of surgery-related complications and unfavorable postoperative functioning, possibly due to the anatomically narrow canal and relatively poor "transitional" blood supply in this region of the spine [12, 13]. With spinal nerve sheath tumor surgery, surgical complications are more common in cervical and lumbosacral tumors than in thoracic lesions [17].

Intraoperative imaging and neuronavigation are helpful tools to precisely localize lesions, lessen exposure, and preserve of normal spinal function. Bony exposure and extent can be optimized before dural incision, which may also be tailored to reduce the incidence of complications, such as leakage of cerebrospinal fluid (CSF) or accidental neural tissue damage.

Careful microsurgical technique is necessary to avoid postoperative neurological complications and infections. Despite precise techniques, a number of the patients may report sensory symptoms, such as dysesthesia after surgery due to surgical manipulation and dissection of the cord's posterior columns. Sensory disturbances may last a long time, but will usually improve postoperatively after a few months. They can often be persistent, which can interfere with early postoperative rehabilitation. They also may not respond to medical treatment. Residual symptoms may reduce patients' quality of life in a long-term. To avoid this, patients should receive neurophysiologic monitoring throughout surgery. Postoperative neurologic deficits after SCT surgery can also happen due to nerve root injury or avulsion, removal of a functional nerve root, or spinal cord manipulation with glial scarring (Fig. 25.1) [18].

Kalakoti et al. analyzed surgical risk factors and postoperative complications following resection of benign intradural spine tumors in adults in both low volume and high volume centers [24]. The study showed that there was a decreased risk for the most unfavorable outcomes for patients who underwent surgery at high volume centers. Inpatient postoperative risks included mortality (0.3%), wound complications (1.2%), cardiac complications (0.6%), deep vein thrombosis (1.4%), pulmonary embolism (2.1%), and neurological complications, including dural tears (2.4%).

Fisahn et al. analyzed readmission, reoperation, and complication rates of spinal cord tumor surgery highlighting how it is still involved with morbidity even in experienced and specialized centers [25]. In an analysis of National Surgical Quality Improvement Program (NSQIP) registry, Karhade et al. reported that 10.2% of patients undergoing surgery for spinal tumors were readmitted within 30 days, 5.3% underwent a reoperation, and 14.4% experienced a major complication [26]. The most common complications were surgical site infections (3.6%), systemic infections (2.9%), and venous thromboembolism (VTE) (4.5%). The strongest predictors of adverse events were comorbidities, preoperative steroid use, and a higher American Society of Anesthesiologists (ASA) classification [26]. Weber et al., reported a 50% increase in the mean hospital cost per patient with cerebrospinal fluid (CSF)-related postoperative complications after elective spinal surgery.

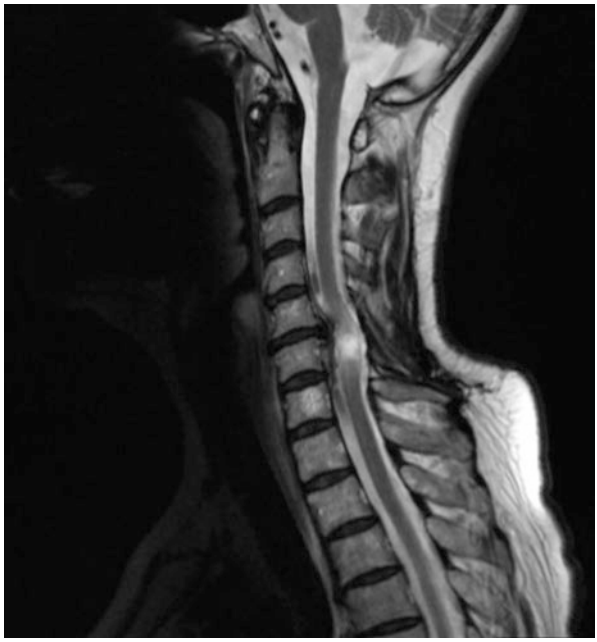

Fig. 25.1 Postoperative T-2 weighted sagittal MRI showing progressive degenerative changes—spondylosis and herniated cervical disk at C5/6 with kinking of the spinal cord—and MRI signal intensity change after removal of intradural intramedullary tumor and 2 level laminectomies 2 years after surgery

Furthermore, these complications may lead to additional complications, creating a vicious circle and even lethal outcomes [27].

In this chapter, we discuss different surgical complications, and their prevention and treatment.

25.2 CSF Dissemination, Seeding and Metastasis

SCT can disseminate through CSF pathways and cause metastases along the neural axis, albeit infrequently (Fig. 25.2). This is common in malignant and more aggressive SCT, such as grade III and IV astrocytomas and intradural chordomas, but has been reported also in myxopapillary ependymomas and meningiomas [28–30]. Surgical or secondary seeding of myxopapillary ependymomas after surgery is relatively uncommon—but usually occurs after subtotal resection—with recurrence at the site of resection in adults, and more often in the pediatric population, together with the disseminated disease. However, primary seeding of myxopapillary ependymoma has been reported both in adult and pediatric population [30]. Arnautović and Al-Mefty found a case of cervical spine chordoma with surgical seeding as a consequence of the implantation of tumor cells along the surgical route in the neck muscles and subcutaneous tissue [28]. Ito et al., reported a case of intraspinal meningioma with malignant transformation from atypical to anaplastic meningioma with distant hematogenous metastasis [29]. Careful postoperative craniospinal magnetic resonance imaging (MRI) evaluation and surveillance with and without contrast should

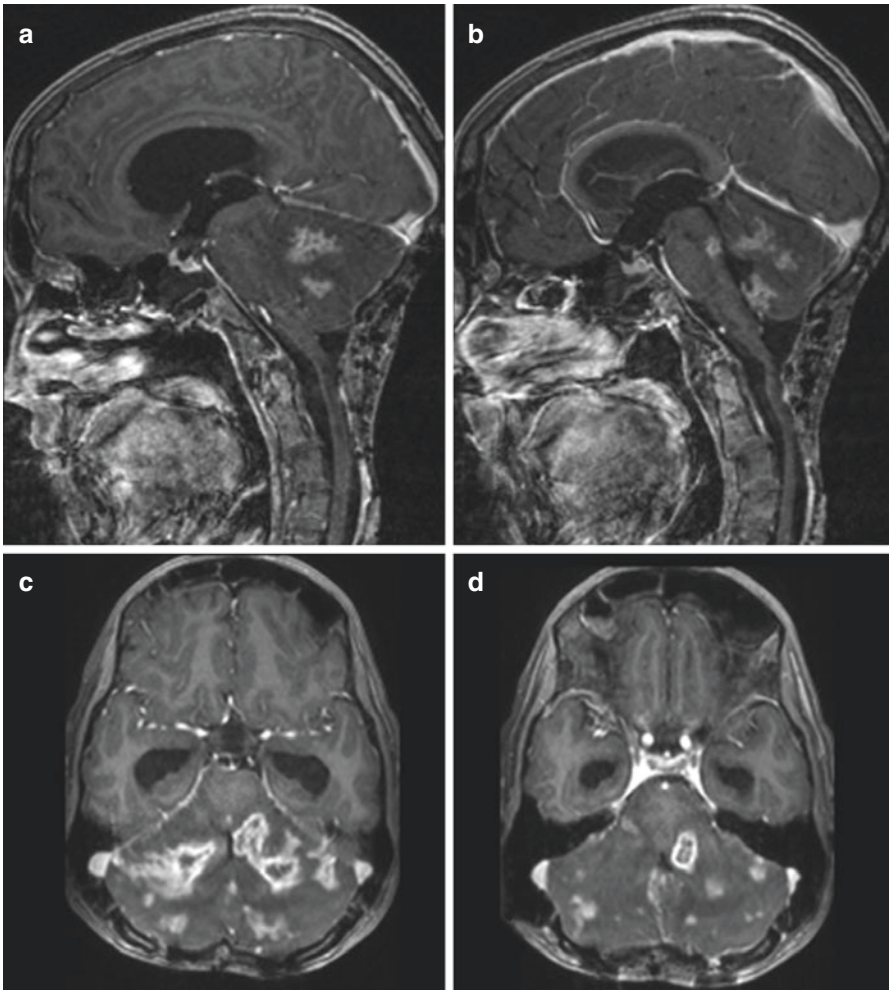

Fig. 25.2 Postoperative T-1 weighted MRIs with contrast. (**a**, **b**) Sagittal and (**c**, **d**) axial views showing diffuse enhancing cerebellar metastases 2 years after resection of pediatric primary spinal intramedullary embryonal tumor with multilayered rosettes (former PNET)

be considered regularly during follow up and in case of unexpected or unexplained neurological deterioration.

These complications can be provoked by surgical manipulation and/or partial resection and will need to be treated with additional surgery, irradiation, and/or chemotherapy. However, radiation therapy after subtotal resection of spinal cord tumors may complicate future surgery since the spinal cord can be damaged with effective radiation doses. Additionally, it can create spinal column deformity and produce a secondary malignancy as well [31, 32].

Introduction of radiosurgery helped to minimize these concerns. Promising results with low rates of complications have been shown with stereotactic radiosurgery treatment for benign tumors, but further studies are needed to determine the indications and outcome profile of stereotactic radiosurgery for intradural spinal tumors [33].

25.3 Spinal Column Deformities

Spinal column deformities are a possible postoperative complication of early or late intradural spinal tumor surgery (Fig. 25.3). Adequate approach to such tumors may require extensive laminectomies which may result in spinal instability that may require further surgical treatment involving spinal instrumentation and fusion [32, 34, 35]. Advancement of preoperative spinal column degenerative changes and/or development of the new changes during the follow-up can be exaggerated or caused by inadequate or extensive bone decompression for the removal of SCT (Figs. 25.1 and 25.3). Careful preoperative planning, analysis of MRI scans, computerized tomography (CT) scans in sagittal, coronal, and axial reconstruction (including bone windows and anterior-posterior, lateral, dynamic, flexion and extension X-rays) are essential in planning the extent and type of operative bone resection and the possible need for simultaneous instrumented fusion.

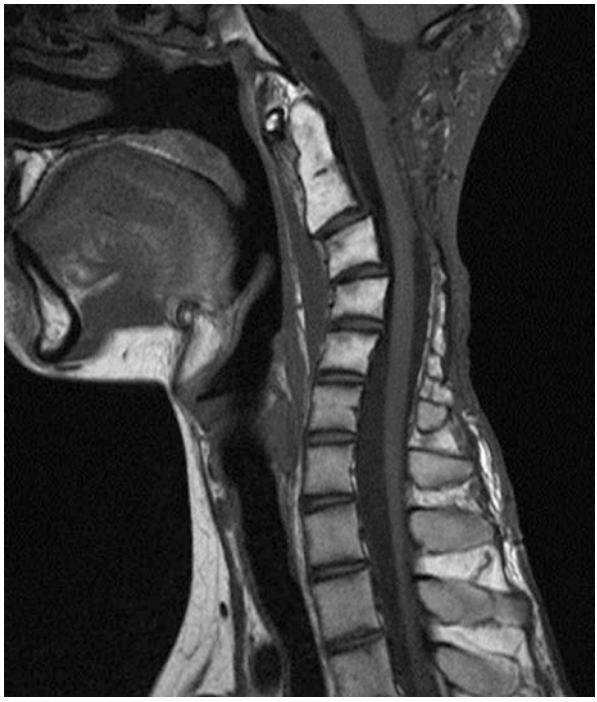

Fig. 25.3 Postoperative T-1 weighted sagittal pre-contrast MRI showing kyphotic deformity in a 16-year-old patient after multiple laminectomies in the upper cervical spine

Papagelopoulos et al. found that 28% of children and young patients treated with lumbar or thoracolumbar multisegment laminectomy for intraspinal tumors exhibited spinal column deformity and instability [35]. Laminoplasty for prevention of spinal deformity after spinal intradural tumor surgery is a strategy used by many authors [36]. In 1989, Chiou et al., reported that unilateral approaches were advantageous for spinal tumor surgery with fewer complications, especially for juxtamedullary benign tumors [37]. With a unilateral technique, stability can be preserved due in part to the protection of musculoligamentous attachments and posterior bony elements [38].

Less invasive approaches—or minimally invasive surgical (MIS) approaches—recently have gained popularity in spinal intradural surgery. MIS techniques showed efficacy and safety for the treatment of spinal intradural tumors with no increased complications. Some authors reported a reduced complication rate with a significant decrease in hospital costs [39–42]. Parihar et al., reported a study with endoscopic management of spinal intradural extramedullary tumors in 18 patients with a short follow-up [43]. Although it is a technically demanding procedure, endoscopic management for this kind of pathology was shown to be efficacious and safe. The advantages for spinal intradural tumor MIS may include decreased operative blood loss, shorter hospitalization, and less postoperative pain. Disadvantages include prolonged operative times, decreased surgical exposure, and decreased difficulty with closing the dura due to a limited surgical corridor and a steep learning curve. To date, however, MIS approaches have not gained widespread acceptance in SCT surgery.

25.4 Complications Related to Anesthesia

In order to obtain the best surgical results, it is necessary to optimize the management of preoperative and perioperative anesthesia. Any potential health problem and preoperative risk factors should be evaluated and any comorbidity that arises should be addressed. For surgeries expecting blood loss, 1 or 2 blood doses should always be reserved for transfusion. (Anesthetic considerations will be discussed in a separate chapter of this book.)

25.5 Surgical Positioning Complications

Correct positioning of the patient for spine surgery is imperative and of great importance. Complications associated with surgical positioning are rare, and therefore tend to be underreported in the literature. The risk for these complications can be minimized with careful surgical planning and close detailed attention during the patient's positioning, using prevention strategies to avoid complications.

25.5.1 Pressure Injuries

Decubitus ulcers, or pressure sores, are local skin and underlying tissue injuries resulting from prolonged pressure during a surgical procedure due to inappropriate positioning. Prone positioning places pressure on the forehead, chin, shoulders, thorax, pelvis, knees, and ankles. Prolonged pressure lasting for a few hours can cause tissue ischemia and resulting necrosis. The risk factors for the development of ulcers are older age, obesity, diabetes, and the administration of steroids, although the duration of surgery may be the biggest risk factor. Appropriate padding and attention during positioning should be given to protect bony prominences and joints (e.g., the facial area, elbows, anterior superior iliac spines, knees, and feet). External genitals must be free of pressure or traction caused by urethral catheters.

Compartment syndrome after spine surgery is rare, albeit anterior thigh and anterior tibial compartment syndromes have both been reported. Two cases of anterior thigh compartment syndrome after lumbar spine surgery have been reported [44]. Both patients were obese and positioned on a Jackson table with well-padded bony prominences, but the thigh and iliac crest pads were switched in order to increase lumbar lordosis. Postoperatively, the patients complained of moderate quadriceps weakness with pain and stiffness in their thighs. In one case, the patient improved and postoperative MRI of the thighs revealed local muscle necrosis. In the other case, the patient had severe pain and thigh swelling. Consequently, fasciotomy was performed on postoperative day 2. In spite that, the patient developed rhabdomyolysis and acute kidney injury [44].

25.5.2 Hemodynamic Complications

Prone positioning during spinal tumor surgery can seriously affect the patient's vascular system. If the abdomen is not free of compression during the surgery, this can restrict the blood flow through the inferior vena cava, which then results with swelling of the epidural veins. Consequently, the blood stasis in the spinal canal can cause excessive bleeding in the surgical field, which can aggravate the operation, significantly extend the time of the procedure, and increase blood loss. There is a risk of hypovolemia with postural hypotension and reduced cardiac function in the prone position combined with the excessive blood loss can deteriorate hypoperfusion to multiple organ systems, leading to acute kidney failure. Abdominal compression during surgery in the prone position and increased intraabdominal pressure should be avoided with proper positioning on the surgical table using appropriate frames and supports. Although rare, complications following peripheral arterial and vein compression during surgical positioning can also be avoided with properly secured pressure points (i.e., carotid/jugular, femoral).

25.5.3 Ophthalmologic Complications

The incidence of perioperative visual loss after spine surgery ranges from 0.02–0.2% with an increased risk related to prone positioning and comorbidities like diabetes mellitus and coagulopathies. Various causes of perioperative visual loss have been described, including direct compression, anterior and posterior ischemic optic neuropathy, central retinal artery or vein occlusion, cortical blindness, acute closed-angle glaucoma, and amaurosis [45].

Ischemic optic neuropathy is the most common cause of perioperative visual loss. Risk factors include anemia, diabetes, obesity, male gender, Wilson frame use, microvascular pathology, prolonged operative time, longer anesthetic duration, increase in orbital venous pressure due to Trendelenburg positioning and placement of the head below the heart, intraoperative hypotension, and extensive blood loss. Patients usually notice prodromal blurred vision or immediate vision loss upon waking from general anesthesia, which can result in complete blindness with no effective treatment available.

Central retinal artery occlusion (headrest syndrome) is the second-most common cause of perioperative visual loss after spine surgery in prone position. Suggested etiology includes thromboembolism or increased intraocular pressure from direct compression of the ocular bulb, which disrupts perfusion of the retina. Patients usually have unilateral periorbital ecchymosis and visual loss that is irreversible with no effective treatment. A cherry-red spot on the macula can be located with fundoscopic exam.

Cortical blindness is a result of decreased perfusion of the occipital lobe visual cortex. Etiology includes thromboembolism, hypotension, or cardiac arrest. Symptoms are usually barely conspicuous. Fundoscopy is usually normal, but visual field testing will reveal visual field defects. Unilateral cortical blindness is present with contralateral homonymous hemianopia, and bilateral cortical blindness may cause complete peripheral vision loss. After initial ischemic insult, symptoms usually ameliorate without treatment, but full recovery is rare.

Acute angle-closure glaucoma can result from prone positioning in susceptible patients. In 2010, Singer and Salim reported a case of bilateral acute angle-closure glaucoma after spine surgery with eye pain and nausea [46]. Optional treatment is laser iridotomy.

Amaurosis represents the permanent or transient (*amaurosis fugax*) loss of vision without obvious eye lesion. Etiology is proposed to be thrombosis or embolic stroke of the ophthalmic artery. Subconjunctival hemorrhage is an infrequent asymptomatic complication of spine surgery in the prone position with no need for treatment.

25.5.4 Prevention of Ophthalmologic Complications

Strategies to prevent or reduce the risk of ophthalmologic complications are proper positioning with avoidance of ocular bulb compression, neutral-head or slight

head-up position, reverse Trendelenburg positioning and the employment of frames that prevent abdominal compression. Diminishing orbital venous pressure or intraocular pressure reduces the risk for perioperative visual loss. Limiting prolonged intraoperative hypotension and the duration of anesthesia is also helpful. Special caution and care should be taken in high-risk patients with obesity and comorbidities like diabetes, vascular disease, anemia, or in patients where excessive blood loss and prolonged operation is expected. Lubrication of the cornea (ocular ointment) and adequate eye occlusion are necessary to avoid direct corneal damage [45]. Using adherent googles for eye protection may help minimize ophthalmologic complications.

25.5.5 Neurological Complications

As a result of inadequate prone positioning, certain neurological complications such as brachial plexus injury, acute cervical myelopathy or spinal cord infarction can occur.

Brachial plexus injury. The brachial neural plexus is under increased risk of traction injury. Postoperative brachial plexus injury and other peripheral nerve injuries are considered common complications due to inadequate positioning during spinal surgery. A neuropraxia or axonotmesis are the most common types of injury. Recovery is expected, but complete improvement is rarely achieved. Hypovolemia, hypothermia, diabetes mellitus, and other adverse conditions increase the risk of nerve injury.

In 2010, Uribe et al. reported a review of postoperative brachial plexus injuries identified in 17 out of 517 patients after spine surgery in prone position [47]. The risk for the injury was higher with the hyper-abduction of the arm, extension and external rotation of the arm, rotation and lateral flexion of neck, and application of shoulder braces. Intraoperative electrophysiological monitoring (SSEPs and MEPs) was used to identify the injury in 15 patients, as well as for the prevention of further injury. No electrophysiological evidence of injury was noticed in the remaining two patients who had transient upper extremity weakness postoperatively that resolved within few weeks [47].

Spinal cord injury. Although a rare complication, injury of the spinal cord can happen during spinal surgery. It may happen indirectly in patients who have concomitant cervical spine disease with severe stenosis or degenerative instability, and can be more common among the elderly population. It is advisable to obtain X-rays of the cervical spine in all patients who may have a suspected cervical spine degenerative disease. It is important to pay attention and carefully manage the neck during intubation, as well as during the positioning of the patient. This injury may result from a combination of neck extension during endotracheal intubation and inappropriate prone positioning, muscle relaxation during anesthesia, and rough manipulation during surgery.

Spinal cord infarction. Following prone positioning, spinal cord infarction is rare but can happen in severe hypotension during surgery, especially when the

patient is hypovolemic. This type of injury occurs during spinal intradural tumor surgery when spinal cord blood supply is endangered due to surgical manipulation. Meticulous surgical technique is necessary to preserve spinal cord vascularization and avoid mechanical damage to the neural tissue.

A rare case of neurologic deterioration after spinal cord tumor surgery was reported due to intradural tension pneumorrhachis [48]. Development of syringomyelia years after removal of benign spinal extramedullary neoplasm may also lead to late neurological deterioration [49].

25.5.6 Other Peripheral Neuropathies

These rare but important perioperative complications can result in significant patient disability and loss of function. In 2009, Welch et al. reported the incidence of perioperative peripheral nerve injury at a single institution during a 10-year period as 0.03–0.1% [50]. The most common perioperative peripheral nerve injury was ulnar neuropathy, which occurred in 0.5% of surgical patients, primarily men between 50–75 years of age. It occurred in 3 out of 7 patients who had developed permanent neuropathy with residual symptoms. The injury had a delayed onset with symptoms developing within a few days postoperatively. The symptoms included the loss of hand grip strength, discomfort, and numbness [50].

Patients with sensory deficits have a better chance for complete recovery compared with those who have combined motor and sensory deficits. Permanent injury leads to a claw-like deformity due to atrophy of the intrinsic muscles of the hand. Injury can occur due to excessive flexion of the elbow or direct pressure on the nerve over the cubital tunnel (or the collateral ulnar artery and vein), or if the arm of the patient accidentally falls off of the arm board during surgery, both of which resulting in reduced perfusion and ischemia.

Cho et al. reported lateral femoral cutaneous nerve neuropathy—or meralgia paresthetica—as a result of direct compression, which accounted for an incidence of up to 24% after spinal surgery in prone position [51]. Compression usually occurs due to the placement of pelvic bolsters near the anterior superior iliac spine. Risk increases with the duration of surgery and degenerative spinal disease with previous damage of the lumbar nerve roots. Patients postoperatively complain of paresthesia in the thigh, although complete resolution is expected within several months.

25.5.7 Intraoperative Neurophysiological Neuromonitoring

The modalities of intraoperative monitoring include somatosensory evoked potentials (SSEP) and motor evoked potentials. SSEP monitoring is used to detect peripheral nerve conduction abnormalities that show peripheral nerve stress and threaten injury. It indicates position modification to protect peripheral nerves from injury under general anesthesia during surgery. The incidence of position related

significant upper extremity SSEP changes during spine surgery ranges from 1.8 to 15% [52].

25.5.8 Airway and Vascular Complications

Some rare airway and vascular complications are associated with prone positioning during spine surgery. Tongue-bite protector devices or strategies should always be considered with patients in the prone position. Miura et al. reported a case of massive tongue swelling, causing airway obstruction after spinal surgery [53]. Orpen et al. reported 2 cases of bilateral avascular necrosis of the femoral head and 1 case of unilateral avascular necrosis after lumbar spine surgery [54]. Signs of early osteoarthritis were seen on preoperative radiographs, which increased probable susceptibility to ischemic insult. Pressure on the inguinal area with artery compression, combined with reduced venous outflow and hypotension, were related to avascular necrosis of the femoral head.

25.6 Wound Complications

Local surgical-site complications are important causes of postoperative morbidity following spinal surgery. Disruption of skin sutures or failure of the wound to heal can lead to rupture of the wound closure, seroma or hematoma formation, wound dehiscence, and wound infection (superficial or deep wound abscess). Risk factors that contribute to wound healing complications are excessive suture tension, poor blood supply, diabetes, steroid treatment, malnutrition, radiotherapy, and immunosuppressive therapy. All wound complications can lead to wound defects and scarring with poor cosmetic appearance.

Seroma and hematoma are excessive collections of serous fluid or blood in the wound of the surgical site. Hematomas are frequently the result of inadequate primary hemostasis, unrecognized preoperative bleeding diathesis, or increased use of preoperative anticoagulants and prophylactic treatments for deep vein thrombosis. They can cause the skin incision to separate and predispose wound infection since there is no skin barrier against causative bacteria, which can then get into deeper layers of the wound. Clinical manifestations usually appear a few days postoperatively. Seroma or hematoma in the wound may be asymptomatic or manifest with swelling, pain or drainage. Their presence increases the pressure to the wound and compresses surrounding blood vessels, causing wound ischemia and possible tissue necrosis. Hematomas can also cause necrosis due to induction of cytotoxic mechanism by free-radicals. Local erythema, wound induration, fever, and leukocytosis are possible if the collection is infected. Late postoperative hematoma a few days after surgery usually occurs due to the infection that damages vessels at the operation site. Additional diagnostic assessment can be done with ultrasound, CT and MRI to verify the extent of collection, which is especially important in case of possible CSF leak and pseudomeningocele formation. Treating these complications can

sometimes be difficult because it includes fine-needle aspiration, which usually needs to be repeated and carries the risk of infection entering the wound. In many cases the surgical re-exploration is recommended. To prevent seroma and hematoma formation, delicate surgical technique with careful control of bleeding is imperative. Since fluid collects in surgically-created "dead spaces," it is important to diminish or eliminate these potential spaces. Quilting sutures may be used to reduce the "dead space" formation and drains can be inserted for fluid drainage, which is carefully monitored postoperatively, so that the wound layers would close more easily and the body's natural fibrin glue could connect the layers for better wound healing.

Wound dehiscence is a partial or complete disruption of wound closure along the surgical incision. This is a serious complication that may lead to local infection, wound opening, and the possibility of repeated dehiscence. Management includes analgesics, fluid resuscitation, prophylactic antibiotics, early cutting and re-suture of the edges under general anesthesia for clean wounds, or secondary wound closure with frequent sterile dressing changes to the wound and debridement for infected wounds. Prevention is achieved through reducing stress on the wound edges by adequate undermining, avoiding physical stress, adequate nutrition, diabetes control, and certain medications, such as corticosteroids. Sterile strips may be used to reinforce the suture line.

Wound infection is a relatively frequent complication after spinal surgery. These complications significantly increase the length of hospital stay and hospitalization costs. The most common form is a superficial wound infection that occurs during the first week postoperatively and presents with localized pain, redness, and slight discharge or pus draining. It is necessary to make wound culture sampling for appropriate antibiotic treatment according to antibiogram. Wound debridement and cleansing should be regularly done with frequent sterile dressing changes that allow the tissue to granulate. The wound heals by secondary intention over several weeks. Early or delayed closure of infected wounds is not recommended because it is associated with relapse of infection and wound dehiscence.

Cellulitis and abscesses usually present within the first few weeks postoperatively, but can be seen later, even after hospital discharge. They present with pyrexia and local signs of redness and a painful lump due to pressure and inflammation. Cellulitis is treated with antibiotics. An abscess is a collection of pus, bacteria, and debris; treatment—aside from antibiotic use—is surgical incision and drainage. Superficial abscesses can drain spontaneously or require suture removal and probing of the wound, but deeper abscesses require surgical re-exploration for deeper tissues to be inspected for integrity and the source of infection. The wound is left open to heal by secondary intention. Deep chronic abscess can form a wound sinus with possible fistula formation, which requires surgical re-exploration.

To minimize the risk for wound infection, it is important to identify and treat all infections distant to surgical site, as well as to delay elective surgery until the infection is treated. Preoperative hyperglycemia should be avoided and blood glucose level optimized. The night before surgery, patients need to have a shower/

bathe with antiseptic soap. Preoperatively, attention should be given to proper asepsis and surgical site preparation. Commitment to generally accepted surgical principles of delicate and minimal tissue dissection and proper wound closure is important.

Antibiotic prophylaxis for the prevention of wound infection is recommended because the consequences of infection after spinal intradural surgery can be severe. The selected antibiotic should be effective against the predicted pathogens likely to be encountered during the surgical procedure with good tissue penetration and cost effectiveness. Antibiotics are administered intravenously, generally 30–60 minutes prior to surgical incision. The timing of administration is very important because the concentration of the antibiotic should be at therapeutic levels during the time of surgery and for a few hours postoperatively. Usually, the administration of antibiotics is continued postoperatively for the duration of drains *in situ*.

The incidence of antimicrobial resistance has increased over the past few decades and it is of great importance to minimize the continuing emergence of antibiotic pathogen resistance because the current rate of development of new antibiotic treatments is insufficient. It is critically important to avoid unnecessary antibiotic administration and to increase the effectiveness of prescribed antibiotics. Methods of prevention and effective treatment are mandatory to reduce the frequency, morbidity, and costs associated with surgical site infections.

25.7 Other Infective Complications

25.7.1 Meningitis

Meningitis is the most intimidating cause of morbidity and mortality in neurosurgical patients. It can be a serious complication and life-threatening condition after spinal surgery. The reported incidence of postoperative meningitis varies between 0.4 and 7% [55, 56]. In the study by McClelland et al. [56], the incidence of postoperative meningitis was 0.4% out of 492 spinal surgery cases. The most common causative organism was *Staphylococcus aureus*. The incidence of meningitis after spinal surgery is higher in patients with intradural tumors due to dural opening with possible postoperative CSF leak. Every accidental dural tear with CSF leak after spinal surgery increases the chance of developing meningitis. Other risk factors include diabetes, alcoholism, compromised immune system, and immunosuppressive therapy. In case of suspected meningitis, a CSF sample should be taken for gram stain and microbial culture. Antibiotic or a combination of antibiotics should be given empirically or based on sensitivity from gram stain results [57]. Good CSF drug penetration is mandatory. In combination with antimicrobial treatment, corticosteroids reduce the inflammation in the subarachnoid space and improve the outcome of bacterial meningitis. Meningitis is sometimes difficult to treat and without proper prevention, it may become a severe complication that significantly increases the length of hospital stay and the cost of medical treatment, especially in cases with multidrug-resistant infections.

25.7.2 Urinary Tract Infection

Nosocomial urinary tract infections are the most common of all hospital-acquired infections. The risk for developing nosocomial urinary infections increases in patients with urinary catheters, older patients, and those with comorbidities, such as diabetes and obesity. Almost 80% of hospital-acquired urinary tract infections are associated with urinary catheters. Patients with spinal cord tumors or injury have an increased risk for urinary tract infection because of retention and chronic catheter use. The causative organisms usually originate from the patient's endogenous intestinal flora. The most common cause of infection is *Escherichia coli*, although other bacteria or fungi may be the cause of infection, too. Preventive measures include sterile equipment and catheterization using an aseptic technique for insertion. Nosocomial pathogens have a higher antibiotic resistance than simple urinary infections. Urinary tract infections should be treated with targeted antibiotics only after a urine sample microbiological analysis.

25.7.3 Pneumonia

Postoperative pneumonia is a hospital-acquired or ventilator-associated disease after endotracheal intubation. It is the second most common nosocomial infection after urinary tract infection and the leading cause of mortality attributed to infection. Pneumonia is usually bacterial and most infections are caused by gram-negative aerobes like *Pseudomonas aeruginosa, Klebsiella pneumoniae, Enterobacter species, Serratia,* and *Acinetobacter species.* However, *Methicillin-resistant Staphylococcus aureus* (MRSA) is the predominant gram-positive pathogen. Preventive strategies may be nonpharmacological and pharmacological. Major strategies for effective prevention of postoperative pneumonia are good postoperative care, infection-control practice, and surveillance of local nosocomial infection rates.

25.8 CSF-Related Complications after Intradural Spinal Tumor Surgery

The incidence of CSF-related complications after intradural spinal tumor surgery is hypothesized to be underreported, but still remains high nevertheless. It has been reported between 5–18% of patients [1–12, 20, 21, 55]. CSF leak is a potential and common complication after any dural opening, occurring accidentally or during intradural tumor surgery, which can lead to significant morbidity and mortality. It can be asymptomatic or cause intracranial hypotension with persistent headaches, nausea, and vomiting. Neuropathic pain and neurologic deficits can be caused by neural elements' herniation (protrusion) out of dural opening. Locally, it can present with wound swelling or CSF drainage through the skin incision, which can be seen as leakage that creates a central reddish spot with a surrounding halo on

wound-coverage gauze or bed sheets. Consequently, there is a high risk for the development of meningitis, and/or pseudomeningocele and fistula formation.

MRI remains the gold standard in diagnostics of CSF fistulae and their complications (Fig. 25.4). If CSF leak is suspected, additional confirmation can be achieved with the analysis for Beta-2 transferrin, which is a specific protein marker for CSF.

Treating these complications is a vexing problem and often requires prolonged post-operative bed rest, surgical re-exploration, placement of an external lumbar drain, and a prolonged use of antibiotics [12–16, 18–20]. Despite Mayfield and

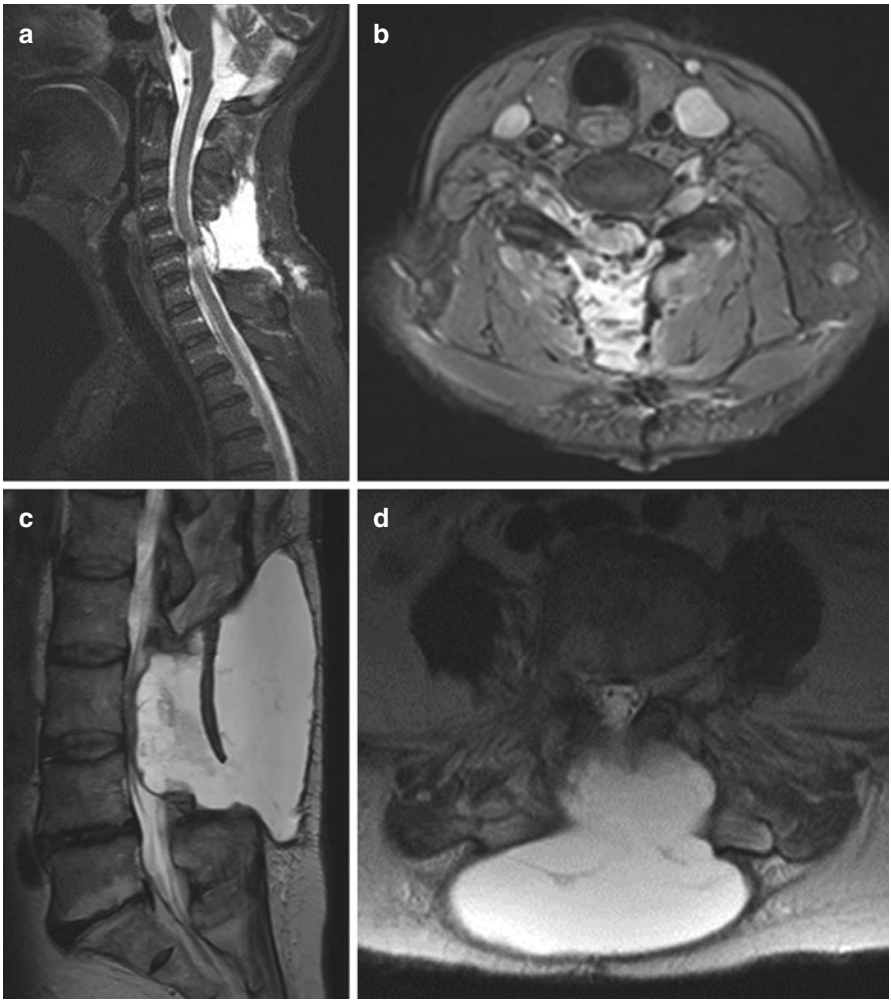

Fig. 25.4 Postoperative T-2 weighted sagittal and axial MRIs showing CSF leak into dorsal tissue with giant pseudomeningocele and fistula formation compressing the thecal sac after intradural tumor surgery in cervical (**a**, **b**) and lumbar spine (**c**, **d**)

Black's recommendation to use a fat graft to prevent spinal surgery CSF complications [58, 59], the current practice has not gained routine use. However, some authors have prospectively adopted the intraoperative use of autologous fat grafting for dural closure. Arnautović reported a case series of 40 consecutive patients treated surgically for spinal intradural tumors with no CSF-related complications postoperatively using this technique [60].

Two recent studies evaluated the efficacy of polyethylene glycol sealants in an attempt to decrease the rate of CSF-related complications after intradural spinal surgery [61, 62]. Goodwin et al. reported that CSF leaks occurred in 5% of patients and meningitis occurred in 1% in their series [61]. Similarly, Wright et al. compared the use of polyethylene glycol sealant with standard dural closure [62]. The rate of complications related to CSF leak requiring re-operation in the sealant treated group was 7% compared with 13% in the standard dural closure cohort. Besides that, each cohort had an additional 4% rate of pseudomeningocele formation that did not require re-operation.

The effect of CSF-related complications on outcomes is particularly important in older patients with medical comorbidities. Such patients may not tolerate the prolonged bed rest required to manage the CSF-related postoperative complications. An increased number of elderly patients with intradural spinal tumors (ISTs) who require surgical treatment have also been reported by Sacko et al. [16]. The additional complications mentioned earlier can also jeopardize an otherwise successful surgery and rehabilitation process.

25.8.1 Prevention Strategies

After tumor resection the dura is usually closed primarily, if possible. Sometimes a dural patch graft may be necessary for dural closure (autologous fascia lata, thoracodorsal fascia patch graft, or artificial dural substitute patches) (Fig. 25.5).

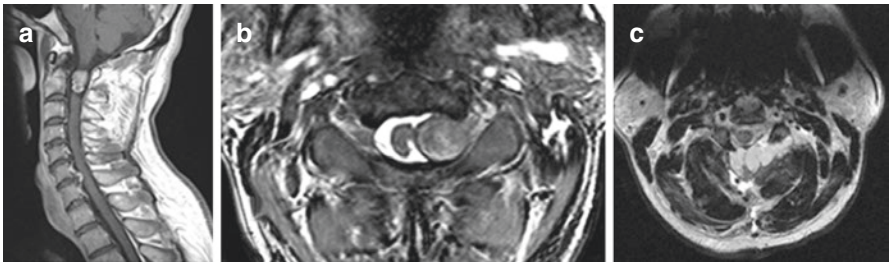

Fig. 25.5 (**a**) Post-contrast sagittal T1-weighted MRI showing the enhancing tumor intradural, extramedullary tumor (schwannoma at C1–C2). (**b**) Axial T2-weighted MRI showing the left-sided tumor involving the C1–C2 intervertebral foramen and compressing the spinal cord. (**c**) Postoperative axial T2-weighted MRI showing the radical tumor resection. Note the fat graft overlying the dura dorsally and reinforcing dural closure

Meticulous closure technique is obligatory, especially for repeated surgeries or a previously irradiated spine. Bed rest is recommended for 24 to 48 hours after surgery to minimize CSF pressure on the dural closure. Thromboprophylaxis is needed during this period, after which gradual mobilization and physical therapy should commence. Any suspicion of CSF leak should be treated early; wound revision is necessary to prevent further complications.

25.8.2 The Technique of Dural Closure by Autologous Fat Grafting

If the dural incision is in the midline after watertight dural closure, the Valsalva maneuver is performed at 30 cm H_20 for 5–10 s to ensure the dura is closed properly. If any area in the suture line leaked CSF, an additional suture is placed and a piece of fat tissue cut and positioned inside the stitch, which is then tightened. This maneuver reinforces the dural closure.

If the dural incision is T-shaped (i.e., for dumbbell, intra/extradural, or foraminal tumors), or Y-shaped (i.e., for sacral canal/foraminal tumors), the dural incision in the midline and its T or Y-shaped extension over the spinal nerve root are closed in running fashion with 5–0 Prolene stitches. Multiple pieces of fat tissue are then incorporated into single additional dural sutures to achieve watertight closure and reinforce the dural closing. When suturing is complete, a layer of fat tissue 6–8 mm thick is placed over the entire exposed dura to obliterate the dead space remaining after a laminectomy or facetectomy. The fat tissue allograft nicely conforms to the allotted space and serves as filler. The fat graft also creates light pressure on the dural suture line, lessening the chance of CSF seepage and pseudomeningocele formation. In other words, the graft prevents a potential low-pressure space into which CSF may migrate and form a pseudomeningocele, later producing CSF leak. Finally, fibrin glue is applied over the graft to conclude the procedure.

The spinal dura appears to be the thickest dorsally in the midline and thins laterally, particularly along the dural sleeves of the spinal nerve roots. Therefore, a running dural midline suture is used to achieve watertight closure after the tumor is removed, and then the Valsalva maneuver is used to ensure it. Still, there is no guarantee that the suture line will not weaken or that a leak will not occur after the patient is mobilized postoperatively, when CSF fully replenishes and patient engages in full physiologic CSF pressure challenges on the dural suture line. However, CSF may still seep into the low pressure dead-space created after a laminectomy, leading to a pseudomeningocele formation or CSF leak. Reinforcing the dural suture line with autologous fat is useful, particularly in cases when the Valsalva maneuver revealed CSF seepage. In addition, the fat graft obliterates the dead space created by a laminectomy and muscle dissection, and generates gentle pressure to the dural suture line. After 1 year follow-up, MRI scans of the spine usually show that the fat autograft is totally reabsorbed avoiding any scar formation.

In some cases, it may be impossible to achieve watertight dural closure. These patients are particularly at risk for CSF leak and, therefore, may clearly benefit from the concept of autologous fat grafting. The cases are as follows:

- An intradural spinal tumor in a sacral location
- A craniospinal intradural tumor requiring a Y-shaped dural incision and patch grafting
- When the tumor invades the dura (e.g., meningioma) and necessitates dural excision to achieve radical resection and subsequent dural patching
- If the lesion is a dumbbell intradural extramedullary spinal tumor extending into the intervertebral foramen and beyond

The fat graft is always harvested on the left side of abdominal wall to prevent possible confusion in the case of a future appendectomy or other abdominal surgery on the right side (Fig. 25.6). Fat deposits are abundant in the abdominal wall area even in patients with a low Body Mass Index (BMI). There is no significant time or expense added to surgery, nor complications like infection, hematoma, or cosmetic problems. In addition, fat autograft carries no risk of hypersensitivity reaction or infectious disease transmission. A separate skin incision is favored for the tissue removal, rather than harvesting fat from the subcutaneous tissue in the area of the primary incision. This approach prevents the development of additional tissue pouches in the primary surgical area that may favor a pseudomeningocele or hematoma formation and jeopardize wound healing.

The prospective use of autologous fat grafting ensures watertight dural closure and obliterates the dead space created during surgical exposure, muscle dissection, and bone removal. This technique appears to significantly reduce, if not completely eliminate, postoperative CSF-related complications in patients

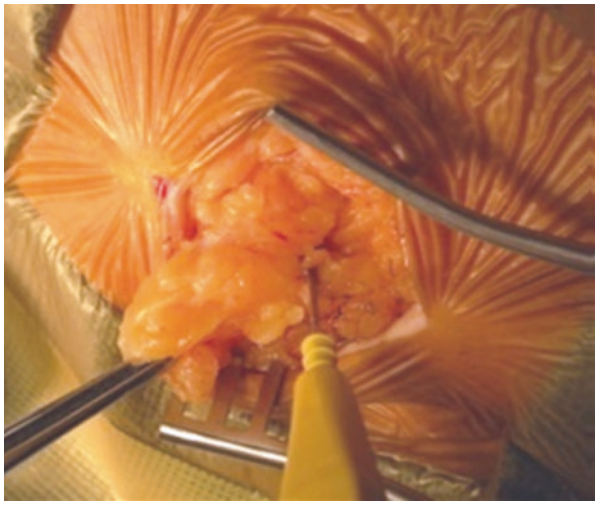

Fig. 25.6 Left abdominal wall fat graft harvesting

with ISTs, without adding any significant operative time, expenses or complications.

25.9 Deep Vein Thrombosis and Pulmonary Embolism

Spinal surgery is classified as a moderate risk for deep vein thrombosis (DVT), which is a major cause of morbidity but can be prevented with thromboprophylaxis. In terms of SCT surgery, there is a potentially difficult decision between balancing the risk of a thromboembolic accident and the risk of permanent neurological damage from postoperative bleeding in the spinal canal. Yamasaki et al. found that the overall incidence of DVT in patients undergoing lumbar spine surgery was 32.3%, but the incidence depends on the invasiveness of the procedure. Among those patients, 15.8% received anticoagulant therapy and none of them experienced pulmonary embolism (PE) or epidural hematoma. A follow-up vein ultrasonography 3 weeks postoperatively showed resolution of DVT in 86.7% of cases [63].

Dhillon et al. reported data from retrospective analysis of 6869 consecutive patients after spinal surgery and found that the risks of spinal epidural hematoma were low and equivalent to patients who received or did not receive chemoprophylaxis [64]. The authors concluded that anticoagulation therapy is safe for patients at high risk for thromboembolic complications from day 1 to day 3 after surgery. Fawi et al. reported a review of 2181 patients with elective spinal surgery, where a perioperative protocol involving mechanical anti-embolism stockings, adequate hydration, and early post-operative mobilization was effective in significantly reducing the incidence of thromboembolic complications [65]. The addition of low molecular weight heparin (LMWH) was reported safe in patients at higher risk of developing thromboembolic events.

Mosenthal et al. published a systematic review and meta-analysis of 28 articles on thromboprophylaxis in spinal surgery [66]. They found that the incidence of thromboembolic complications after spinal surgery is not well established due to variety of the small number of studies available. The incidence of DVT and PE was relatively low, regardless of prophylaxis type. The authors concluded that the role of thromboprophylaxis in spinal surgery remains undetermined. They also suggested the use of chemoprophylaxis because of the relatively high rate of fatal PE they discovered in 6% of the cases in their series.

Successful management of thromboembolic incidents depends on preoperative risk evaluation, including prophylactic treatment and early diagnosis, in order to avoid PE and other complications.

25.10 Complications of Immobilization and Bed Rest

Prolonged bed rest with inactivity and immobilization inevitably leads to complications, which are often much easier to prevent than to treat. Necessitated bed rest due to illness or recuperation after surgery for intradural and spinal cord tumors,

paralysis, loss of sensation, and immobilization of the spine may complicate primary disease and become an even greater problem. Geriatric patients, those with neurological deficit, and those with different comorbidities have a greater risk of developing these complications.

25.10.1 Cardiovascular Complications

Cardiovascular complications include increased heart rate, decreased cardiac reserve, orthostatic hypotension, VTE, and myocardial infarction.

25.10.2 Musculoskeletal Complications

Muscle weakness and atrophy together with the loss in muscle strength and endurance are commonly caused by prolonged immobilization. Nearly half of normal muscle strength is lost within few weeks of immobilization, which can prevent verticalization and early rehabilitation of the patient. Unfortunately, the rate of recovery for these patients is slow.

25.10.3 Joint Contractures

Contractures are fixed deformities of joints as a consequence of immobilization and are commonly seen in patients with paralysis. Unsuitable bed positioning can result in joint deformities, particularly in the lower extremities. Contractures can be painful, limit positioning, complicate bathing and bed transfers, increase the risk of pressure sores, and lengthen hospital stay. Treatment of contractures is based on prevention with a goal of performing active or passive range-of-motion (ROM) exercises, changing the positions of immobile joints regularly, and using resting splints. Established contractures are treated with passive ROM and terminal stretching for 30 seconds. Contraindications to aggressive management of immobilized or contracted joints include fractures, osteoporosis, acute arthritis, ligamentous instability, and insensitive areas.

25.10.4 Osteoporosis

Disuse osteoporosis is bone loss during long-term immobilization. It can lead to fractures of the spinal vertebrae, resulting in kyphosis and chronic back pain.

25.10.5 Decubitus Ulcers

Pressure sores or decubitus ulcers are localized areas of cellular necrosis over bony prominences subjected to external pressure greater than capillary pressure for

prolonged period of time. These complications occur most often in patients with spinal cord injuries and elderly patients. Obese and comatose patients are at particular risk for pressure sores. Patients in supine position usually get sores on the sacrum and heels, while sitting patients have sores on the ischial tuberosity. In patients who lie on their sides, sores occur on their hips and ankles. The most common problem associated with decubitus ulcers is infection with both aerobic and anaerobic bacteria. Deeper tissue and bone infection can result in sinus formation, periostitis, and osteomyelitis. Draining ulcers can be a source of large daily water and protein loss. Prevention of pressure sores depend on relieving the pressure by means of repositioning the patient every few hours via turning. Meticulous skin care and nursing are of utmost importance in prevention of pressure sores. Factors that interfere with healing include a necrotic ulcer surface, tissue hypoxia, malnutrition, infection, and improper wound care. Treatment is based on blood supply restoration to ulcer tissue by relieving localized pressure. It is essential to surgically remove all necrotic tissue. Granulation can be improved with available ready-made wound dressings that allow better wound healing. Surgery is sometimes indicated for deep pressure sores (Grades 3 and 4) and ulcers larger in diameter. Current surgical practice involves excising the ulcer and covering the defect with skin or myocutaneous flap.

25.11 Conclusion

The gravest complications in the surgical treatment of SCTs—those having high morbidity and mortality rates—are thromboembolism and infections like meningitis. Therefore, preventive measures are the primary concern of every neurosurgeon dealing with such an issue with the goal being improved management outcomes. CSF leak is an important topic when considering surgical strategies to avoid complications since leaks can be easily prevented by executing a meticulous and effective surgical protocol.

The best surgical strategy is prevention, which includes careful preoperative, perioperative, and postoperative surgical planning and anticipation and prevention of all surgical complications. If any occur, complications should be detected and treated as early as possible. Nursing care of the highest standard and daily bedside visits with the patient by neurosurgeon are of utmost importance.

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Rehabilitation of Patients with Primary Intradural Tumors of the Spinal Cord

26

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26.1 Introduction

Spinal cord injury (SCI) from primary intradural tumors, and their treatment, pose a multitude of complex medical and psychosocial challenges. Generally, it results in devastating loss of function, lifelong complications and a significant adjustment for the patient, family and caregivers. The rehabilitation of patient with spinal cord tumors requires early consideration and counseling on prognosis, potential impairments, activity limitations and participation restrictions. Tumor histology is the most important predictor of neurological outcome after surgical resection because it predicts resectability and recurrence [1]. Successful rehabilitation must be patient centered, goal oriented and include the active participation of the patient as well as an interdisciplinary team. Timely focus on rehabilitation facilitates patient education regarding expectations and the transition from acute care to home. The participation in a rehabilitation program improves function, mood, quality of life and survival of patients with spinal cord tumors [2].

In this chapter, we will utilize the World Health Organization (WHO) International Classification of Function (ICF) to outline the impact of spinal cord tumors on quality of life. There are four main definitions in the ICF described in Table 26.1.

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Table 26.1 World Health Organization international classification of functioning

Definitions
Disease: A pathologic condition resulting in signs or symptoms.
Impairments: Problems in body function or structure such as a significant deviation or loss of a body part or organ system.
Activity limitations: Difficulties an individual may have in executing activities of daily life.
Participation restrictions: Problems an individual may experience in involvement in life situations.

26.2 Disease: Primary Intradural Tumors of the Spinal Cord

Primary tumors of the spinal cord are relatively rare lesions representing 2–4% of all tumors arising from the central nervous system [3] and about 15% of tumors affecting the spinal cord [4]. Secondary tumors (i.e., metastatic lesions) to the spinal cord account for the remaining 85% of spinal cord injuries from oncologic entities. According to the WHO pathology classification (Table 26.2), the majority of primary tumors of the spinal cord are classified as low grade and the median age at presentation is 41 with a range of 18–47 [5]. The most common presenting symptoms of intradural tumors include pain (72%), motor weakness (55%), sensory loss (39%) and sphincter disturbance (15%). Meningiomas are the most common histologic type making up 29% of all intradural tumors, followed by nerve sheath tumors (24%) and ependymomas (23%) [6]. Primary Intradural tumors of the spinal cord are subdivided into intramedullary and extramedullary.

26.2.1 Intramedullary Tumors

Nighty percent of intramedullary neoplasms are astrocytomas and ependymomas [7]. Pain, weakness and paresthesia are present on diagnosis. Syringomyelia syndrome, from tumor-associated syrinx, with loss of pain/temperature sensation and motor dysfunction, may also be present. The diagnostic modality of choice is magnetic resonance imaging (MRI) of the spine, with features including focal or holocord spinal cord expansion, syrinx, T2-weighted and fluid-attenuated inversion recovery (FLAIR) image hyperintensity, and T1 hypointensity.

Ependymomas are most prevalent in the adult population and are classified into two pathological type, cellular (classic) and myxopapillary. Cellular ependymomas (WHO Grades 2 and 3) arise from the intraspinal canal and occur at the level of the cervical and thoracic spine, while the myxopapillary type (WHO Grade 1) originate from the filum terminale, thus exclusively found at the conus medullaris. They represent about 23% of all primary spinal cord tumor and males have the highest incidence rate, 0.21 per 100,000 person/year [6]. These tumors are largely benign and have an indolent course, with the exception of rarely occurring anaplastic ependymoma (WHO grade 3). Surgical resection is the most effective treatment yielding 90–100% local control rate; even with residual tumor is left behind. External beam

Table 26.2 Summarized 2016 WHO Grading System for Spinal Cord Tumors

Classification	Histology	Specific type	Grade
Neuroepithelial tumors	Astrocytic tumors (glial tumor)	Pilocytic astrocytoma	I
		Pleomorphic xanthoastrocytoma	II
		Fibrillary astrocytomas	II
		Anaplastic astrocytoma	III
		Glioblastoma multiforme	IV
	Oligodendroglial tumors	Oligodendroglioma	II
		Anaplastic Oligodendroglioma	III
	Ependymal cell tumors	Ependymoma	II
		Myxopapillary Ependymoma	I
		Subependymoma	I
	Mixed Gliomas	Mixed oligoastrocytoma	II
		Anaplastic oligoastrocytoma	III
	Neuronal and mixed neuronal/glial tumors	Gangliocytoma	I
		Ganglioglioma	I/II
		Anaplastic ganglioglioma	III
		Desmoplastic infantile ganglioglioma	I
		Dysembryoplastic Neuroepithelial tumor	I
		Paraganglioma	I
Peripheral nerve tumors		Schwannoma	I
		Neurofibroma	I
		Malignant peripheral nerve tumor	II/IV
Hematopoietic tumors		Primary malignant lymphoma	
Meningeal tumors		Meningioma	I
		Atypical meningioma	II
		Anaplastic meningioma	III
		Hemangioblastoma	I

radiotherapy, at doses of 45–54 Gy, is indicated for locoregional partially resected WHO Grades 2 and 3 tumors. Chemotherapy is limited to patients for which surgery and radiation are not an option or those that have failed previous treatment. Chemotherapeutic agents used include etoposide and platinoid salts; temozolomide appears to be ineffective. The 5-year survival for ependymomas is estimated to be 100% for grade 1 tumors, 98% for grade 2 tumors, and 64% for grade 3 tumors [8].

The second most common intramedullary tumor of the spinal cord are astrocytomas, 75% of which are low-grade fibrillary astrocytomas (WHO Grade 2), with 5-year survival greater than 70% [9]. The remaining 25% of astrocytomas include anaplastic (WHO Grades 3 and 4) with a low survival rate, and pilocytic (WHO Grade 1) with good prognoses. Histologically, these tumors tend to infiltrate adjacent tissue and are not amenable to en bloc surgical resection [9]. Biopsies are usually performed for tissue diagnosis, as differentiation from ependymoma is not possible through MRI. Radiation therapy is recommended for patients with high-grade histology, biopsied only tumor or those with evidence of disease

progression. For tumors recurring after initial radiotherapy re-irradiation is recommended if tissue-spearing methods can be used (i.e., cyberknife, tomoradiotherapy). Chemotherapy has not been found to be a highly effective treatment for spinal astrocytomas and is reserved for tumors progressing after treatment with surgery and radiation. Alkylator-based chemotherapy—such as temozolomide—is used based on the data for treatment of intracranial tumors and limited evidence in spinal cord [10].

Intramedullary hemangioblastomas, are the third most common, accounting for 2–8% of all intramedullary tumor. Ten to thirty percentage of spinal hemangioblastomas are associated with the diagnosis of Von Hippel-Lindau (VHL) syndrome [11], and present as recurring or multiple tumors. They are more common in males and present during the fourth decade of life. The histopathological features are identical for solitary lesions and those associated with VHL. Intramedullary hemangioblastomas form at the dorsal aspect of the spine and patients usually present with sensory proprioception deficits, subarachnoid or intramedullary hemorrhages are rare. Hemangioblastomas can be differentiated from other intramedullary tumors on MRI, they appear as hypervascular homogenously enhancing nodule with associated peritumoral edema and syrinx [12]. Surgical resection the primary mode of treatment of hemangioblastomas; the well-defined margins allow for complete resection. Nevertheless, intraoperative bleeding from the highly vascular tumor can result in subtotal resection. Embolization is avoided given the high risk of complications.

Stereotactic radiosurgery is emerging as an effective treatment with over 80% of symptom control, to be considered especially for those with VHL syndrome and recurrent hemangioblastomas [13].

Other rare spinal intramedullary tumors include gangliomas, oligodendrogliomas, paragangliomas, melanocytomas, lipomas, and lymphomas [7]. This tumor behave similarly to their peripheral counterparts and treatment is guided by their histopathologic grade, neurologic baseline, as well as presence of cystic component [6].

26.2.2 Intradural Extramedullary Tumors

The majority of intradural extramedullary tumors in the spinal cord are nerve sheath tumors (i.e., schwannomas and neurofibromas), and meningiomas; together they account for 53% of all intradural tumors [6]. Schwannomas are benign tumors (WHO Grade 1) arising from the dorsal root ganglion, more commonly seen in adults, and frequently in association with a diagnosis of Neuro Fibromatosis 2 (NF2). Young adults with NF2 often develop multiple schwannomas and have higher risk of malignant transformation. Pain and paresthesia on palpation are the typical symptoms on initial clinical presentation, although it may be asymptomatic and identified incidentally on imaging studies. Surgical resection of symptomatic patients is recommended, with stereotactic radiosurgery being offered for poor surgical candidates. Asymptomatic schwannomas can be followed clinically and with serial imaging [14].

Neurofibromas originate from peripheral sensory nerves and they tend to encase the nerve rather than displace the nerve, as seen in schwannomas. Patients with NF1 develop multiple spinal cord neurofibromas that increase in number with age and have a higher incidence of malignant transformation. Routine surveillance with MRI is recommended to monitor rate of growth as it may indicate malignant transformation. Surgical resection is recommended for symptomatic patients or for those with fast growing tumors, there is a limited role for chemotherapy or radiotherapy.

Meningiomas are tumors arising from the arachnoid cap cells and make up about 25% of all intradural spinal cord tumors, the vast majority (95%) are benign [15]. Spinal meningiomas predominantly affect females (80%), and 80% are localized to the thoracic spine. Multiple tumors are present at diagnosis 2% of cases, and are typically associated with NF2 patients. A recent study suggests that neither the degree of cord compression, tumor occupancy of canal, or residual compression after surgery should be used for prognosis in patients undergo resection of a spinal meningiomas [16]. This implies that good outcomes are possible even if substantial compression is present prior to surgery.

26.3 Impairments

26.3.1 Motor and Sensory Deficits

Patients with spinal cord tumors present with motor and sensory deficits that correlate to the degree of disruption of neural pathways at the site of the lesion. The most widely used tool to quantify the extent of motor and sensory impairment is the America Spinal Injury Association Impairment Scale (AIS) [16]. It systematically examines the extent and severity of a patient's spinal cord injury and is useful for determination of rehabilitative needs and expected functional outcomes. It In general, the neurological deficits in primary spinal cord tumor prior to surgical resection are mild to moderate and remain unchanged after surgery. The slow growth of these typically benign tumors results in an insidious onset of deficits, however periods of rapid growth or expansion by syrinx formation can be observed. One exception to the rule are astrocytomas; given the infiltrative histopathologic nature of the tumor they are at higher risk of worsening neurological status after surgical resection [1]. Histopathology was found to be a strong predictor of functional neurologic outcomes after resection of primary spinal cord tumors, conversely location of the tumor does not significantly predict outcome. Advances in microsurgical techniques and intraoperative nerve monitoring have reduced the associated intraoperative morbidity of these tumors.

26.3.2 Spasticity

A classic manifestation of injury to the upper motor neurons is spasticity, a velocity dependent increase in muscle tone caused by imbalance in the inhibitory and

excitatory input to the α-motor neurons. Spasticity may cause pain and interfere with hygiene and function. Symptoms may be generalized, affecting muscles below the level of the lesion, or localized to particular muscle groups. Mild spasticity may be managed with range of motion and stretching exercises or splinting. Chemodenervation of spastic muscles with injections of botulinum toxin or phenol can be considered for localized severe spasticity. For generalized spasticity, oral agents, including baclofen, dantrolene, benzodiazepines, and tizanidine are the first line of systemic treatment. The side effect profile of these drugs includes dizziness, drowsiness, weakness, blurry vision, dry mouth. Patients may have refractory spasticity or low tolerance to the adverse effect of the oral agents, in these cases intrathecal baclofen may be considered [17].

26.3.3 Pain

Pain is one of the most frequent presenting symptoms of primary spinal tumors, seen in 52–80% of all patients, with a higher incidence in Schwannomas and Ependymomas [9, 18]. The pain can be characterized as back pain, radicular pain or central pain. Central dysesthesia pain syndrome, is perceived at the anesthetic levels at and below the level of injury. The suspected etiology is loss of spinothalamic systems with preservation of function of the dorsal columns. This syndrome is characteristically difficult to manage and most patients do not get significant pain relief from the available treatments. A multi-disciplinary approach is needed. Cognitive behavioral therapy can help patients manage symptoms. Exercise and physical modalities are useful adjuvants. Amitriptyline, gabapentin and pregabalin are the most studied drugs with demonstrated efficacy for treatment of pain associated with spinal cord injury [19]. Pregabalin is the only medication with US Food and Drug Administration (FDA) approval for this indication.

26.3.4 Neurogenic Bowel

Neurogenic bladder and bowel dysfunction is commonly seen in spinal cord tumors. Its presentation and management will depend on the level of injury and involvement of upper and/or lower motor neurons innervating the key structures. Upper motor neuron bowel dysfunction causes constipation and impaction due to inadequate emptying, and symptoms are aggravated by immobility and use of opioid pain medications. Implementation of a bowel program will prevent incontinent bowel movements, abdominal discomfort and pain, improving the quality of life and participation in daily activities. A bowel program should include stool softeners, prokinetic agents, suppositories and digital stimulation to take advantage of the recto-colic reflex. The program should be performed at least every 2 days and scheduled 30 min after a meal in order to benefit from the gastro-colic reflex. Injuries below the conus medullaris result in areflexic bowel; these patients have a higher risk of

incontinence and benefit from the use of oral bulk forming agents and daily manual evacuation [20]. Patients may have the sufficient ability to carry out the bowel program themselves; in other cases, the caregivers will require training prior to discharge from the rehabilitation unit.

26.3.5 Neurogenic Bladder

The presentation of neurogenic bladder dysfunction is variable, and includes, incontinence, urgency, frequency, retention, and frequent urinary tract infections. The goals of neurogenic bladder management are to ensure social continence, adequate bladder emptying maintaining low detrusor pressures, avoid bladder stretch injury, prevent damage to upper urinary tract from high intravesicular pressures, as well as prevent urinary tract infections and reduce injury to the kidneys [21]. Lesions above the conus medullaris that injure upper motor neurons (UMNs) result in a small overactive spastic bladder unable to store urine. In these cases, anticholinergic medications (e.g., oxybutynin and tolterodine) are used to promote relaxation of the detrusor muscle improving urinary storage. UMN injury may also result in a tight spastic sphincter, administration of oral alpha-blockers (i.e., tamsulosin) is recommended to relax the sphincter. Many patients with UMN lesions will also have detrusor-sphincter dyssynergia. The bladder and urethral sphincter contract simultaneously. In these cases, an alpha-blocker along with an anti-cholinergic may be needed. Patients with injuries involving the sacral micturition center develop a large areflexic bladder combined with a spastic sphincter resulting in an over filed bladder that is unable to empty. Management of this issue includes intermittent catheterization, alpha-blockers and cholinergic medications, such as bethanechol. Further details on neurogenic bladder management can be found in Samson et al. [21].

26.3.6 Sexual Dysfunction

In a similar manner as bladder and bowel function, sexual dysfunction presentation in spinal cord injury (SCI) is dependent on the involvement of lower or upper motor neurons. In males with injury of UMN above the level T11 are capable of having reflexive erections. Psychogenic erections require intact hypogastric plexus, which originates from level T11 to L2. Men with injury to the lower motor neurons (LMNs) often do not experience reflexive erections, however, may attain psychogenic erections depending on the degree of involvement off distal injury [20]. The ability to ejaculate is more profoundly affected by damage to the spinal cord; most men with complete spinal cord injury cannot produce an ejaculate during intercourse [21]. Augmentative techniques such as electro-ejaculation, prostate massage or penile vibratory stimulation use for fertility purposes are able to produce ejaculation in 86% of patients with lesions above T10 [22]. Sexual function in both males and

female with spinal cord injury can often affected by psychologic factors. For example, feeling unattractive, having less self-confidence, and difficulties in finding a partner, also play a role [23]. In females, sexuality is negatively affected by the physiologic factors as loss sensation, difficulties achieving an orgasm, neurogenic bladder or bowel and difficulties positioning independently. Acute injury to the spinal cord may cause amenorrhea; however, menses return in 6–12 months for the majority of women, and fertility is unaffected.

26.3.7 Skin Integrity

Patients with spinal cord injury are at high risk of developing pressure ulcers given their sensory deficits, decreased mobility, catabolic metabolic state, as well as bowel and bladder incontinence. Ulcers most commonly develop at the sacrum (43%), heels (19%), ischium (15%) [24], they are difficult to treat and may lead to serious medical complications such as osteomyelitis and sepsis. The mechanism of injury involves local soft tissue ischemia from persistent pressure (>2 h) that exceeds supra capillary pressure and shearing forces causing mechanical injury to the epidermis. Prevention of the formation of ulcers is of extreme importance in this population, and emphasis should be placed on intermittent pressure relieve techniques, frequent skin checks and proper nutrition.

26.3.8 Autonomic Dysfunction

Spinal cord lesions above the level of the eighth thoracic spine are at risk of presenting with dysregulations of the autonomic system including orthostatic hypotension, poikilothermia, and autonomic dysreflexia. The mechanism behind the dysregulation is the disruption of the descending central sympathetic outflow. Orthostatic hypotension is provoked when the patient tilts upward greater than 60°, causing a persistent drop in blood pressure due to the loss of the normal compensatory sympathetic response increasing venous resistance. The patients typically report lightheadedness, dizziness, and nausea and on exam, they have tachycardia with drop in blood pressure. Conservative management includes repositioning, elastic stockings, abdominal binder, increased fluid intake and ace wrapping to bilateral lower extremities. Anticholinergic or alpha-blockade medications, as well as tizanidine may contribute to orthostasis. Pharmacologic options include salt tabs, physostigmine, alpha-adrenergic agonist (midodrine) and mineralocorticoid (fludrocortisone). It is important to be cognizant that management is only needed temporarily since orthostasis lessens with time as spinal postural reflexes develop.

Autonomic dysreflexia is a syndrome caused by massive imbalanced reflex sympathetic discharge. Is characterized by a sudden increase in blood pressure, 20–40 mm HG greater than baseline resulting from noxious stimuli below the neurologic level of injury. This is usually accompanied by bradycardia. Unrecognized, it can lead to stroke, myocardial infarct and sudden death [25]. The trigger in

autonomic dysreflexia is a noxious stimulus, commonly a distended bladder, increasing spinal reflexive sympathetic output causing regional vasoconstriction and thus an increase in blood pressure. The response to increased pressure is a vagal discharge causing bradycardia and the central inhibitory input to the spinal sympathetic discharge. However, the latter fails to be transmitted through the severed spinal cord resulting in persistent hypertension. Sign and symptoms of autonomic dysreflexia include headache, sweating, flushing, elevated blood pressures, piloerection and pupillary constriction. The first step in management is sitting the patient upright, loosen clothing, followed by identification and removal of noxious stimulus. Removal of stimulus should resolve symptoms; if the source is not identified and elevated blood pressure persists, pharmacologic management of the hypertension is indicated. Acutely nitro paste can be applied and then removed once the inciting stimulus is removed. Figure 26.1 gives an algorithm for management.

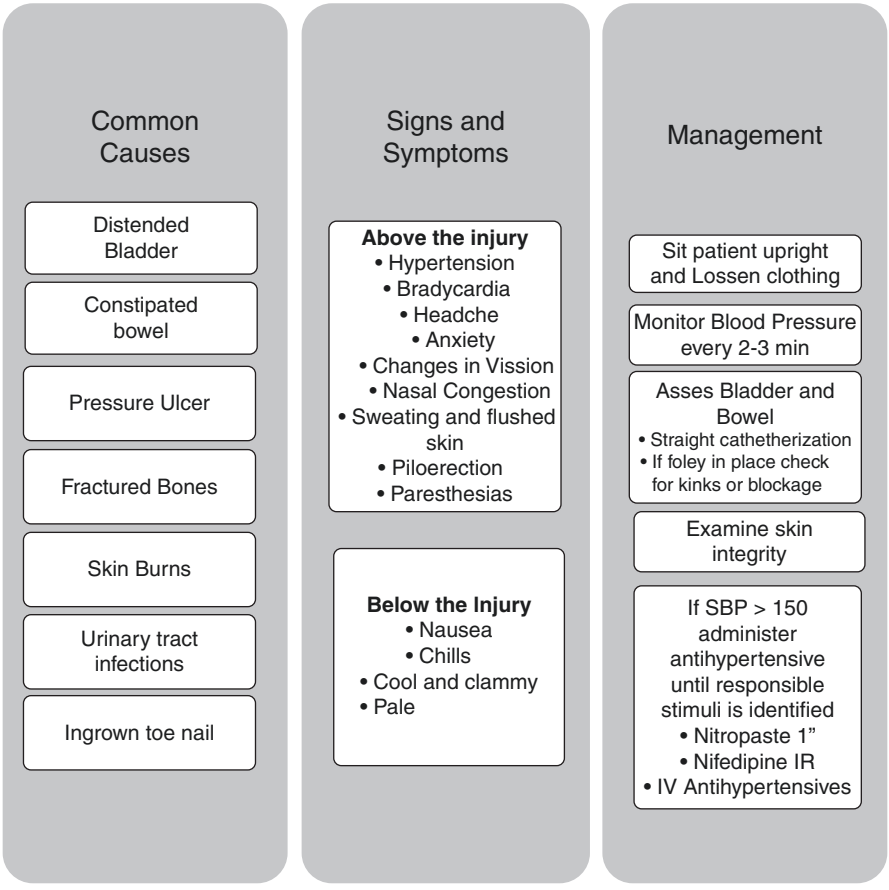

Fig. 26.1 Algorithm for management of autonomic dysreflexia

26.3.9 Psychosocial Impact

Impaired function of the spinal cord results in marked physical disability and secondary medical problems affecting, not only the quality of life of the patient but of all the family and caregivers involved. These patients at higher risk of suffering from depression, anxiety, PTSD and suicide [26]. Social support, emotional and functional, are associated with better quality of life and reported well-being. Special attention should be placed on the psychological component of the early rehabilitation process as patients learn to cope with any new impairments. In patients with poorer prognosis, there needs to be a robust discussion of treatment goals and advanced directives.

26.4 Activity Limitation

Table 26.3 describes activities that can be accomplished by individuals with complete lesions at each of the myotomal levels of spinal cord injuries. It is important to note that this information is based on *complete* levels of injury, and most spinal cord tumors cause *incomplete* lesions. On the other hand, these are optimal levels of function in young, healthy patients, and patients with spinal cord tumors may be older, debilitated or suffer from co-morbidities that impede optimal function.

Equipment may ameliorate some activity limitations. These can include ambulatory aids (i.e., walkers or crutches), braces, wheelchairs, and exoskeletal robotics.

26.5 Participation Restriction

While laws such as the United Nations Convention on Rights of People with Disability or the Americans with Disabilities Act have gone a long way in decreasing environmental and societal barriers to participation, many impediments remain. For example, most laws provide for wheelchair accessibility in public accommodations, they do not provide for accessible private housing.

Employment remains a challenge as well. While specific data for spinal cord tumors do not exist, we have overall data for people with disabilities. In the U.S. in 2016, 20% of people with disability participated in the workforce, compared with 68.5% of able-bodied individuals in patients with spinal cord injuries, 13% are employed 1 year after injury [27].

26.6 Rehabilitation Course

The rehabilitation course after spinal cord tumors often involves several levels of care. Most commonly, patient will receive physical and occupational therapy beginning day 1 postoperatively after resection. Early mobilization can prevent secondary complications and shorten length of stay.

Table 26.3 Functioning, limitations, and suggestions for functioning aids per spine level

Motor pattern	Expected functional outcome[a]	Suggested equipment
	C1–C3	
Weakness pattern: Total paralysis of UE, trunk, LE; ventilator dependent Possible movement: Neck flexion, extension, rotation	Dependent in personal care and ADLs, bed mobility, pressure relief Require ventilator due to diaphragm paralysis Able to control power wheelchair with head/chin control Able to control aspects of environment with assistive technology	Two ventilators (bedside, portable), suction equipment, generator, back-up battery Padded reclining shower/commode chair Full electric hospital bed with Trendelenburg feature; specialized mattress Transfer board, power or mechanical lift with sling Power recline and/or tilt wheelchair Environmental control unit
	C4	
Weakness pattern: Paralysis of UE, trunk, LE; inability to cough, ↓ endurance & respiratory reserve (paralysis of intercostals) Possible movement: Neck flexion, extension, rotation, scapular elevation, inspiration	Dependent in personal care and ADLs, bed mobility, pressure relief Able to breathe without ventilator Able to control power wheelchair with head/chin control Able to control aspects of environment with assistive technology	If not vent-free: See above Padded reclining shower/commode chair Full electric hospital bed with Trendelenburg feature; specialized mattress Transfer board, power or mechanical lift with sling Power recline and/or tilt wheelchair Mouth stick, high-tech computer access Environmental control unit Attendant operated van
	C5	
Weakness pattern: No elbow extension, pronation, wrist and hand movement; total paralysis of trunk, LE Possible movement: Shoulder flexion, abduction, extension, elbow flexion, supination, scapular adduction and abduction	Can assist with personal care and ADLs Can complete some tasks with assistive devices such as feeding Can assist with bed mobility and transfers Can operate a power wheelchair with hand control or manual wheelchair on flat indoor surfaces	Padded reclining shower/commode chair Full electric hospital bed with Trendelenburg feature; specialized mattress Transfer board, power or mechanical lift with sling Long opponens splint, spiral splint, universal cuff, utensils with built up handles, ADL splints (wash mitt, razor holders), dressing aides (pant loops, sock aide, long shoe horn), gooseneck mirror Adaptive devices as needed for page turning, writing, button pushing Power recline and/or tilt wheelchair Environmental control unit Modified van with lift

(continued)

Table 26.3 (continued)

Motor pattern	Expected functional outcome[a]	Suggested equipment
	C6	
Weakness pattern: No wrist flexion, elbow extension, hand movement; total paralysis of trunk, LE Possible movement: Scapular protraction, some horizontal adduction, forearm supination, wrist extension	Potential for physical independence with some personal care and ADLs (self-catheter for bladder management) using assistive devices & splints; some assistance with bowel management Potential for functional grasp via tenodesis Potential to be independent with transfers, some assist with bed mobility Independent with communication +/− equipment Potential to live independently with supportive care	Padded tub bench with cutout commode or shower commode chair Transfer board or mechanical lift Full electric hospital bed or full to king standard bed Power wheelchair vs. manual wheelchair Adaptive devices: Universal cuff, tenodesis splint, resting hand splint, adapted utensils, built-up handles, plate guard, dressing: Button hook, sock aide, long shoe horn; hand held shower, writing splint for keyboard use, button pushing, page turning
	C7–C8	
Weakness pattern: Paralysis of trunk, LE; limited grasp release and dexterity Possible movement: Elbow extension; ulnar/wrist extension; wrist flexion; finger flexions and extensions; thumb flexion/extension/abduction	Independent with personal care and ADLs, bed mobility and transfers; greater function use of hands May need adaptive device for communication Able to drive with vehicle modifications Potential to live independently	Padded tub bench with cutout commode or shower commode chair Transfer board Full electric hospital bed or full to king standard bed No splints for hand function (lumbrical bar as needed) Adaptive devices as needed for eating, dressing, bathing (e.g., gooseneck mirror, hand held shower) Manual wheelchair Standing frame Modified vehicle
	T1–T9	
Weakness pattern: Lower trunk & LE paralysis Possible movement: Upper extremities fully intact; limited upper trunk stability. Endurance increased secondary innervation of intercostals	Independent in personal care and ADLs, transfers. May require assistive equipment due to lack of trunk stability Live independently	Transfer board Manual wheelchair Standing frame Hand controls for driving

Table 26.3 (continued)

Motor pattern	Expected functional outcome[a]	Suggested equipment
	T10–L1	
Weakness pattern: Paralysis of both LE Possible movement: Good trunk stability	Independent in respiratory function, personal care and ADLs, communication, transportation and homemaking. Standing is independent. Can engage in functional ambulation activities, with some assist to independent. Live independently	Manual wheelchair Standing frame Forearm crutches or walker KAFO
	L2-S5	
Weakness pattern: Partial paralysis of lower extremities Possible movement: Good trunk stability. Partial to full control of LE	Independent in respiratory function, personal care and ADLs, communication, transportation and homemaking. Standing is independent, and they can engage in functional ambulation activities, Live independently	Manual wheelchair Standing frame Forearm crutches or cane as needed Ambulate with lower limb orthosis (e.g., KAFO, AFO, or walking aid) Drive with hand controls

[a]Personal care and ADLs include bladder and bowel management, eating, dressing, grooming, and bathing.
ADL activity of daily living, *AFO* ankle, foot orthosis, *KAFO* knee, ankle, foot orthosis, *LE* lower extremity, *UE* upper extremity.

In 2015, New et al. [28] proposed a framework and practical considerations for managing persons with spinal cord dysfunction (SCD) secondary to tumors. This was based on the Neurologic, Oncologic, Medical, Pain and Support status of the patient (NOMPS criteria). The criteria were important in informing the decision to admit persons with SCD due to tumors to spinal rehabilitation units, and as a basis for practical considerations to guide rehabilitation management of this population. Neurologic referred to the AIS level, oncologic referred to grading of the tumor, medical referred to comorbidities that can influence participation in rehabilitation, pain referred to optimizing symptom management, and support referred to family and friends, whose presence or absence can influence discharge planning options.

Most patients will require further rehabilitation in order to return the community. Because of their complex medical and nursing care postoperatively, this should usually be done in an acute hospital rehab unit or a freestanding rehab hospital. At this level of care, patients receive daily physician and nursing care, along with at least 3 h/day physical an occupational therapy. These facilities usually have a high degree

of experience in treating spinal cord disorders. Length of stay will vary widely depending upon the impairment level. Typically, patients stay inpatient between 1 and 6 weeks. Some patients who have less nursing and medical needs, or who are unable to tolerate intensive therapies, may be managed in skilled nursing facilities. Once the inpatient stay is complete, patients will usually have outpatient or home-based therapies for several months.

26.6.1 Rehabilitation Outcomes

There are numerous studies investigating outcomes of rehabilitation in patients with SCD due to tumor. It is important to note that most studies do not make a distinction between metastatic and primary tumors of the spinal cord.

The Functional Independence Measure (FIM) is the most commonly used functional measure of disability and outcome. It is used to track changes in functional ability of a patient in response to rehabilitation intervention. It is a composite measure consisting of 18 items involving two basic domains (13 motor and 5 cognitive tasks) assessing six areas of function (i.e., self-care, sphincter control, mobility, locomotion, communication, and social cognition).

Patients with SCD due to tumor showed significant functional improvement between admission and discharge (or FIM change). However, in comparison with persons with traumatic SCI, the FIM change is lower. People with spinal cord tumors tend to have a lower FIM on admission and discharge. The FIM efficiency (FIM change per week) is comparable between patients with SCD secondary to tumor compared with traumatic SCI [29–31]. Patients with spinal cord tumor had a shorter length of stay and similar rates of discharge back to the community when compared to those with traumatic SCI [31, 32].

In comparison with *other causes of non-traumatic spinal cord dysfunction* (e.g., transverse myelitis, infection, vascular etc.), FIM efficiency and FIM gains (total FIM and motor subscores) are lower in those with spinal cord tumors. There is no significant difference in the length of stay in inpatient rehabilitation. Survival rate is also higher in non-traumatic SCD. Discharge to the community is comparable between both groups [33].

The presence of pain has a negative influence on the rehabilitation process. Patients with pain tend to have a longer length of stay, less FIM motor efficiency and lower FIM motor scores on discharge. Thus, the presence of pain should not preclude one from participating in a rehabilitation program, but more importantly, its management should be part of rehabilitation goals [34].

There are varying reports on survival of patients with spinal cord tumors after inpatient rehabilitation. A Median survival range from 3 to 30 months [35–37]. One study reported that those patients with primary tumors had a significantly greater median survival than those with metastatic tumors (9.5 months vs. 2.8 months [38].

There is evidence that patient can maintain or improve upon their functional gains after being discharged from inpatient rehabilitation. 75–80% maintained

self-care and mobility skills post discharge [29]. In one study 73% achieved independent function post discharge [38].

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Correction to: History of Spinal Surgery and Surgical Treatment of Spinal Intradural Tumors

Bruno Splavski

Correction to:
Chapter 1 in: K. I. Arnautović, Z. L. Gokaslan (eds.),
***Spinal Cord Tumors*, https://doi.org/10.1007/978-3-319-99438-3_1**

This book was inadvertently published with interchanged figures 1.8 and 1.9. These figures has now been updated.

A correction to this chapter can be found at https://doi.org/10.1007/978-3-319-99438-3_1

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Correction to: Epidemiology of Spinal Cord Tumors

Kenan I. Arnautović and Ziya L. Gokaslan

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Figures 2.1, 2.2, 2.3, and 2.4 were swapped in the original publication so the legends did not match with the figures. The figures and legends have been correctly placed now.

- Figure 2.2 has been changed as Figure 2.1.
- Figure 2.4 has been changed as Figure 2.2.
- Figure 2.1 has been changed as Figure 2.3.
- Figure 2.3 has been changed as Figure 2.4. Legend of Figure 2.4 is provided below: Fig. 2.4: (**a**) Preoperative sagittal MRI of an intradural meningioma which is located anterior to the spinal cord. (**b**) The T2 axial contrast-enhanced MRI revealing a broad-based extramedullary mass lesion which is compressing spinal cord posteriorly. (**c**) Intraoperative view that is showing the dural protrusion anteriorly following C7 corpectomy and removal of anterior longitudinal ligament. (**d**) Intraoperative view of the meningioma following dural opening

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Index

A
Abdominal compression, 491
Acute angle-closure glaucoma, 492
Adjuvant therapy
  dermoid tumors, 419
  epidermoid tumors, 419
  gangliogliomas, 403
  holocord intramedullary tumor, 423
  lipomas, 421
  neurocytomas, 411
  neuroenteric cysts, 407
  paragangliomas, 405
  PSOs, 409
  SCGs, 414
  SCSEs, 412
  SCT, 416
Airway and vascular complications, 495
Amaurosis, 492
American College of Cardiology/American Heart Association guidelines, 128
American Society of Anesthesiologists (ASA), 128
America Spinal Injury Association Impairment Scale (AIS), 515
5-Aminolevulinic acid (5-ALA), 234
Amitriptyline, 516
Anaplastic astrocytoma, 344, 348, 356
Anaplastic ependymoma, 328–331, 343, 345, 512
Anaplastic gangliogliomas (AGGs), 402
Anemia, 138
Aneurysmal bone cysts, 389
Anterior cord syndrome, 93, 94
Anterior ischemic optic neuropathy (AION), 133
Antimicrobial resistance, 497
Apparent diffusion coefficient (ADC), 173, 343
Arteriovenous malformations (AVMs), 19
Astrocytomas, 351, 355, 397, 468, 513
  BRAF mutation, 339
  diagnostic imaging, 340, 342
  differential diagnostics, 56, 57, 59, 60
  diffuse astrocytomas, 344
  epidemiology, 39, 40
  genetics and molecular variables, 344
  malignant transformation, 337, 338
  MAPK-ERK/PI3K pathways, altration in, 345
  neuropathology, 74–75
  surgery, 348
Autologous blood transfusion, 139
Autologous fat grafting, dural closure of, 501, 502
Autonomic dysfunction, 518, 519
Autonomic dysreflexia, 518
Axial back pain, 392
Axial diffusivity (AD), 343

B
Ballance, Charles, 11
Benzel, Edward, 20
Bevacizumab, 355
Bilateral fractured pedicles, 460
Bipolar coagulation, 16
Bipolar electrocautery, 401
Blood conservation using Antifibrinolytics Randomized Trial (BART), 140
Blood-spinal cord barrier (BSCB), 47, 48
Brachial neural plexus injury, 493
BRAF mutations, 338
Breast carcinoma metastasis, 372, 373
Brown-Sequard syndrome, 150, 366
Bulbocavernosus reflex (BCR), 112, 121, 122

C
Capillary hemangiomas, 440–442
Capsular ligaments, 458
Cardiovascular complications, 504

K. I. Arnautović, Z. L. Gokaslan (eds.), *Spinal Cord Tumors*,
https://doi.org/10.1007/978-3-319-99438-3

Cartilaginous tumors, 390, 391
Cauda equina, 43
Cauda equine, 111, 112
Cavitron ultrasonic surgical aspirator (CUSA), 18, 19, 351
Cellular ependymoma, 328, 329
Cellulitis, 496
Central nervous system (CNS), 96, 281
Central retinal artery occlusion (CRAO), 133, 492
Cerebellar metastasis resection, 372, 374
Cerebrospinal fluid (CSF) tests, 13, 14, 96, 330
Cervical cord subepedymoma, 412
Cervical neurocytoma, 410
Cervical spinal cord lipoma, 420
Cervical spine, 439, 447, 461, 469
Chemotherapy, 333, 354–356, 414
Chirurgia Magna, 5
Chondromas, 390, 391
Chondrosarcomas, 391
Chordomas, 381, 383, 384
Classic ependymoma, 328, 329
Clear cell ependymoma, 329
Coccygeal ligament, 43
Compartment syndrome, 133
Complete cord transection, 93
Complete transverse myelopathy, 93
Complications after spinal surgery
  anesthesia, related to, 490
  CSF dissemination, seeding and metastasis, 487–489
  CSF-related complications
    autologous fat grafting, dural closure by, 501, 502
    CSF leaks, 498, 499
    neuropathic pain and neurologic deficits, 498
    polyethylene glycol sealants, 500
    prevention strategies, 500
  DVT, 503
  immobilization
    cardiovascular complications, 504
    decubitus ulcer, 504, 505
    joint contractures, 504
    musculoskeletal complications, 504
    osteoporosis, 504
  intraoperative imaging and neuronavigation, 486
  meningitis, 497
  microsurgical technique, 486
  pneumonia, 498
  pulmonary embolism, 503
  spinal column deformities, 489, 490
  spondylosis and herniated cervical disk, 486, 487
  surgical positioning
    acute angle-closure glaucoma, 492
    airway and vascular complications, 495
    amaurosis, 492
    central retinal artery occlusion, 492
    cortical blindness, 492
    hemodynamic complications, 491
    intraoperative neurophysiological neuromonitoring, 494
    ischemic optic neuropathy, 492
    neurological complications, 493, 494
    peripheral neuropathies, 494
    pressure injuries, 491
    prevention of, ophthalmologic complications, 493
  urinary tract infection, 498
  wound complications (*see* Wound complications)
Computed tomography (CT)
  chordomas, 383
  dumbbell tumors, 437
  Ewing's sarcoma, 393
  IMSCTs, 340
  intradural metastatic disease, 368
  intramedullary metastasis disease, 368
  SCEs, 330
Congenital neuri-lemmomatosis, 64
Congenital tumors
  chordomas, 383, 384
  definition of, 382
  sacrococcygeal teratoma, 382, 383
Conventional schwannoma, 82, 83
Cord lipomas, 399
Cortical blindness, 134, 492
Corticospinal tract (CST), 111
Craniocervical junction gangliogliomas, 402
Craniospinal intradural tumor, 502
CSF-related complications
  autologous fat grafting, dural closure of, 501, 502
  CSF leaks, 498, 499
  neuropathic pain and neurologic deficits, 498
  polyethylene glycol sealants, 500
  prevention strategies, 500
Cup sign, 15

D

Decubitus ulcer, 504, 505
Deep vein thrombosis (DVT), 232, 503
Denosumab, 390

Deoxyribonucleic acid (DNA), 188
Dermoid tumors
  adjuvant therapy, 419
  clinical presentation, 417
  diagnosis, 417
  pathology, 418, 419
  surgery, 419
Diffuse astrocytomas, 344
Diffuse gliomas, 345
Diffusion tensor imaging (DTI), 55, 343
Diffusion tensor tractography (DTT), 56, 343
Disseminated Glioblastoma, 346, 347
Double lumen endobronchial tube (DLT), 129, 130
Draining ulcers, 505
Dumbbell tumors, 439–444
  classification, 434, 435
  complications, 448, 449
  differential diagnosis
    radiological presentation, 436, 437
    symptoms, 435, 436
  epidemiology, 434
  meningiomas, 438
  metastasis, 446
  MPNSTs, 446, 447
  neurofibromas, 437, 438
  non-schwannoma non-neurofibroma, 433
  paravertebral neurogenic tumors with intraspinal extension, 443, 446
  schwannomas, 433, 437, 438
  surgical approach, 447, 448
  vascular lesions, 440, 442, 443
Durotomy, 401
Dysembryogenic theory, 416

E
Eden Classification, 434, 435
Electromyography (EMG), 135, 137, 400
Enlarging pre-sacral mass, 387
Ependymal cysts, 406
Ependymoblastoma, 328
Ependymomas, 34–36, 56–59, 72–73
Epidemiology
  astrocytomas, 39, 40
  clinical features, 39
  clinical presentation, 33
  ependymomas, 34–36
  extradural pathology, 31, 32
  extramedullary tumors, 32
  genetic factors, 33
  hemangioblastomas, 35
  hemangioma, 34
  incidence, 33
  intradural-intramedullary tumors, 32
  intradural pathology, 31, 32
  lipomas, 39
  meningiomas, 37, 38
  metastatic tumors, 31
  neurofibromas, 39
  non-malignant pathologies, 34
  primary spinal cord tumors, 32, 33
  schwannomas, 36, 37
  vertebral column tumors, 31
Epidermoid tumors
  adjuvant therapy, 419
  clinical presentation, 417
  diagnosis, 417
  pathology, 418, 419
  surgery, 419
Epithelial membrane antigen (EMA), 73
Etoposide, 513
Ewing's sarcoma, 392, 393
External beam radiation therapy (EBRT), 470, 472, 473, 476, 513
Extradural spinal cord tumor, 86, 87
Extradural tumors, 15, 72
Extraventricular neurocytomas (EVNs), 409

F
Facetectomy, 457, 460, 461
Fasciotomy, 491
Flexible fiber-optic bronchoscope, 129
Fluid-attenuated inversion recovery (FLAIR) image, 512
Fluorescence *in situ* hybridization (FISH), 96
Fractional anisotropy (FA), 343
Free run electromyography (fEMG), 137
Functional Independence Measure (FIM), 524
Fundoscopy, 492

G
Gabapentin, 516
Gadolinium, 399, 436
Gadolinium-diethylenetriamine pentaacetic acid (Gd-DTPA), 436
Gadolinium-enhanced magnetic resonance imaging (Gd-MRI), 96
Gangliogliomas, 57, 60–62, 351, 398
  adjuvant therapy, 403
  AGGs, 402
  clinical presentation, 402
  imaging, 402
  pathology, 402, 403
  surgical intervention, 403
  T1 and heterogeneous enhancement, 399

Ganglioneuroma, 385, 386, 446
Germ cell tumors, 413
Giant cell tumors, 389, 390
Glial fibrillary acidic protein (GFAP), 73, 406, 408
Glioblastomas, 341
  adult glioblastoma, 344, 345
  chemotherapy, 355, 356
  pediatric glioblastoma, 344, 345, 354
  radical resection, 348
  surgical outcome, 352, 353
Gliomas, 337, 338, 468
Gowers, William, 8, 9
Gross total resection (GTR), 342, 348, 351, 353, 406, 440, 442, 448, 462

H
Headrest syndrome, 492
Hemangioblastomas, 35, 61, 76–77, 442, 468, 474, 514
  clinical presentation, 244, 245
  diagnostic tool, 245–247
  histopathology, 244
  literature review, 254–267
  male-to-female ratios, 243
  medical therapies, 253
  neurological outcome, 254
  in pregnancy, 252, 253
  preoperative embolization, 254
  radiosurgery, 253
  surgical treatment, 246–253
  tumor recurrence, 254, 268
  VHL disease, 245
Hemangioma, 34
Hematoma, 495, 496
Hemodynamic complications, 491
High cervicomedullary intradural tumors, 459
High grade gliomas, 348
Holocord anaplastic astrocytoma, 342
Holocord intramedullary tumor, 422
  adjuvant therapy, 423
  clinical presentation, 421
  diagnostic imaging, 422
  pathology, 422
  surgical intervention, 422, 423
Holocord oligodendroglioma, 408
Hydrocephalus, 346, 347, 399, 469
Hydrodynamic theory, 347
Hydrosyringomyelia, 149
Hypoxia-induced growth factor (HIF-1), 244

I
IDH1/2 mutations, 212
Infiltrating lesions, 400
Instrumented fusion, 460–462
  biomechanical stability, 458, 459, 462, 463
  laminectomy, 457, 458
  minimally-invasive unilateral approach, 463
  mini-open interlaminar and trans-spinous approaches, 464
  muscle- and facet joint-preserving laminectomies, 463
  post-operative deformity, surgical treatment of, 463
  post-operative iatrogenic instability, 458
  spinal cord tumor resection, 458, 459, 462, 463
  tissue-sparing technique, 464
Intensity-modulated radiation therapy (IMRT), 471
Inter-train interval (ITI), 115
Intracranial astrocytoma, 356
Intracranial ependymomas, 330
Intracranial meningioma, 195, 196
Intradural-extramedullary spinal cord tumors (IESCTs), 15, 173–175, 514, 515
  conventional schwannoma, 82, 83
  definition, 71
  meningioma, 78–82
  MPNSTs, 85, 86
  myxopapillary ependymoma, 77, 78
  nerve sheath tumors, 82
  neurofibroma, 83–85
Intradural intramedullary tumors, 15
Intradural metastatic disease, 365
  clinical presentation and evaluation, 366–367
  epidemiology, 366
  follow-up, 371
  imaging, 367
    CT, 368
    MRI, 368
    nuclear-imaging, 368
  multimodal treatment algorithm, 371
  treatment intervention
    planning, 369
    radiation, 370, 371
    surgery, 370
Intradural spinal tumors (ISTs), 500
Intramedullary astrocytoma, 352
Intramedullary dermoid cysts, 417
Intramedullary ependymoma, 354
Intramedullary epidermoid cysts, 417
Intramedullary hemangioblastomas, 514
Intramedullary lipomas, 419–421
Intramedullary metastasis disease
  clinical presentation and evaluation, 366
  CT, 368
  epidemiology, 366
  follow-up, 371
  imaging, 367, 368

MRI, 368
multimodal treatment algorithm, 371
non-small lung cancer intramedullary metastasis, 372
nuclear-imaging, 368
renal cell carcinoma metastasis, 373
treatment intervention
planning, 369
radiation, 370, 371
surgery, 370
Intramedullary neoplasms, 512–514
Intramedullary spinal cord tumors (IMSCTs), 109–111, 397
adjuvant therapy, 354–364
astrocytomas, 74–75
clinical presentation, 339, 340, 342, 343
definition, 71
diagnostic imaging, 340
ependymomas, 72–73
epidemiology, 468
genetics, 343–345
gliomas, 337
hemangioblastomas, 76–77
histology, 343–345
hydrocephalus, 346, 347
malignant transformation, 338
molecular markers, 338
molecular subtyping, 343–345
pathology, 343–345
radiation therapy (*see* Radiation therapy)
surgical intervention, 347–349
surgical outcome, 352–353
surgical technique, 349–351
symptoms for, 398
Intraoperative neurophysiological monitoring (IOM), 494
cervical myelopathy patients, 111
conus medullaris, 111, 112
dorsal column mapping, 115, 116
double stimulation paradigm, 115–120
D-wave collision technique, 115, 117
extradural tumors, 111
IMSCTs, 109–111
lumbosacral nervous system
BCR, 121, 122
cauda equine, 122
neurophysiological signals, 120
technical aspects, 120, 121
MEPs, 112–114
SEPs, 114
surgical strategy, 109
Intraspinal lipomas, 421
Intratumoral and peritumoral cysts, 413
Ischemic optic neuropathy (ION), 133, 492
Isocitrate dehydrogenase (IDH), 74, 75
Isocitrate dehydrogenase (IDH) 1 and 2 gene mutations, 306, 338

J
Joint contractures, 504

K
Karnofsky performance scale/status (KPS), 340, 367
Kurze, Theodore, 17
Kyphosis, 457, 458, 463
Kyphotic deformity, 489

L
Laminectomy, 350, 353, 401, 457, 458, 463, 501
Laminoplasty, 353
Laminotomy, 401
Lateral femoral cutaneous nerve neuropathy, 494
Leptomeningeal metastasis, 66, 446
Lipomas, 39, 398
adjuvant therapy, 421
clinical presentation, 420
diagnostic imaging, 420
intramedullary lipomas, 419
lumbosacral lipomas, 419
pathology, 421
spinal dysraphism, 420
surgical intervention, 421
Location of disease, Mechanical stability, Neurological risk, Oncological parameters, and Preferred treatment (LMNOP), 369, 471
Loss of heterozygosity (LOH), 212
Lower motor neurons (LMNs), 517
Low-grade astrocytoma, subtype indeterminate (LGSI), 193
Low-grade gliomas, 338
Low molecular weight heparin (LMWH), 503
Lumbar spine, 448
Lumbosacral lipomas, 419

M
Magnetic resonance angiography (MRA), 22
Magnetic resonance imaging (MRI), 18, 55, 303, 304, 399
dumbbell tumors, 437
IMSCTs, 340
intradural metastatic disease, 368
intramedullary metastasis disease, 368
lipomas, 420

Magnetic resonance angiography (*cont.*)
neurocytomas, 409
neuroenteric cysts, 405
paragangliomas, 404
PSO, 407
SCEs, 329
SCT, 415
Malignant peripheral nerve sheath tumors (MPNSTs), 85, 86, 446, 447
Malignant spinal dumbbell tumors, 446, 447
Malignant transformation, 338
Malis, Leonard, 17
McCormick classification, 340, 469
Mechanistic target of rapamycin (MTOR) pathway, 188
Meningeal tumors, 148–150
Meningiomas, 433, 512
diagnosis, 65, 66
dumbbell meningiomas, 438, 443
epidemiology, 37, 38
neuropathology, 78–82
prognosis, 515
Meningitis, 497
Mesenchymal chondrosarcoma, 447
Metastatic sacral tumors, 381, 393
Methicillin-resistant Staphylococcus aureus (MRSA), 498
Meticulous closure technique, 501
Meticulous skin care and nursing, 505
Meticulous surgical technique, 494
Microsurgery, 356
Microtubule-associated protein-2 (MAP-2), 410
Midline durotomy, 350
Midline myelotomy, 331
Mineralocorticoid, 518
Minimally invasive surgical (MIS) approaches, 490
Misplaced germ cell theory, 416
Mitogen-activated protein kinase (MAPK) pathway, 403
Monopolar electrocautery, 401
Motor and sensory deficits, 515
Motor evoked potentials (MEPs), 22, 111–114, 136, 231, 251, 277, 400
Multimodality intraoperative monitoring (MIOM), 180
Multiple endocrine neoplasia II (MEN II), 201
Multiple schwannomas, 162
Musculoskeletal complications, 504
Myelography, 56
Myelopathic signs, 95
Myelotomy, 401
Myxoid liposarcoma (MLS), 447
Myxopapillary ependymomas (MPEs), 77–78, 330
adjuvant radiotherapy, 294–295
aggressive behavior, 274
classification system, 275–281
computed tomography, 385
definition, 273
diagnosis, 57, 59, 330
direct monitoring of corticospinal tracts, 349
ectopic sites, 281
extent of resection, 284–292
extraneural metastasis, 281
follow-up, 296
imaging, 277–279
microscopic morphology, 274
molecular differences, 274–275
molecular genetics, 274–275, 329
outcome and survival, 295–296
primary seeding, 294
primary treatment, 385
recurrence, 293
secondary seeding, 294
surgical technique
C-arm, 282
cauda equine, 281, 283
direct nerve root stimulation, 283
isolated proximal filum terminale, 283, 284
laminectomy, 282
marginal en bloc resection, 282
micro-scissors and bipolar instrument, 284
neurological recovery, 282
subarachnoid space, 284
surgical videos, 282
ultrasonography, 282
upward retraction, 283
surgical treatment, 332
symptoms, 275, 277
T1 and T2-weighted sequences, 385
urinary incontinence and numbness, 327
WHO Grade 1, 328

N

National Surgical Quality Improvement Program (NSQIP) registry, 486
Neoadjuvant therapy, 473
Nerve sheath tumors (NSTs), 71
Neurilemmoma, *see* Schwannoma
Neurinoma, *see* Schwannoma
Neurocytomas, 398
adjuvant therapy, 411

clinical presentation, 409
diagnostic imaging, 409
EVNs, 409
pathology, 410
surgical interevention, 411
Neuroenteric cysts, 398, 399, 406
adjuvant therapy, 407
associated pathologies, 405
clinical presentation, 405
diagnostic imaging, 405
pathology, 406
surgical intervention, 406, 407
Neurofacomatosis
allied tumors, 188, 189
NF1
diagnostic criteria, 188, 190
ependymomas, 193
epidemiology and genetics, 188
intramedullary gliomas, 192
PMAs, 193
screening, 190
symptoms, 190–192
NF2
cervical cord and cervicomedullary junction, 197, 198
diagnostic criteria, 194
epidemiology and genetics, 193–194
screening, 194
symptoms, 195–197
WHO grade I myxopapillary ependymoma, 198
VHL disease
diagnostic criteria, 199
epidemiology, 198
gene encode, 199
hemangioblastoma, 201, 202
intramedullary hemangioma, 201, 202
screening protocols, 199
symptoms, 200, 201
Neurofibromas
diagnosis, 64, 65
dumbbell neurofibroma, 437, 438
epidemiology, 39
imaging, 386, 387
neuropathology, 83–85
routine surveillance, 515
ventral nerve roots, 386
Neurofibromatosis type I (NF1), 33, 82
diagnostic criteria, 188, 190
ependymomas, 193
epidemiology and genetics, 188
intramedullary gliomas, 192
PMAs, 193
screening, 190
symptoms, 190–192
Neurofibromatosis type 2 (NF2), 82, 96
cervical cord and cervicomedullary junction, 197, 198
diagnostic criteria, 194
epidemiology and genetics, 193–194
screening, 194
symptoms, 195–197
WHO grade I myxopapillary ependymoma, 198
Neurogenic bladder, 517
Neurogenic bowel, 516
Neurogenic sacral tumors
ganglioneuromas, 385, 386
myxopapillary ependymomas, 385
neurofibroma s, 386, 387
schwannoma, 386, 387
Neurological aspects
clinical presentation
anatomic location, 92
Brown-Séquard syndrome, 93
cauda equina syndrome, 95
central cord syndrome, 94
conus medullaris syndrome, 94
dorsal cord syndrome, 94
pain, 92
segmental syndrome, 93
sphincter dysfunction, 92
symptoms, 92
ventral cord syndrome, 93, 94
diagnosis, 95–96
familial tumor syndrome, 96–98
L2 schwannoma, 104, 105
lipoma layer, 103, 104
overview, 91
pathological T4 compression fracture, 99, 100
physical examination, 95
T12–L1 schwannoma, 102, 103
Neurologic, Oncologic, Medical, Pain and Support status of the patient (NOMPS criteria), 523
Neuromuscular blockade (NMB), 136, 137
Neuron-specific enolase (NSE), 76
Neurophysiological monitoring, 349
airway management
challenges, 128
endotracheal intubation, 129–130
evaluation, 129
extubation, 130
tumor and surgical approach, 128
anesthetic agents
EMG, 135, 137
evoked potential monitoring, 134

Neurophysiological monitoring (*cont.*)
MEPs, 136
recommendations, 137–138
SSEPs, 135, 136
volatile halogenated inhalation, 134
blood conservation
acute normovolemic hemodilution, 139
autologous blood transfusion, 139
complications, 138
fibrinolytics, 140–141
hypotensive anesthesia, 140
intraoperative cell salvage, 141
Jehovah's Witnesses, 138
positioning devices, 140
preoperative interventions, 138
pain management, 141–142
preoperative assessment, 127–128
prone positioning
cardiovascular effects, 130–131
neurologic complications, 131–133
perioperative visual loss, 133–134
respiratory changes, 131
Non-radicular pain, 436
Non-schwannoma non-neurofibroma dumbbell tumors, 433
Non-small lung cancer intramedullary metastasis, 372, 374
Non-steroidal anti-inflammatory drugs (NSAIDs), 128, 388
Nosocomial urinary tract infections, 498
Nucleus proprius, 49

O
Occipital headache, 150
Oligodendrocyte transcription factor (OLIG2) expression, 73
Oligodendrogliomas, 398
Ophthalmic injury, 232
Osseous sacral tumors
aneurysmal bone cysts, 389
cartilaginous tumors, 390, 391
Ewing's sarcoma, 392, 393
giant cell tumors, 389, 390
osteoid osteomas and osteoblastomas, 388, 389
osteosarcoma, 392
Osteoblastomas, 388, 389
Osteoid osteomas, 388, 389
Osteoplastic laminoplasty, 350
Osteoporosis, 504
Osteosarcoma, 392
Oxybutynin, 517

P
Papillary ependymoma, 329
Paragangliomas
adjuvant therapy, 405
clinical presentation, 404
diagnostic imaging, 404
origin of, 404
pathology, 404
surgical intervention, 405
Paraspinal plexiform neurofibromas (PNs), 192
Paravertebral neurogenic tumors with intraspinal extension, 443, 446
Pediatric intramedullary spinal cord tumors (IMSCTs)
vs. adult features, 302, 303
astrocytomas, 305–306
characteristics, 302, 303
chemotherapy, 317
clinical presentation, 303–304
disease control, 318
ependymomas, 307–308
high-grade astrocytomas, 306, 307
intramedullary gangliogliomas, 308–309
intramedullary hemangioblastomas, 308
MRI, 303, 304
radiation therapy, 317
surgery
extra-medullary stage, 309–310
intramedullary stage, 310–315
neurologic electro-physiologic monitoring, 316
postoperative complications, 316, 317
special micro-instruments, 315, 316
treatment rationale, 309
Perioperative peripheral nerve injury, 494
Peripheral neurofibromatosis, *see* Neurofibromatosis type I (NF1)
Phakomatoses, *see* Neurofacomatosis
Physostigmine, 518
Pilocytic astrocytomas, 212, 338, 344
Pilomyxoid astrocytoma (PMAs), 193
Platelet-derived growth factor receptor (PDGFR), 345
Platinoid salts, 513
Pneumonia, 498
Polymerase chain reaction (PCR), 96
Positron emission tomography (PET)
intradural metastatic disease, 368
intramedullary metastasis disease, 368
SCEs, 330
Posterior cord syndrome, 94
Posterior ischemic optic neuropathy (PION), 133

Posterior spinal ligaments, 457
Posterior tension band, 457, 458
Pott, Percival, 5
Pregabalin, 516
Pressure injury, 232, 491
Primary cranial teratomas, 415
Primary intradural tumors
  activity limitation, 520
  impairments
    autonomic dysfunction, 518, 519
    motor and sensory deficits, 515
    neurogenic bladder, 517
    neurogenic bowel, 516
    pain, 516
    psychosocial impact, 520
    sexual dysfunction, 517, 518
    skin integrity, 518
    spasticity, 515, 516
  intradural extramedullary tumors, 514, 515
  intramedullary neoplasms, 512–514
  participation restriction, 520
  rehabilitation
    courses, 520, 523, 524
    outcomes, 524
  WHO pathology classification, 512
Primary intramedullary spinal cord lymphoma, 399
Primary sacral tumors, 381
Primary spinal oligodendrogliomas (PSOs)
  adjuvant therapy, 409
  clinical presentation, 407
  diagnostic imaging, 407
  pathology, 408, 409
  surgical interevention, 409
Progesterone receptor (PR) positivity, 79
Proton beam therapy, 332
Pseudomeningocele, 499–502
Pseudorosettes, 328
Pulmonary embolism (PE), 503
pVHL, 199

Q
Quilting sutures, 496

R
Radial diffusivity (RD) values, 343
Radiation myelopathy, 94
Radiation therapy, 23, 513
  biopsy/partial resection, 354
  conventional EBRT, 470
  effective radiation doses, 488
  intradural metastatic disease, 370, 371
  intramedullary metastasis disease, 370, 371
  large expansile intradural mass, 475
  local tumor control, 332
  management strategies, 471, 472
  metastatic sacral tumors, 393
  outcomes, 472–474
  radiographic stability, 477
  SBRT, 470, 471
  SRS, 470, 471
  stereotactic radiosurgery, 332
  tumor recurrence, 477
Radiculopathy, 469
Radio frequency electrical currents, 16
Ras-mitogen-activated protein kinase (Ras-MAPK) pathway, 409
Receptor activator of nuclear factor **κ**-B ligand (RANKL), 390
Regions of interest (ROI), 343
Renal cell carcinoma (RCC), 76, 201, 373, 375
Ribonucleic acid (RNA), 308
Rostral and caudal cysts, 342

S
Sacral spinal tumors
  congenital tumors
    chordomas, 381, 383, 384
    definition of, 382
    sacrococcygeal teratoma, 382, 383
  metastatic sacral tumors, 381, 393
  neurogenic sacral tumors
    ganglioneuromas, 385, 386
    myxopapillary ependymomas, 385
    neurofibroma, 386, 387
    schwannoma, 386, 387
  osseous sacral tumors
    aneurysmal bone cysts, 389
    cartilaginous tumors, 390, 391
    Ewing's sarcoma, 392, 393
    giant cell tumors, 389, 390
    osteoid osteomas and osteoblastomas, 388, 389
    osteosarcoma, 392
  primary sacral tumors, 381
Sacrococcygeal teratoma, 382, 383
Schwannomas, 433, 514
  ADC, 173
  clinical presentation, 163
  clinical symptoms, 165
  complication rate, 181
  diagnosis, 172

Schwannomas (*cont.*)
displacement of nerves/visceral organs, 386
dumbbell tumor, 178–179
epidemiology, 36, 37
etiology, 161–162
extradural tumor management, 176–178
histology, 162
imaging, 386, 387
indication, 165
intradural extramedullary tumor, 173–175
intramedullary tumor, 175, 176
intraoperative neural monitoring, 180
lumbosacral pain, 386
macroscopic aspect and localization, 162–163
NF2, 196
postoperative neurological deficits, 165
recurrence, 180, 181
radiological presentation, 436–438
sacral schwannoma, 179, 180
surgical approach, 165–167, 173
surgical treatment, 163–164
T1-weighted imaging, 172
T2-weighted imaging, 172
Schwannomatosis, 97, 162
Scoliosis, 340
Sensory evoked potentials (SEPs), 111, 114
Sensory impairment, 339
Sensory level, 93
Seroma, 495, 496
Severe scoliosis, 398
Sexual dysfunction, 517, 518
Skeletal traction, 16
Skin integrity, 518
Smith, Edwin, 2
Somatosensory evoked potentials (SSEPs), 22, 132, 133, 135, 136, 400, 494
Sontag, Volker, 20
Spasticity, 515, 516
Sphincter dysfunction, 339
Spinal column deformities, 489, 490
Spinal cord
BSCB, 47, 48
cervical nerves, 46
functional anatomy
gray matter, 48–49
white matter, ascending tracts, 51–53
white matter, descending tracts, 49–51
gastrulation abnormalities, 44
gross anatomy, 46, 47
ingression, 44
levels, 44, 45
marginal layer, 44
matrix layer, 44
metastases, 66, 67
overview, 43
paired nerves, 45
primary neurulation, 44
secondary neurulation, 44
thoracic and lumbar spines, 46
vasculature, 46–47
ventral mantle layer, 44
Spinal cord astrocytomas
classification, 211
high grade, 237
low-grade
average patient history, 212
biomarkers, 212
blood pressure management, 233
chemotherapy, 237
diagnosis, 213–214
extent of surgical resection, 218–228, 233
fluorescein, 234
histologic findings, 212
intraoperative ultrasonography, 234
laminoplasty and laminectomy, 234, 235
malignant transformation, 236
molecular biology, 212
neuro-monitoring, 234
radiotherapy, 236, 237
recurrence, 236
surgical complications, 231–232
surgical outcome, 218–228, 235
surgical technique, 229–231
survival rates, 235–236
symptoms, 213
treatment, 214–218
US-based neuronavigation system, 233
Spinal cord dissemination, 66
Spinal cord dysfunction (SCD), 523, 524
Spinal cord ependymomas (SCEs), 338, 468, 512
cervical, 326
chemotherapy, 355
clinical presentation, 326
diagnostic imaging, 329, 330, 342
epidemiology, 325
molecular genetics, 329
NF2 and loss of expression of Merlin, 345
pathology, 328, 329
RELA fusion type, 345
subtypes of, 345
surgical intervention, 348
surgical outcome, 353
treatment
chemotherapy, 333
radiation therapies, 332

surgical resection, 330–332
Spinal cord germinomas (SCGs)
adjuvant therapy, 414
clinical presentation, 413
diagnosis, 413
pathologic and histological features, 414
surgery, 414
Spinal cord infarction, 493
Spinal cord injury (SCI), 493, 517
Spinal cord subependymomas (SCSEs), 398
adjuvant therapy, 412
clinical presentation, 411
diagnosis, 411
MRI, 399
pathology, 412
surgery, 412
Spinal cord teratomas (SCTs), 398, 415
adjuvant therapy, 416
clinical presentation, 415
diagnosis, 415
pathology, 416
surgery, 416
Spinal cord tumors
extradural, 325
intradural-extramedullary, 325
intradural-intramedullary, 325
Spinal epidural hematoma, 503
Spinal extraosseus chordoma (SEC), 447
Spinal meningioma
clinical presentation, 150
complication avoidance, 155
epidemiology, 147–149
neuroimaging, 151
pathology, 148–150
surgical treatment
anterior approach, 154
operative technique, 154–155
pediculotomy, 152
posterior approach, 151, 152
T-line concept, 152, 153
Spinal nerve sheath tumor surgery, 486
Spinal radiotherapy (SRT), 370
Spinal reconstruction surgery, 448
Spinal schwannomas, 63, 64
Spinal surgery
antiquity
Alexandrian school, 3
Edwin Smith papyrus, 2
evidence of, 2
Galen of Pergamon, 4
history, 20–23
middle ages
Avicenna, 4
dogmatic scholasticism, 4, 5
Vesalius, Andreas, 5
modern medicine and surgery
advancement, 6
Brown-Séquard, Charles Edouard, 6
Cushing, Harvey, 15–16
developments in 1990s, 19, 20
developments in 1960s, 17–18
early 1950s, 16–17
elective surgical methods, central nervous system, 8–9
Elsberg, Charles A., 12–15
evolution of, 7
Horsley, Victor, 9–12
imaging in 1980, 18–19
innovators, 20
Koch, Robert, 6
Lister, Joseph, 6
Macewen, William, 7
Morton, William, 6
Pasteur, Louis, 6
wound dressing material, 6
Spine Instability Neoplastic Score (SINS), 369
Stereotactic body radiotherapy (SBRT), 470, 471, 473
Stereotactic radiosurgery (SRS), 332, 470, 471, 473, 474, 514
Stereotactic spinal radiosurgery (SSRS), 370
Stookey, Byron, 13
Subependymomas, 328, 329, 345
Supplemental spinal fusion, 457
Surveillance, Epidemiology, and End Results (SEER) database, 468
Synaptophysin (SYN), 410
Syncytiotrophoblastic giant cells (STGCs), 413
Syringomyelia syndrome, 317, 512

T

Tamsulosin, 517
Tanycytic ependymoma, 58
Tarlov, Isadore, 16
Temozolomide (TMZ), 237, 355, 356, 423, 513, 514
Thoracic anaplastic astrocytoma, 341
Thoracic spine, 448
Thromboprophylaxis, 501, 503
Tissue-sparing technique, 464
Tizanidine, 518
Tolterodine, 517
Tranexamic acid (TXA), 140
Triggered EMG (tEMG), 137
True rosettes, 328
Tumor suppressor protein 53 (TP53), 307

U
Ulnar neuropathy, 494
Ultrasound, 401
Unilateral cortical blindness, 492
Upper motor neurons (UMNs), 517
Upper thoracic lesions, 486
Urinary tract infection, 498

V
Valsalva maneuver, 501
Vascular endothelial growth factor (VEGF) inhibitors, 201
Vascular lesions, 437, 440, 442, 443
Venous air embolism (VAE), 232
Ventral posterolateral nucleus (VPL), 52
Vestibular schwannomas (VS), 193, 195, 196
Volumetric modulated arc therapies (VMAT), 471
Von Hippel-Lindau (VHL) disease, 468, 474, 514
  diagnostic criteria, 199
  epidemiology, 198
  gene encode, 199
  genetic factors, 33
  hemangioblastomas, 76, 77, 201, 202, 245
  intramedullary hemangioma, 201, 202
  NF2, 96, 97
  screening protocols, 199
  symptoms, 200, 201
Von Recklinghausen disease, *see* Neurofibromatosis type I (NF1)

W
Warburg metabolic phenotype, 275
World Health Organization (WHO) classification, 72, 511
Wound complications
  cellulitis and abscesses, 496
  seroma and hematoma, 495, 496
  wound dehiscence, 496
  wound infection, 496
    antibiotic prophylaxis, 497
    delay elective surgery, 496

Z
"Zellballen" pattern, 404